SURGICAL INFECTIONS
Volume 14, Number 1, 2013
© Mary Ann Liebert, Inc.
DOI: 10.1089/sur.2011.097

Review Article

Use of Silver in the Prevention and Treatment of Infections: Silver Review

Amani D. Politano, Kristin T. Campbell, Laura H. Rosenberger, and Robert G. Sawyer

Abstract

Background: The use of silver for the treatment of various maladies or to prevent the transmission of infection dates back to at least 4000 B.C.E. Medical applications are documented in the literature throughout the 17th and 18th centuries. The bactericidal activity of silver is well established. Silver nitrate was used topically throughout the 1800s for the treatment of burns, ulcerations, and infected wounds, and although its use declined after World War II and the advent of antibiotics, Fox revitalized its use in the form of silver sulfadiazine in 1968.
Method: Review of the pertinent English-language literature.
Results: Since Fox's work, the use of topical silver to reduce bacterial burden and promote healing has been investigated in the setting of chronic wounds and ulcers, post-operative incision dressings, blood and urinary catheter designs, endotracheal tubes, orthopedic devices, vascular prostheses, and the sewing ring of prosthetic heart valves. The beneficial effects of silver in reducing or preventing infection have been seen in the topical treatment of burns and chronic wounds and in its use as a coating for many medical devices. However, silver has been unsuccessful in certain applications, such as the Silzone heart valve. In other settings, such as orthopedic hardware coatings, its benefit remains unproved.
Conclusion: Silver remains a reasonable addition to the armamentarium against infection and has relatively few side effects. However, one should weigh the benefits of silver-containing products against the known side effects and the other options available for the intended purpose when selecting the most appropriate therapy.

Silver has been used for centuries in the treatment of various maladies or to prevent the transmission of infection [1–3]. It has been applied topically, by ingestion, and as a container for or deposit in liquids to decontaminate or preserve them [1,2]. Although its use fell out of favor with the advent of antibiotics, refrigeration, and pasteurization, silver has seen a rebirth as a component of various medical devices with the intention of reducing infection (Table 1). We review the literature pertaining to many of the modern medical uses of silver.

History

The use of silver for the treatment or prevention of infection dates back to at least 4000 B.C.E. [1] and was well documented in the medical literature throughout the 17th and 18th centuries [2]. There are several treatises dedicated to the historical applications of silver [1–3]. Persian kings insisted on drinking only out of silver vessels, not because such cups denoted wealth but for their ability to preserve fresh water [1]. Silver nitrate was used topically throughout the 1800s for the treatment of ulcerations and infected wounds and to prevent gonococcal ophthalmic infections in newborns and was ingested for the treatment of stomach ulcers [1,2].

Other noteworthy medical applications of silver include wire or coated suture [1,4,5], topical therapy for osteocutaneous fistulae, and foil coverings for burn wounds [2]. For example, Sims used silver wire to close vesicovaginal fistulae in post-partum women when closure with silk sutures had failed [1,5]. Doctor Sims also advocated the use of silver urinary catheters during the recovery period. With the advent of antibiotics circa World War II, the use of silver for many of these functions declined, only to be revived in the 1960s by Moyer and Fox, as described below [reviewed in 3].

Mechanism of Action

Although silver and other metals have been known to have antimicrobial activity for some time [2], the mechanisms behind this bactericidal activity have been elucidated only recently. The term "oligodynamic action," coined in the 1890s [6], refers to the toxic effect of metal ions on microorganisms

Department of Surgery, University of Virginia, Charlottesville, Virginia.

Table 1. Summary of Silver Applications for Treatment of Infections

Modality	*Pros*	*Cons*	*Cost effectiveness*	*Recommendation*
Topical application for burns	• Several preparations available • Reduced infection rates • Prolonged silver ion release with some preparations • Potentially fewer dressing changes • Better wound healing and skin graft adherence	• Several preparations available • Concern about toxicity for host cells • Electrolyte leaching with silver nitrate	Favors use of prolonged-release silver, although no comparison of all products is available [53]	Difficult to compare wide variety of applications; recommended for initial/early decontamination of burn wounds
Topical application for ulcers	• Several preparations available • Potentially longer wear time for dressings • Reduction in wound size; less odor and exudate • Less pain	• Several preparations available • Potentially more frequent office visits and longer total duration of wound care • Several studies failed to show benefit in overall wound healing	Some studies favor use of silver-releasing foam dressing [55,60,62], whereas others show higher cost [59,61]	Current data do not support routine use of silver for this application
Surgical incisions	• Fewer surgical site infections in cardiac, colorectal, or lower extremity revascularizations • Shorter time to re-epithelialization of skin graft donor sites [69]	• Longer time to re-epithelialization of skin graft donor sites in one study [68] • Studies of silver-impregnated mesh or suture material are still in early phases	Cost comparison data not available	Current data do not support routine use of silver for this application
Blood stream infections	• Reduced catheter colonization and CR-BSI rates with CSS catheters (more so with second-generation catheters)	• Benefit may not be seen with low institutional baseline infection rates • Use of antibiotic-impregnated catheters may confer greater reduction of infections	Favors use of CSS and RM catheters in high-risk patients or with high baseline infection rates [96,97]	Recommended if elevated institutional CR-BSI rates despite a comprehensive control program
Urinary tract infections	• Reduced infection rates in some studies with use of silver-alloy catheters	• Studies are heterogeneous • Several large studies did not find benefit	Favors use of silver alloy catheters [109]	Recommended if baseline infection rates are high
Ventilator/endotracheal tubes	• Lower incidence of VAP • Reduced mortality rate in patients with VAP	• Higher mortality rate in patients without VAP • Use of care bundles may negate contribution of silver-coated tubes	Favors use of silver-coated tubes [131]	Recommended if elevated institutional VAP rates despite a comprehensive control program
Orthopedic hardware	• Decreased bacterial adherence to silver-coated external fixation pins • Better cyto-compatibility • Fewer infections when combined with chlorhexidine for pin-site dressings • Lower infection rates with silver-coated implant devices	• Increased serum silver concentrations in one study • Early-phase studies only; need further investigation	Cost comparison data not available	Current data do not support routine use of silver for this application
Vascular prostheses	• Lowered rates of infection when used as primary prosthesis, although differing results have been reported	• Inconsistent data regarding risk of reinfection • May activate neutrophils and inhibit their antibacterial properties	Cost comparison data not available	Current data do not support routine use of silver for this application
Heart valves	• Low rates of recurrent endocarditis in early studies	• Higher rates of embolization • More moderate and severe paravalvular leaks • Substantial need for reoperation	No longer available	Not recommended

CR-BSI = catheter-related blood stream infection; CSS = chlorhexadine–silver sulfadiazine; RM = rifampicin–minocycline; VAP = ventilator-associated pneumonia.

and often has been used to describe the antimicrobial action of silver [6–8]. Silver was shown to complex with DNA in vitro using radio-labeled silver sulfadiazine (SSD), and both silver nitrate and SSD had the greatest degree of bacterial binding of all silver salts tested [7]. Additional studies have demonstrated that silver causes precipitation of DNA within bacteria [9,10]. Furthermore, the combination of sub-inhibitory concentrations of sodium sulfadiazine and SSD resulted in bacterial inhibition, suggesting a synergistic effect [7].

Silver also exerts bactericidal activity by binding strongly with membranes and cell wall proteins [6,9,11], likely because of its interaction with thiol groups on enzymes [11–13]. Although high concentrations of silver have been shown to interact with skin cells, the concentration required to alter cell respiration is 25 times that needed to halt growth of *Pseudomonas aeruginosa* [14]. However, silver cations complex with chloride in wound exudate, precipitating the metal and rendering it inactive against pathogens [14]. In order to overcome this effect, patients treated with silver nitrate or SSD require more frequent dressing changes for reapplication of the silver compound [15].

More recently, silver technology has focused on the use of nanoparticles (nanocrystalline silver) as an antimicrobial agent. Nanocrystalline silver releases sub-crystalline particles of uncharged metallic silver containing fewer than eight atoms [15]. These particles react less rapidly with chloride ions, allowing silver to be released from the carrier dressing for a longer period of time [15]. Free radicals produced from silver nanocrystals may perpetuate membrane damage [12,16–20].

Silver nanoparticles also permeate cells, interfering with bacterial respiratory chain enzymes [12,18,20] to inhibit energy production and growth. The bactericidal activity of silver is dependent on particle size; 10-nm particles exhibit complete interaction with the bacteria, whereas larger particles do not, suggesting that nanoparticles exert greater bactericidal effects [20]. Although the molecular mechanisms of the action of silver against bacteria continue to be investigated, it is clear that silver nanoparticles are powerful bactericidal agents.

Topical Application for Burns

Although topical silver historically was used on burns [1,2], it had fallen out of favor after the advent of antibiotics and was not widely considered again until the 1960s. Moyer published on the use of silver nitrate topical solution for burns, and Fox is credited with revitalizing its use in the form of SSD [2,21,22].

Gauze bandages soaked in silver nitrate solution and used to dress burn wounds were believed to reduce water loss from the burn surface as well as provide antimicrobial protection [23]. However, this technique required frequent attention, with reapplication of silver nitrate solution every two hours and dressing changes at least twice daily, and caused electrolyte imbalance secondary to the egress of electrolytes into the dressing in response to the hypotonicity of the silver nitrate solution [23]. This imbalance continues until wound epithelialization is complete and is treated initially by frequent monitoring and repletion of electrolytes and subsequently by routine dietary supplementation with less frequent monitoring [8,23,24]. If electrolyte depletion persists, an isotonic colloidal silver albuminate solution is recommended [8].

The novel combination of silver nitrate and sodium sulfadiazine to create SSD cream has hastened complete recovery in patients [22]. In addition, dressing changes are needed less frequently and electrolyte abnormalities are less likely with this formulation [22,25].

Silver sulfadiazine has been modified by co-compounding with other molecules. The addition of cerium was purported to increase activity against gram-negative bacteria, although several studies comparing the two compounds failed to demonstrate direct benefit [26–28]. One study showed a reduced time to re-epithelialization or grafting and overall shorter hospital stays in patients treated with the cerium–SSD combination [29]. Addition of 0.2% chlorhexadine to SSD decreased burn wound colonization, specifically with *Staphylococcus aureus* [30–32] and *Enterococcus faeaclis* [32,33], but did not lower the infection rate or improve overall healing significantly [30]. The addition of hyaluronic acid to SSD improved time to healing and reduced local edema [34,35].

In contrast to the uses of silver salts described above, more recent products utilize nanocrystalline silver particles incorporated into various dressing materials such as mesh, activated charcoal, hydrofibers or hydrocolloids, or polymer matrices [25]. These products are numerous and have been reviewed elsewhere [25,36–38]. Nanocrystalline silver releases small particles of silver over a long period of time, increasing the wound surface area in contact with the silver particles and the duration of that contact [38,39]. A systematic literature review showed a lower incidence of infection ($p < 0.0001$) with nanocrystalline applications compared with either silver nitrate or SSD for the treatment of burn patients, as well as lower costs and decreased pain scores [40].

The use of silver-impregnated nylon cloths with an applied weak direct current results in electrochemical oxidation of the silver particles with periodic or sustained release of the ion [39,41]. This method increases silver penetration and is active against a wide variety of pathogens [39,41,42]. In infected burn animal models, the application of a current to a silver-coated nylon surface anode achieved greater survival than in animals treated without current, whereas both were superior to uncoated nylon either with or without applied current [43]. This method also improved survival following escherotomy of the infected wound at up to three days [44]. Additionally, use of silver nylon with applied direct current on either split-thickness or meshed composite skin grafts was associated with significantly less wound contraction, more rapid adherence and epithelialization, and increased hair follicle regeneration compared with silver nylon without current [45–47].

Studies comparing SSD with other forms of burn therapy have suggested that SSD may not be the best treatment. In a randomized trial, early surgical debridement and split-thickness skin grafting of indeterminate-thickness burns was associated with shorter hospital stays and lower costs, whereas patients treated with SSD had irregular burn scars and more late complications [48]. Burn wound coverage with other temporary biologics also has demonstrated faster and less painful healing [49–51]. Thus, although silver treatments may have a role in the management and decontamination of burn wounds, both the variety of dressing choices and the various other surgical options must be considered when selecting the appropriate treatment for each patient.

A cost-effectiveness analysis comparing SSD with a silver-containing soft silicone dressing found reduced costs for treatment and better treatment-related analgesia, less frequent dressing changes, shorter hospitalization, and reduced outpatient interventions with the silicone dressing compared with SSD [52]. Although the difference was not statistically significant, time to healing was shorter on average with the silicone dressing. A separate study comparing SSD/chlorhexidine with a nanocrystalline silver dressing found reduced infections and antibiotic use, shorter hospitalization time, and lower overall costs with the nanocrystalline preparation [53].

Topical Application for Ulcers

Following its resurgence for the treatment of burns, the ability of topical silver to reduce bacterial burden and promote healing of chronic wounds and ulcers was evaluated. The results of these studies differ widely, and a recurring theme in the relevant meta-analyses is the need for more rigorous trials before any conclusive statements can be made [54–58]. Because of the countless products available for the management of chronic wounds, both with and without silver, an in-depth review of each is beyond the scope of this review but can be found elsewhere [25,36,37]. The variety of products and the heterogeneity of studies evaluating them provide insufficient evidence that silver dressings are consistently superior to non-silver dressings for the treatment of chronic or infected ulcers, but there is some evidence supporting the use of silver-containing products for short-term wound care in specific patient populations. The major studies, systematic reviews, and meta-analyses are summarized below.

The VULCAN trial randomized patients with lower-extremity venous ulcers present for longer than six weeks to receive either a silver-releasing dressing or a non-adherent dressing. There was no significant difference between the groups in wound healing at 12 weeks, but the silver dressings were associated with much higher costs [59]. However, a comparison study found a silver-releasing foam dressing to be more cost-effective than other silver-containing products, including an ionic silver hydrofiber dressing and a silver-impregnated activated charcoal dressing [60]. Other concerns related to use of silver dressings are a greater frequency and number of visits and longer total duration of wound care, which may increase costs [61]. Additional studies have had differing results [57], but some suggest that silver dressings increase wear time and therefore improve cost-effectiveness [55,62].

In one systematic review, three trials comparing topical SSD with placebo or inert dressings failed to show superiority in ulcer healing with SSD [56]. The same review evaluated six studies of silver-impregnated dressings; only one trial demonstrated a positive result for the silver arm [63], and the meta-analysis showed no overall benefit [56].

A 2006 Cochrane review of three randomized trials for infected or contaminated ulcers found no difference in complete wound healing, but did see a greater reduction of ulcer size with silver foam compared with conventional therapy [54,62,63]. Other benefits of the silver dressings were seen with respect to odor reduction and decreased drainage [54]. Two other meta-analyses demonstrated a significant reduction in the size of chronic, non-healing or infected wounds, pain, odor, and exudates, as well as improvements in wound bed composition, wound edge maceration, and patient satisfaction with a silver dressing [55,57]. A more recent meta-analysis again supported the benefit of silver in providing greater reduction in wound size in the short term, but long-term results and data on complete healing are lacking [58].

Surgical Incisions

Silver dressings have been used on operative incisions. The use of a silver-impregnated dressing (with or without concomitant vacuum apparatus) in post-operative mediastinitis with continued positive cultures despite surgical debridement and antibiotic therapy showed conversion to negative cultures and ultimate wound closure with the silver dressing [64]. Another analysis compared mediastinitis rates after cardiac surgery when a silver dressing was used routinely and found a significant decrease in the incidence of infection compared with standard dressings, although the methodology of this study was less rigorous [65]. A randomized controlled study evaluated post-operative application of silver nylon dressings following colorectal surgery and found a significantly lower rate of surgical site infection in the silver-treated group [66]. A before-and-after cohort trial demonstrated similar significant results after lower-extremity vascular reconstruction [67].

In addition, silver dressings have been tested as donor site dressings following split-thickness skin grafting. One study found no differences in bacterial colonization of the wound, but noted that the silver nanocrystalline-impregnated dressings had a longer time to re-epithelialization than a hydrophilic occlusive polyurethane dressing [68]. However, another study showed decreased time to re-epithelialization and less pain associated with use of a silver-ionic hydrofiber dressing compared with a paraffin gauze dressing [69].

The application of a silver coating to the specialized foam used with the wound vacuum system has been shown in vitro to maintain those characteristics unique to the foam's specific structure, as well as to provide antibacterial activity against *S. aureus* and *P. aeruginosa* [70]. This technology may assist in preparing infected chronic venous stasis wounds for skin grafting, ultimately leading to better healing [71].

Other applications of silver for infection control in surgical procedures can be found throughout the literature. In vitro analysis of a nanocrystalline silver-coated polypropylene mesh suggested that the bactericidal actions are dose-dependent for the concentration of silver applied to the mesh, but that medium and high doses maintained a zone of bacterial inhibition around the mesh even in biological fluids and could prove beneficial for infection reduction in implantable devices [72].

Since the previously described use of silver wire as a suture material, the notion has been revisited, and several in vitro and in vivo animal studies are investigating the antibacterial properties and biocompatibility of silver-coated silk, nylon, and Vicryl (polyglactin 910; Ethicon, Somerville, NJ) sutures [73–75]. Pratten et al. [74] demonstrated decreased attachment of *S. epidermidis* to silver-doped bioactive glass-coated silk sutures compared with uncoated silk. Testing of these sutures is in the early phases, and how they will compare with commercially available triclosan-impregnated sutures is unclear.

Blood Stream Infections

Catheter-related blood stream infections (CR-BSI) remain a substantial concern for patients in intensive care units (ICUs), as such infections are associated with longer ICU and hospital stays, death, and higher cost [76–80]. Similar to what has been seen with ventilator care and the incidence of pneumonia, educational and behavioral campaigns can reduce these risks [81,82]. In addition, several variations of catheter design have been introduced, including silver alloy, silver iontophoretic, first- (external only) or second- (external and internal) generation chlorhexadine–silver sulfadiazine (CSS) catheters, and antibiotic-impregnated catheters [83–91].

In multiple studies, silver alloy-coated catheters did not confer a benefit over standard catheters [83,84], and silver iontophoretic catheters produced mixed results [85,86]. Several independent trials and meta-analyses have demonstrated reduced central venous catheter colonization and CR-BSI with the use of CSS rather than uncoated catheters [87–92]. One of the most cited meta-analyses showed a significant reduction in catheter colonization (odds ratio [OR] 0.44; 95% confidence interval [CI] 0.36, 0.54; $p < 0.001$) as well as in CR-BSI (OR 0.56; 95% CI 0.37, 0.84; $p = 0.005$) with CSS catheters [92]. When separated by catheter type, second-generation CSS catheters showed significantly less colonization and, although the difference was not statistically significant, lower CR-BSI rates than in patients having first-generation catheters [89].

Not all studies have shown the same benefit, however [93–95]. Implementation of behavioral and educational measures in one ICU decreased the CR-BSI rate. Subsequently, this group performed a before-and-after study of routine use of a CSS catheter and found it did not confer any additional benefit with regard to the rate of CR-BSI [93]. Additionally, although CSS catheters may reduce the rates of catheter colonization or CR-BSI compared with uncoated catheters, in studies that included rifampicin–minocycline (RM) catheters, the antibiotic-coated devices conferred even greater benefit [89–91].

Current recommendations are to use either a CSS or an RM-impregnated central venous catheter for patients expected to require a catheter for longer than five days if the institutional rate of CR-BSI is not decreasing despite a comprehensive infection-control program. This program should include education, appropriate site selection (avoiding the femoral vessels), maximum sterile barrier application during catheter insertion, and chlorhexidine skin preparation [81]. In the setting of high-risk patients or high baseline rates of CR-BSI, use of CSS catheters has been cost-effective [96]. Additionally, a decision-model analysis supported use of either CSS- or RM-coated catheters over uncoated catheters as more cost-effective, although the RM-coated catheters yielded greater cost savings [97].

Urinary Tract Infections

The first study investigating the incorporation of silver ions into a urinary catheter with the intention of reducing the risk of infection was done by Akiyama and Okamoto [98]. They demonstrated a lower incidence of bacteriuria in patients having the new catheter design rather than conventional catheters. Since then, several studies have examined this question, although they have differed in the silver application used (silver oxide vs. silver alloy), trial design (retrospective cohort, randomized, or block randomized), and outcomes [99–107].

Early large-scale trials evaluating silver oxide-coated catheters failed to show any benefit and even suggested they were associated with a higher rate of staphylococcal infections [104,107]. However, one study noted a significant benefit for women who received the silver oxide catheters [107]. A meta-analysis of eight clinical trials found an overall reduction in the risk of bacteriuria in patients receiving silver-coated urinary catheters (OR 0.59; 95% CI 0.42, 0.84) [108]. There was significant heterogeneity between these trials, and further evaluation showed that the benefit was obtained only with the silver alloy catheters (OR 0.24; CI 0.11, 0.52) and not silver oxide-coated catheters (OR 0.79; CI 0.56, 1.10). However, the trials using silver alloy catheters were completed at a single institution and therefore have been criticized by some authors [102,108]. Another single-institution study evaluating silver-alloy/hydrogel urinary catheters demonstrated a 57% risk reduction ($p = 0.002$) in a two-year period compared with a similar period using uncoated catheters and found this reduction to be associated with significant cost savings [109].

Two subsequent large studies failed to demonstrate a protective effect of silver alloy catheters [102,105]. A 2008 Cochrane review reported no significant reduction in infection rates with silver oxide catheters but found a significant decrease in asymptomatic bacteriuria with silver alloy catheters when catheterization lasted either less than (RR 0.54; 95% CI 0.43, 0.67) or greater than one week (RR 0.64; 95% CI 0.51, 0.80) [110]. Silver oxide catheters are no longer available in the United States [108].

Additional methods employing silver to decrease the incidence of urinary tract infections include a catheter system with a device that releases silver ions into the collected urine [111] and application of silver sulfadiazine cream to the urethral meatus [112]. The silver-releasing collection device showed no significant decrease in infections, leading to the conclusion that silver should not be limited to the intraluminal system. Especially in women, it appears that perineal contamination tracking on the extraluminal surface of the catheter is the method of inoculation of the bladder, especially with gram-negative organisms [113]. In addition, the use of topical silver at the meatus did not decrease the incidence of infection [112].

Ventilator/Endotracheal Tubes

Ventilator-associated pneumonia (VAP) is the most common hospital-acquired infection [114] and is associated with substantial morbidity, many deaths, and high cost [115–117]. Several measures have been investigated with the goal of reducing the incidence of VAP. These include practice care bundles [118] and improvements in the design of endotracheal tubes to resist colonization, decrease accumulation of secretions, and reduce the transmission of secretions from above to below the cuff [119–123].

Early animal studies, laboratory investigations, and randomized trials of the effect of silver-coated endotracheal tubes on device colonization, airway colonization, and device safety and tolerability have shown positive results [124–127].

Intubation with a silver-coated tube for less than 24 h prevented biofilm formation and decreased intraluminal mucus accumulation but did not affect airway colonization compared with an uncoated tube [124]. Additional studies have reported lower bacterial burdens in lung parenchyma in a dog model [126], decreased airway colonization for as long as seven days [127], reduced transmission of bacteria to the lower airway following buccal inoculation [125], and less bacterial contamination of the tube after extubation [125,127] with the use of silver-coated tubes. The continued presence of silver on coated tubes has been shown for as long as three weeks, and coated tubes have demonstrated lower colonization rates for 19 of 21 bacterial strains tested [125]. However, although many of these studies assessed colonization, few correlated that event with VAP [127], and no explanation was offered for the greater adherence of two bacterial species to the silver-coated tubes than to uncoated tubes [128].

The NASCENT trial compared silver-coated and uncoated endotracheal tubes for patients expected to be intubated for greater than 24 h and observed rates of VAP of 4.8% in those patients who received a silver-coated tube compared with 7.5% in those receiving the uncoated tube ($p = 0.03$). Patients with silver-coated tubes had a lower risk of VAP at any time and showed a delay in time to occurrence of VAP compared with the control group [121]. Retrospective cohort analysis of the NASCENT data showed fewer deaths in patients with VAP who had the silver tube, but in patients without a diagnosis of VAP, the mortality rate was significantly higher in the group having a silver tube [129]. The authors suggested that use of the silver tube in patients with VAP may have contributed to a lower overall bacterial burden and less multidrug-resistant organisms ultimately causing pneumonia, a finding that also explains the fact that delayed-onset VAP was protective in this study even though it was a risk factor for death from VAP in other reports [130].

These studies suggest that there is at least some benefit from silver-coated endotracheal tubes in reducing bacterial burden both on the tube and in the airway. However, even if the decrease is small, two studies have shown that there is a low cost associated with the silver-coated endotracheal tube compared with uncoated tubes [131,132], which may argue in favor of their cost-effectiveness. On the other hand, some authors have suggested that recent declines in rates of VAP are related to the wider application of ventilator bundles [118] designed to provide a small and manageable number of measures designed to reduce risk factors for VAP [133,134]. From that standpoint, both the bundles and the silver-coated tubes share a commonality, in that they both are designed to be simple, routine measures that are more likely to be implemented and adhered to consistently without extraordinary effort by healthcare providers [118,121].

Orthopedic Hardware

In addition to the use of temporary devices containing silver to reduce infections, permanently implanted silver-based hardware has been investigated. These devices are predominantly temporary and permanent orthopedic devices and vascular prostheses.

External fixation pins for fracture management are both extra- and intra-corporeal and therefore carry a risk of contiguous spread of bacteria [135]. Early studies of external fixation pins demonstrated decreased bacterial presence on the intra-corporeal tips of silver-coated pins than on stainless steel pins, as well as less motion with silver pins in animal models [136]. Decreased adherence of all pathogens tested except *S. hemolyticus* to silver-coated pins has been seen in vitro [135]. Furthermore, in one in vitro study, silver coatings were non-cytotoxic and more cyto-compatible than stainless steel pins [137].

A randomized trial using silver-coated pins in lower-extremity fractures noted a non-significant decrease in culture positivity, although this study was notably underpowered [138]. However, an increase in serum silver concentrations prompted the authors to conclude that it was unethical to continue the study without evidence of a clinical benefit. No silver toxicity was reported despite the elevated serum concentration of the metal.

Two prospective trials evaluated the use of an SSD dressing applied to the pin site as a method to decrease infections. Compared with a dry dressing, SSD alone did not show any benefit [139], but a combination of 1% SSD and 5% chlorhexadine produced significant reductions in infection rates ($p = 0.03$) [140].

Initial investigations of silver-coated titanium nanotubules in the construction of implants showed both increased antibacterial activity and better osteoblast adhesion with minimal toxic effects [141,142]. Another investigation of the incorporation of silver into a silicone polymer coating for prostheses demonstrated significant activity in vitro and ex vivo against *S. aureus* and methicillin-resistant *S. aureus* [143]. Here, the silver-coated prostheses were explanted at various times and incubated with bacteria to test adherence. Conversely, a model of direct inoculation of the femoral canal prior to implantation of silver-coated titanium or silver-coated stainless steel wires in a rabbit model failed to demonstrate any difference from the results obtained with uncoated prostheses [144].

A large study of the use of a silver-coated proximal femur or tibia replacement compared with a retrospective cohort of non-coated titanium hardware showed a decrease in the periprosthetic infection rate from 17.6% to 5.9%, although this difference did not reach statistical significance [145]. However, clinical outcomes were improved in patients with the silver-coated implant, as none required amputation after developing an infection, whereas 57% of those who developed infections after insertion of titanium prostheses required amputation. Although these investigators reported absence of toxic effects of the silver-coated prosthesis [146], one patient developed localized argyria secondary to a venous insufficiency that led to skin discoloration [145]. As this is the first study addressing the use of silver-coated megaprosthetics and the initial results are encouraging, further evaluation is warranted.

Vascular Prostheses

Silver-coated vascular grafts have been tested in both animal models and prospective clinical trials. As described above, the rationale behind the use of these grafts is that the action of the silver ions will eradicate bacteria that may otherwise adhere to and infect the synthetic material.

When compared with arterial homografts for the treatment of infected aortic grafts, silver-impregnated grafts were equally effective at preventing recurrent infection [147]. Batt et al. [148] used a silver-coated prosthetic graft for replacement of total or partial excision of infected aortic grafts in 24 patients, including several patients with aortoenteric fistulae. These grafts demonstrated primary and secondary patency rates of 100% at 24 mos and were associated with only one recurrent infection. All other patients remained infection-free by repeated computed tomography (CT) scanning [148]. Additional data from one institution participating in that study suggested that although silver is an acceptable material, the risk of reinfection remains significant [149].

A separate group of investigators used a silver-impregnated graft as the primary prosthesis for treatment of aortic disease in 289 patients and noted low rates of post-operative thrombosis and surgical site or graft infection [150]. A larger retrospective analysis of more than 900 patients showed no difference in the rates of complications between silver-impregnated and standard grafts for both aortoiliac and femorodistal bypasses, with no apparent complications arising from use of the silver grafts [151]. These cases included both primary and repeat procedures but excluded cases of prior graft infection, and the authors found that use of a silver graft did not decrease the risk of subsequent graft infections [151].

One of the effects of silver is to activate neutrophils in vitro, which may inhibit their ability to function against pathogens and aid in wound healing or even cause release of enzymes that promote tissue destruction [152]. Thus, although studies continue to assess the risks and benefits of silver-impregnated vascular grafts, long-term data are lacking, and the routine use of this technology has not become widespread.

Heart Valves

Silver coatings for the sewing ring of prosthetic heart valves have been employed to reduce episodes of valve-related endocarditis. Early reports on animal models had differing results, with some showing reduced inflammation or increased resistance to infection [153,154], whereas another showed no difference in colonization or infection rates compared with uncoated fabric [155].

The Artificial Valve Endocarditis Reduction Trial (AVERT) began enrollment in July 1998 as a multicenter, randomized, controlled comparison of the St. Jude Medical Silzone artificial valve with the conventional cuff [156]. Reports from this trial and others showed promising results, with no increase in hospital morbidity or mortality rates and no recurrent endocarditis at as long as two months and at nine months [157,158]. Another series had one post-operative death from pneumonia, but no evidence of recurrent disease in the remaining patients at 14 months' follow-up [159]. In a trial in 126 patients with more than a year of mean follow-up, patients had a low post-operative stroke rate, and none required reoperation for paravalvular leaks [160].

Despite these positive early results, several reports of higher rates of adverse events began surfacing. One case report documented recurrent endocarditis in a patient with a Silzone valve that required two subsequent replacements [161]. Follow-up studies found a higher rate of embolism in the early post-operative period after mitral valve replacement [162] and a non-significant increase in paravalvular leak diagnosed by echocardiogram at a mean of more than a year from valve replacement [163] with the Silzone valves. Other studies documented a significant increase in the need for reoperation secondary to paravalvular leaks, especially in the first two years after initial surgery [164–166].

Although this finding was not consistent in all studies [167–169], the AVERT trial was stopped in January 2000 because of the need for reoperation for moderate to severe paravalvular leaks, and St. Jude Medical voluntarily withdrew the Silzone valve from the market [164]. Histologic examination of explanted valves showed less dense cellular infiltrates than were obtained with the standard cuff valves [170]. Although enrollment in the AVERT study was at only 807 of the target 4,400 patients at the time the trial was suspended, it is estimated that 36,000 patients had received the Silzone valve before it was removed from the market [164]. Studies did not demonstrate any benefit of the Silzone valves in reducing the risk of prosthetic valve endocarditis compared with the conventional cuffed valve [164,171].

Adverse Effects

The most commonly described side effect of long-term silver use is argyria, a permanent bluish or grayish discoloration of the skin [172]. In fact, this may have been the origin of the term "blue blood" [1]. Although the silver deposit results in a change that can be quite pronounced, there do not appear to be any meaningful adverse consequences of such discoloration [172,173]. A similar discoloration of the eyes is termed "argyrosis" [172]. Absorption of silver occurs predominantly through the mucous membranes and burn wound surfaces [174]. Once absorbed, silver can be deposited in the skin, liver, spleen, kidney, cornea, and muscle tissues [172,174,175]. Localized argyria has been reported in conjunction with implantation of silver-coated orthopedic hardware [145]. In persons with long-term occupational exposure to silver, the degree of ocular deposition correlates with the total duration of exposure, whereas blood silver is more indicative of recent exposure [172,174].

There has been concern about the effect of silver absorption on renal, hepatic, and neurologic function. Silver is cleared from the body in part by the kidneys [176]. In one case report of a dialysis-dependent patient who suffered from a 30% total body surface area burn, an elevated serum silver concentration correlated with a comatose state; plasma exchange and cessation of topical SSD treatment resulted in reversal of the mental status changes and decreased blood silver concentration, whereas reinstitution of SSD correlated with a high serum concentration of silver and return of the adverse mental changes [177]. In this patient, silver was deposited in neural tissue despite reduced serum concentrations after plasma exchange, and silver concentrations in the brain tissue were elevated at autopsy. However, a review of the neurotoxic effects of silver suggests that blood–brain barrier penetration is minimal and that neurologic sequelae are rare [178]. Additionally, one case report described an increase in liver enzymes in a burn patient after treatment with SSD that resolved after discontinuation of therapy [179], although other studies were unable to correlate changes in liver enzymes with serum silver concentrations [180].

Rarer events have been reported. One paper described acute hemolytic anemia following treatment with SSD in a burn patient [181]. The anemia resolved after cessation of SSD use, and subsequent testing revealed a glucose-6-phosphate dehydrogenase deficiency. Other myelopoietic effects of silver therapy include transient leukopenia that does not necessarily increase the incidence of infectious complications [182–184]. Here again, these effects appear to be short-lived and did not result in any serious problems. Cutaneous reaction to silver was seen in a patient with a history of metal sensitivity [185]. In addition, there have been several reports of adverse reactions to the sulfadiazine component of SSD [173].

As described previously, one sequela of the use of silver nitrate as a topical application for the treatment of burn wounds is an electrolyte imbalance caused by ionic exchange at the surface of the burn [3,23]. This often is short-lived and has not been reported with other forms of topical silver. In addition, some studies have shown that silver has a cytotoxic effect on host cells, specifically fibroblasts and keratinocytes [25,186,187]. Although the implications of this laboratory research for the clinical setting warrant further in vivo analysis, these data suggest that discontinuing silver agents once the wound bioburden has been reduced promotes healing. However, the ability of silver to exert toxic effects on human cells may lend it value in the treatment of neoplastic cells, which have poorer recovery from mitotic arrest than do healthy fibroblasts [188].

Conclusion

The bactericidal activity of silver is well documented. Its benefit in reducing or preventing infection can be seen in several applications, including as a topical treatment for burns and chronic wounds and as a coating for both temporary and permanent medical devices. However, silver has been unsuccessful in certain settings, such as the failed silver-coated sewing ring of the Silzone heart valve, and its benefit remains unproved in other settings, such as orthopedic hardware coatings. Continued evaluation of such devices will be necessary to define further those areas in which silver confers benefit.

As new devices incorporating silver into their infection-prevention design are surfacing rapidly, an up-to-the minute tally is nearly impossible. This review aimed to cover the major areas in which silver has been used in medical applications. Whereas for some of these applications, other products have emerged with antibacterial properties, silver remains a reasonable addition to the armamentarium against infection and with relatively few side effects. However, one should weigh the benefits of silver-containing products against the known side effects and the other options available for the specific purpose in selecting the most appropriate therapy.

Author Disclosure Statement

No competing financial interests exist.

References

1. Alexander JW. History of the medical use of silver. Surg Infect 2009;10:289–292.
2. Klasen HJ. Historical review of the use of silver in the treatment of burns I: Early uses. Burns 2000;26:117–130.
3. Klasen HJ. A historical review of the use of silver in the treatment of burns II: Renewed interest for silver. Burns 2000;26:131–138.
4. Reid MR, Zinninger MM, Merrell P. Closure of the abdomen with through-and-through silver wire sutures in cases of acute abdominal emergencies. Ann Surg 1933;98:890–896.
5. Rucker MP. Silver sutures. Bull Hist Med 1950;24:190–192.
6. Clement JL, Jarrett PS. Antibacterial silver. Met Based Drugs 1994;1:467–482.
7. Fox CL Jr, Modak SM. Mechanism of silver sulfadiazine action on burn wound infections. Antimicrob Agents Chemother 1974;5:582–588.
8. Monafo WW. The management of burns II: The silver nitrate method. Curr Probl Surg 1969;Feb:53–66.
9. Feng QL, Wu J, Chen GQ, et al. A mechanistic study of the antibacterial effect of silver ions on *Escherichia coli* and *Staphylococcus aureus*. J Biomed Mater Res 2000;52: 662–668.
10. Rosenkranz HS, Rosenkranz S. Silver sulfadiazine: Interaction with isolated deoxyribonucleic acid. Antimicrob Agents Chemother 1972;2:373–383.
11. Jung WK, Koo HC, Kim KW, et al. Antibacterial activity and mechanism of action of the silver ion in *Staphylococcus aureus* and *Escherichia coli*. Appl Environ Microbiol 2008;74: 2171–2178.
12. Gordon O, Vig Slenters T, Brunetto PS, et al. Silver coordination polymers for prevention of implant infection: Thiol interaction, impact on respiratory chain enzymes, and hydroxyl radical induction. Antimicrob Agents Chemother 2010;54:4208–4218.
13. Schreurs WJ, Rosenberg H. Effect of silver ions on transport and retention of phosphate by *Escherichia coli*. J Bacteriol 1982;152:7–13.
14. Ricketts CR, Lowbury EJ, Lawrence JC, et al. Mechanism of prophylaxis by silver compounds against infection of burns. Br Med J 1970;1(5707):444–446.
15. Dunn K, Edwards-Jones V. The role of Acticoat with nanocrystalline silver in the management of burns. Burns 2004;30(Suppl 1):S1–S9.
16. Kim JS, Kuk E, Yu KN, et al. Antimicrobial effects of silver nanoparticles. Nanomedicine 2007;3:95–101.
17. Pal S, Tak YK, Joardar J, et al. Nanocrystalline silver supported on activated carbon matrix from hydrosol: Antibacterial mechanism under prolonged incubation conditions. J Nanosci Nanotechnol 2009;9:2092–2103.
18. Li WR, Xie XB, Shi QS, et al. Antibacterial activity and mechanism of silver nanoparticles on *Escherichia coli*. Appl Microbiol Biotechnol 2010;85:1115–1122.
19. Xu H, Qu F, Xu H, et al. Role of reactive oxygen species in the antibacterial mechanism of silver nanoparticles on *Escherichia coli* O157:H7. Biometals 2011;25:45–53.
20. Morones JR, Elechiguerra JL, Camacho A, et al. The bactericidal effect of silver nanoparticles. Nanotechnology 2005;16:2346–2353.
21. Fox CL Jr. Silver sulfadiazine—A new topical therapy for *Pseudomonas* in burns. Arch Surg 1968;96:184–188.
22. Stanford W, Rappole BW, Fox CL Jr. Clinical experience with silver sulfadiazine, a new topical agent for control of *Pseudomonas* infections in burns. J Trauma 1969;9: 377–388.
23. Monafo WW, Moyer CA. The treatment of extensive thermal burns with 0.5 per cent silver nitrate solution. Ann NY Acad Sci 1968;150:937–945.
24. Price WR, Wood M. Treatment of the infected burn with dilute silver nitrate solution. Am J Surg 1967;114:641–647.
25. Atiyeh BS, Costagliola M, Hayek SN, Dibo SA. Effect of silver on burn wound infection control and healing: Review of the literature. Burns 2007;33:139–148.
26. Helvig EI, Munster AM, Su CT, Oppel W. Cerium nitrate–silver sulfadiazine cream in the treatment of burns: A prospective, randomized study. Am Surg 1979;45:270–272.

27. Munster AM, Helvig E, Rowland S. Cerium nitrate–silver sulfadiazine cream in the treatment of burns: A prospective evaluation. Surgery 1980;88:658–660.
28. Bowser BH, Caldwell FT, Cone JB, et al. A prospective analysis of silver sulfadiazine with and without cerium nitrate as a topical agent in the treatment of severely burned children. J Trauma 1981;21:558–563.
29. de Gracia CG. An open study comparing topical silver sulfadiazine and topical silver sulfadiazine–cerium nitrate in the treatment of moderate and severe burns. Burns 2001;27:67–74.
30. Inman RJ, Snelling CF, Roberts FJ, et al. Prospective comparison of silver sulfadiazine 1 per cent plus chlorhexidine digluconate 0.2 per cent (Silvazine) and silver sulfadiazine 1 per cent (Flamazine) as prophylaxis against burn wound infection. Burns Incl Therm Inj 1984;11:35–40.
31. Snelling CF, Inman RJ, Germann E, et al. Comparison of silver sulfadiazine 1% with chlorhexidine digluconate 0.2% to silver sulfadiazine 1% alone in the prophylactic topical antibacterial treatment of burns. J Burn Care Rehabil 1991;12:13–18.
32. Fraser JF, Bodman J, Sturgess R, et al. An in vitro study of the anti-microbial efficacy of a 1% silver sulphadiazine and 0.2% chlorhexidine digluconate cream, 1% silver sulphadiazine cream and a silver coated dressing. Burns 2004;30:35–41.
33. Gray JH, Henry DA, Forbes M, et al. Comparison of silver sulphadiazine 1 per cent, silver sulphadiazine 1 per cent plus chlorhexidine digluconate 0.2 per cent and mafenide acetate 8.5 per cent for topical antibacterial effect in infected full skin thickness rat burn wounds. Burns 1991; 17:37–40.
34. Koller J. Topical treatment of partial thickness burns by silver sulfadiazine plus hyaluronic acid compared to silver sulfadiazine alone: A double-blind, clinical study. Drugs Exp Clin Res 2004;30:183–190.
35. Costagliola M, Agrosì M. Second-degree burns: A comparative, multicenter, randomized trial of hyaluronic acid plus silver sulfadiazine vs. silver sulfadiazine alone. Curr Med Res Opin 2005;21:1235–1240.
36. Leaper DJ. Silver dressings: Their role in wound management. Int Wound J 2006;3:282–294.
37. Cutting K, White R, Hoekstra H. Topical silver-impregnated dressings and the importance of the dressing technology. Int Wound J 2009;6:396–402.
38. Fong J, Wood F. Nanocrystalline silver dressings in wound management: A review. Int J Nanomedicine 2006;1: 441–449.
39. Deitch EA, Marino AA, Malakanok V, Albright JA. Silver nylon cloth: In vitro and in vivo evaluation of antimicrobial activity. J Trauma 1987;27:301–304.
40. Gravante G, Caruso R, Sorge R, et al. 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;63:201–205.
41. Falcone AE, Spadaro JA. Inhibitory effects of electrically activated silver material on cutaneous wound bacteria. Plast Reconstr Surg 1986;77:455–459.
42. Becker RO, Spadaro JA. Treatment of orthopaedic infections with electrically generated silver ions: A preliminary report. J Bone Joint Surg Am 1978;60:871–881.
43. Chu CS, McManus AT, Pruitt BA Jr, Mason AD Jr. Therapeutic effects of silver nylon dressings with weak direct current on *Pseudomonas aeruginosa*-infected burn wounds. J Trauma 1988;28:1488–1492.
44. Chu CS, McManus AT, Mason AD, Pruitt BA Jr. Topical silver treatment after escharectomy of infected full thickness burn wounds in rats. J Trauma 2005;58:1040–1046.
45. Chu CS, Matylevich NP, McManus AT, et al. Optimized mesh expansion of composite skin grafts in rats treated with direct current. J Trauma 1997;43:804–811.
46. Chu CS, Matylevitch NP, McManus AT, et al. 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;49:115–125.
47. Chu CS, McManus AT, Okerberg CV, et al. Weak direct current accelerates split-thickness graft healing on tangentially excised second-degree burns. J Burn Care Rehabil 1991;12:285–293.
48. Engrav LH, Heimbach DM, Reus JL, et al. Early excision and grafting vs. nonoperative treatment of burns of indeterminant depth: A randomized prospective study. J Trauma 1983;23:1001–1004.
49. Barret JP, Dziewulski P, Ramzy PI, et al. Biobrane versus 1% silver sulfadiazine in second-degree pediatric burns. Plast Reconstr Surg 2000;105:62–65.
50. Hosseini SN, Karimian A, Mousavinasab SN, et al. Xenoderm versus 1% silver sulfadiazine in partial-thickness burns. Asian J Surg 2009;32:234–239.
51. Gerding RL, Emerman CL, Effron D, et al. Outpatient management of partial-thickness burns: Biobrane versus 1% silver sulfadiazine. Ann Emerg Med 1990;19:121–124.
52. Silverstein P, Heimbach D, Meites H, et al. An open, parallel, randomized, comparative, multicenter study to evaluate the cost-effectiveness, performance, tolerance, and safety of a silver-containing soft silicone foam dressing (intervention) vs silver sulfadiazine cream. J Burn Care Res 2011;32:617–626.
53. Fong J, Wood F, Fowler B. A silver coated dressing reduces the incidence of early burn wound cellulitis and associated costs of inpatient treatment: Comparative patient care audits. Burns 2005;31:562–567.
54. Vermeulen H, van Hattem JM, Storm-Versloot MN, Ubbink DT. Topical silver for treating infected wounds. Cochrane Database Syst Rev 2007;(1):CD005486.
55. Lo SF, Hayter M, Chang CJ, et al. A systematic review of silver-releasing dressings in the management of infected chronic wounds. J Clin Nurs 2008;17:1973–1985.
56. Chambers H, Dumville JC, Cullum N. Silver treatments for leg ulcers: A systematic review. Wound Repair Regen 2007;15:165–173.
57. Lo SF, Chang CJ, Hu WY, et al. The effectiveness of silver-releasing dressings in the management of non-healing chronic wounds: A meta-analysis. J Clin Nurs 2009;18: 716–728.
58. Carter MJ, Tingley-Kelley K, Warriner RA 3rd. Silver treatments and silver-impregnated dressings for the healing of leg wounds and ulcers: A systematic review and meta-analysis. J Am Acad Dermatol 2010;63:668–679.
59. Michaels JA, Campbell B, King B, et al. Randomized controlled trial and cost-effectiveness analysis of silver-donating antimicrobial dressings for venous leg ulcers (VULCAN trial). Br J Surg 2009;96:1147–1156.
60. Scanlon E, Karlsmark T, Leaper DJ, et al. Cost-effective faster wound healing with a sustained silver-releasing foam dressing in delayed healing leg ulcers: A health-economic analysis. Int Wound J 2005;2:150–160.

61. Wang J, Smith J, Babidge W, Maddern G. Silver dressings versus other dressings for chronic wounds in a community care setting. J Wound Care 2007;16:352–356.
62. Jørgensen B, Price P, Andersen KE, et al. The silver-releasing foam dressing, Contreet Foam, promotes faster healing of critically colonised venous leg ulcers: A randomised, controlled trial. Int Wound J 2005;2:64–73.
63. Münter KC, Beele H, Russell L, et al. Effect of a sustained silver-releasing dressing on ulcers with delayed healing: The CONTOP study. J Wound Care 2006;15:199–206.
64. Totaro P, Rambaldini M. Efficacy of antimicrobial activity of slow release silver nanoparticles dressing in post-cardiac surgery mediastinitis. Interact Cardiovasc Thorac Surg 2009;8:153–154.
65. Huckfeldt R, Redmond C, Mikkelson D, et al. A clinical trial to investigate the effect of silver nylon dressings on mediastinitis rates in postoperative cardiac sternotomy incisions. Ostomy Wound Manage 2008;54:36–41.
66. Krieger BR, Davis DM, Sanchez JE, et al. The use of silver nylon in preventing surgical site infections following colon and rectal surgery. Dis Colon Rectum 2011;54:1014–1019.
67. Childress BB, Berceli SA, Nelson PR, et al. Impact of an absorbent silver-eluting dressing system on lower extremity revascularization wound complications. Ann Vasc Surg 2007;21:598–602.
68. Innes ME, Umraw N, Fish JS, et al. The use of silver coated dressings on donor site wounds: A prospective, controlled matched pair study. Burns 2001;27:621–627.
69. Lohsiriwat V, Chuangsuwanich A. Comparison of the ionic silver-containing hydrofiber and paraffin gauze dressing on split-thickness skin graft donor sites. Ann Plast Surg 2009;62:421–422.
70. Payne JL, Ambrosio AM. Evaluation of an antimicrobial silver foam dressing for use with V.A.C. therapy: Morphological, mechanical, and antimicrobial properties. J Biomed Mater Res B Appl Biomater 2009;89:217–222.
71. Gerry R, Kwei S, Bayer L, Breuing KH. Silver-impregnated vacuum-assisted closure in the treatment of recalcitrant venous stasis ulcers. Ann Plast Surg 2007;59:58–62.
72. Cohen MS, Stern JM, Vanni AJ, et al. In vitro analysis of a nanocrystalline silver-coated surgical mesh. Surg Infect 2007;8:397–403.
73. Chu CC, Tsai WC, Yao JY, Chiu SS. Newly made antibacterial braided nylon sutures I: In vitro qualitative and in vivo preliminary biocompatibility study. J Biomed Mater Res 1987;21:1281–1300.
74. Pratten J, Nazhat SN, Blaker JJ, Boccaccini AR. In vitro attachment of *Staphylococcus epidermidis* to surgical sutures with and without Ag-containing bioactive glass coating. J Biomater Appl 2004;19:47–57.
75. Blaker JJ, Nazhat SN, Boccaccini AR. Development and characterisation of silver-doped bioactive glass-coated sutures for tissue engineering and wound healing applications. Biomaterials 2004;25:1319–1329.
76. Renaud B, Brun-Buisson C; ICU-Bacteremia Study Group. Outcomes of primary and catheter-related bacteremia: A cohort and case-control study in critically ill patients. Am J Respir Crit Care Med 2001;163:1584–1590.
77. Blot SI, Depuydt P, Annemans L, et al. Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. Clin Infect Dis 2005;41:1591–1598.
78. Warren DK, Quadir WW, Hollenbeak CS, et al. Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. Crit Care Med 2006;34:2084–2089.
79. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: Excess length of stay, extra costs, and attributable mortality. JAMA 1994;271:1598–1601.
80. Dimick JB, Pelz RK, Consunji R, et al. Increased resource use associated with catheter-related bloodstream infection in the surgical intensive care unit. Arch Surg 2001;136:229–234.
81. O'Grady NP, Alexander M, Burns LA, et al; Healthcare Infection Control Practices Advisory Committee (HICPAC). Summary of recommendations: Guidelines for the Prevention of Intravascular Catheter-Related Infections. Clin Infect Dis 2011;52:1087–1099.
82. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 2006;355:2725–2732.
83. Dünser MW, Mayr AJ, Hinterberger G, et al. Central venous catheter colonization in critically ill patients: A prospective, randomized, controlled study comparing standard with two antiseptic-impregnated catheters. Anesth Analg 2005;101:1778–1784.
84. Bach A, Eberhardt H, Frick A, et al. Efficacy of silver-coating central venous catheters in reducing bacterial colonization. Crit Care Med 1999;27:515–521.
85. Corral L, Nolla-Salas M, Ibañez-Nolla J, et al. A prospective, randomized study in critically ill patients using the Oligon Vantex catheter. J Hosp Infect 2003;55:212–219.
86. Moretti EW, Ofstead CL, Kristy RM, Wetzler HP. Impact of central venous catheter type and methods on catheter-related colonization and bacteraemia. J Hosp Infect 2005;61:139–145.
87. 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;127:257–266.
88. Rupp ME, Lisco SJ, Lipsett PA, et al. Effect of a second-generation venous catheter impregnated with chlorhexidine and silver sulfadiazine on central catheter-related infections: A randomized, controlled trial. Ann Intern Med 2005;143:570–580.
89. Casey AL, Mermel LA, Nightingale P, Elliott TS. Antimicrobial central venous catheters in adults: A systematic review and meta-analysis. Lancet Infect Dis 2008;8:763–776.
90. Wang H, Huang T, Jing J, et al. Effectiveness of different central venous catheters for catheter-related infections: A network meta-analysis. J Hosp Infect 2010;76:1–11.
91. Darouiche RO, Raad II, Heard SO, et al. A comparison of two antimicrobial-impregnated central venous catheters. Catheter Study Group. N Engl J Med 1999;340:1–8.
92. Veenstra DL, Saint S, Saha S, et al. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: A meta-analysis. JAMA 1999;281:261–267.
93. Schuerer DJ, Zack JE, Thomas J, et al. Effect of chlorhexidine/silver sulfadiazine-impregnated central venous catheters in an intensive care unit with a low blood stream infection rate after implementation of an educational program: A before–after trial. Surg Infect 2007;8:445–454.
94. Camargo LF, Marra AR, Büchele GL, et al. Double-lumen central venous catheters impregnated with chlorhexidine and silver sulfadiazine to prevent catheter colonisation in

the intensive care unit setting: A prospective randomised study. J Hosp Infect 2009;72:227–233.
95. Kalfon P, de Vaumas C, Samba D, et al. Comparison of silver-impregnated with standard multi-lumen central venous catheters in critically ill patients. Crit Care Med 2007;35:1032–1039.
96. Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. JAMA 1999;282:554–560.
97. Shorr AF, Humphreys CW, Helman DL. New choices for central venous catheters: Potential financial implications. Chest 2003;124:275–284.
98. Akiyama H, Okamoto S. Prophylaxis of indwelling urethral catheter infection: Clinical experience with a modified Foley catheter and drainage system. J Urol 1979;121:40–42.
99. Liedberg H, Lundeberg T, Ekman P. Refinements in the coating of urethral catheters reduces the incidence of catheter-associated bacteriuria: An experimental and clinical study. Eur Urol 1990;17:236–240.
100. Liedberg H, Lundeberg T. Silver alloy coated catheters reduce catheter-associated bacteriuria. Br J Urol 1990;65: 379–381.
101. Karchmer TB, Giannetta ET, Muto CA, et al. A randomized crossover study of silver-coated urinary catheters in hospitalized patients. Arch Intern Med 2000;160:3294–3298.
102. Thibon P, Le Coutour X, Leroyer R, Fabry J. Randomized multi-centre trial of the effects of a catheter coated with hydrogel and silver salts on the incidence of hospital-acquired urinary tract infections. J Hosp Infect 2000;45: 117–124.
103. Bologna RA, Tu LM, Polansky M, et al. Hydrogel/silver ion-coated urinary catheter reduces nosocomial urinary tract infection rates in intensive care unit patients: A multicenter study. Urology 1999;54:982–987.
104. Riley DK, Classen DC, Stevens LE, Burke JP. A large randomized clinical trial of a silver-impregnated urinary catheter: Lack of efficacy and staphylococcal superinfection. Am J Med 1995;98:349–356.
105. Srinivasan A, Karchmer T, Richards A, et al. A prospective trial of a novel, silicone-based, silver-coated Foley catheter for the prevention of nosocomial urinary tract infections. Infect Control Hosp Epidemiol 2006;27:38–43.
106. Schaeffer AJ, Story KO, Johnson SM. Effect of silver oxide/ trichloroisocyanuric acid antimicrobial urinary drainage system on catheter-associated bacteriuria. J Urol 1988;139: 69–73.
107. Johnson JR, Roberts PL, Olsen RJ, et al. Prevention of catheter-associated urinary tract infection with a silver oxide-coated urinary catheter: Clinical and microbiologic correlates. J Infect Dis 1990;162:1145–1150.
108. Saint S, Elmore JG, Sullivan SD, et al. The efficacy of silver alloy-coated urinary catheters in preventing urinary tract infection: A meta-analysis. Am J Med 1998;105:236–241.
109. Rupp ME, Fitzgerald T, Marion N, et al. Effect of silver-coated urinary catheters: Efficacy, cost-effectiveness, and antimicrobial resistance. Am J Infect Control 2004;32: 445–450.
110. Schumm K, Lam TB. Types of urethral catheters for management of short-term voiding problems in hospitalised adults. Cochrane Database Syst Rev 2008;(2):CD004013.
111. Reiche T, Lisby G, Jørgensen S, et al. A prospective, controlled, randomized study of the effect of a slow-release silver device on the frequency of urinary tract infection in newly catheterized patients. BJU Int 2000;85:545–549.
112. Huth TS, Burke JP, Larsen RA, et al. Randomized trial of metal care with silver sulfadiazine cream for the prevention of catheter-associated bacteriuria. J Infect Dis 1992;165: 14–18.
113. Daifuku R, Stamm WE. Association of rectal and urethral colonization with urinary tract infection in patients with indwelling catheters. JAMA 1984;252:2028–2030.
114. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 2004; 32:470–485.
115. Hugonnet S, Eggimann P, Borst F, et al. Impact of ventilator-associated pneumonia on resource utilization and patient outcome. Infect Control Hosp Epidemiol 2004;25: 1090–1096.
116. Safdar N, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: A systematic review. Crit Care Med 2005;33:2184–2193.
117. Warren DK, Shukla SJ, Olsen MA, et al. Outcome and attributable cost of ventilator-associated pneumonia among intensive care unit patients in a suburban medical center. Crit Care Med 2003;31:1312–1317.
118. Institute for Healthcare Improvement. Available at http://www.ihi.org. Accessed July 29, 2011.
119. Efrati S, Deutsch I, Antonelli M, et al. Ventilator-associated pneumonia: Current status and future recommendations. J Clin Monit Comput 2010;24:161–168.
120. Doyle A, Fletcher A, Carter J, et al. The incidence of ventilator-associated pneumonia using the PneuX System with or without elective endotracheal tube exchange: A pilot study. BMC Res Notes 2011;4:92.
121. Kollef MH, Afessa B, Anzueto A, et al; NASCENT Investigation Group. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: The NASCENT randomized trial. JAMA 2008;300:805–813.
122. Lacherade JC, De Jonghe B, Guezennec P, et al. Intermittent subglottic secretion drainage and ventilator-associated pneumonia: A multicenter trial. Am J Respir Crit Care Med 2010;182:910–917.
123. Asai T, Shingu K. Leakage of fluid around high-volume, low-pressure cuffs apparatus: A comparison of four tracheal tubes. Anaesthesia 2001;56:38–42.
124. Berra L, Kolobow T, Laquerriere P, et al. Internally coated endotracheal tubes with silver sulfadiazine in polyurethane to prevent bacterial colonization: A clinical trial. Intensive Care Med 2008;34:1030–1037.
125. Rello J, Afessa B, Anzueto A, 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;38:1135–1140.
126. Olson ME, Harmon BG, Kollef MH. Silver-coated endotracheal tubes associated with reduced bacterial burden in the lungs of mechanically ventilated dogs. Chest 2002;121:863–870.
127. Rello J, Kollef M, Diaz E, et al. Reduced burden of bacterial airway colonization with a novel silver-coated endotracheal tube in a randomized multiple-center feasibility study. Crit Care Med 2006;34:2766–2772.
128. Palmore TN, Henderson DK. Testing the tube: Assessing silver as a potential “silver bullet” for preventing

ventilator-associated pneumonia. Crit Care Med 2010;38: 1220–1221.
129. Afessa B, Shorr AF, Anzueto AR, et al. Association between a silver-coated endotracheal tube and reduced mortality in patients with ventilator-associated pneumonia. Chest 2010;137:1015–1021.
130. Kollef MH, Silver P, Murphy DM, Trovillion E. The effect of late-onset ventilator-associated pneumonia in determining patient mortality. Chest 1995;108:1655–1662.
131. Shorr AF, Zilberberg MD, Kollef M. Cost-effectiveness analysis of a silver-coated endotracheal tube to reduce the incidence of ventilator-associated pneumonia. Infect Control Hosp Epidemiol 2009;30:759–763.
132. Klompas M. Silver-coated endotracheal tubes and patient outcomes in ventilator-associated pneumonia. JAMA 2008;300:2605.
133. Resar R, Pronovost P, Haraden C, et al. Using a bundle approach to improve ventilator care processes and reduce ventilator-associated pneumonia. Jt Comm J Qual Patient Saf 2005;31:243–248.
134. Zilberberg MD, Shorr AF, Kollef MH. Implementing quality improvements in the intensive care unit: Ventilator bundle as an example. Crit Care Med 2009;37:305–309.
135. Wassall MA, Santin M, Isalberti C, et al. Adhesion of bacteria to stainless steel and silver-coated orthopedic external fixation pins. J Biomed Mater Res 1997;36:325–330.
136. Collinge CA, Goll G, Seligson D, Easley KJ. Pin tract infections: Silver vs uncoated pins. Orthopedics 1994;17: 445–448.
137. Bosetti M, Massè A, Tobin E, Cannas M. Silver coated materials for external fixation devices: In vitro biocompatibility and genotoxicity. Biomaterials 2002;23:887–992.
138. Massè A, Bruno A, Bosetti M, et al. Prevention of pin track infection in external fixation with silver coated pins: Clinical and microbiological results. J Biomed Mater Res 2000; 53:600–604.
139. Yuenyongviwat V, Tangtrakulwanich B. Prevalence of pin-site infection: The comparison between silver sulfadiazine and dry dressing among open tibial fracture patients. J Med Assoc Thai 2011;94:566–569.
140. Ogbemudia AO, Bafor A, Edomwonyi E, Enemudo R. Prevalence of pin tract infection: The role of combined silver sulphadiazine and chlorhexidine dressing. Niger J Clin Pract 2010;13:268–271.
141. Das K, Bose S, Bandyopadhyay A, et al. Surface coatings for improvement of bone cell materials and antimicrobial activities of Ti implants. J Biomed Mater Res B Appl Biomater 2008;87:455–460.
142. Zhao L, Wang H, Huo K, et al. Antibacterial nano-structured titania coating incorporated with silver nanoparticles. Biomaterials 2011;32:5706–5716.
143. Khalilpour P, Lampe K, Wagener M, et al. Ag/SiO(x)C(y) plasma polymer coating for antimicrobial protection of fracture fixation devices. J Biomed Mater Res B Appl Biomater 2010;94:196–202.
144. Sheehan E, McKenna J, Mulhall KJ, et al. Adhesion of *Staphylococcus* to orthopaedic metals: An in vivo study. J Orthop Res 2004;22:39–43.
145. Hardes J, von Eiff C, Streitbuerger A, et al. Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma. J Surg Oncol 2010;101:389–395.
146. Hardes J, Ahrens H, Gebert C, et al. Lack of toxicological side-effects in silver-coated megaprostheses in humans. Biomaterials 2007;28:2869–2875.
147. Pupka A, Skora J, Janczak D, et al. In situ revascularisation with silver-coated polyester prostheses and arterial homografts in patients with aortic graft infection: A prospective, comparative, single-centre study. Eur J Vasc Endovasc Surg 2011;41:61–67.
148. Batt M, Magne JL, Alric P, et al. In situ revascularization with silver-coated polyester grafts to treat aortic infection: Early and midterm results. J Vasc Surg 2003;38:983–989.
149. Batt M, Jean-Baptiste E, O'Connor S, et al. In-situ revascularisation for patients with aortic graft infection: A single centre experience with silver coated polyester grafts. Eur J Vasc Endovasc Surg 2008;36:182–188.
150. Ricco JB; InterGard Silver Study Group. InterGard silver bifurcated graft: Features and results of a multicenter clinical study. J Vasc Surg 2006;44:339–346.
151. Larena-Avellaneda A, Russmann S, Fein M, Debus ES. Prophylactic use of the silver-acetate-coated graft in arterial occlusive disease: A retrospective, comparative study. J Vasc Surg 2009;50:790–798.
152. Tautenhahn J, Meyer F, Buerger T, et al. Interactions of neutrophils with silver-coated vascular polyester grafts. Langenbecks Arch Surg 2010;395:143–149.
153. Illingworth BL, Tweden K, Schroeder RF, Cameron JD. In vivo efficacy of silver-coated (Silzone) infection-resistant polyester fabric against a biofilm-producing bacteria, *Staphylococcus epidermidis*. J Heart Valve Dis 1998;7:524–530.
154. Illingworth B, Bianco RW, Weisberg S. In vivo efficacy of silver-coated fabric against *Staphylococcus epidermidis*. J Heart Valve Dis 2000;9:135–141.
155. Darouiche RO, Meade R, Mansouri M, Raad II. In vivo efficacy of antimicrobial-coated fabric from prosthetic heart valve sewing rings. J Heart Valve Dis 1998;7:639–646.
156. Schaff H, Carrel T, Steckelberg JM, et al. Artificial Valve Endocarditis Reduction Trial (AVERT): Protocol of a multicenter randomized trial. J Heart Valve Dis 1999;8: 131–139.
157. Brutel de la Riviere A, Dossche KM, Birnbaum DE, Hacker R. First clinical experience with a mechanical valve with silver coating. J Heart Valve Dis 2000;9:123–129.
158. Carrel T, Nguyen T, Kipfer B, Althaus U. Definitive cure of recurrent prosthetic endocarditis using silver-coated St. Jude Medical heart valves: A preliminary case report. J Heart Valve Dis 1998;7:531–533.
159. Bertrand S, Houel R, Vermes E, et al. Preliminary experience with Silzone-coated St. Jude Medical valves in acute infective endocarditis. J Heart Valve Dis 2000;9:131–134.
160. Auer J, Berent R, Ng CK, et al. Early investigation of silver-coated Silzone heart valves prosthesis in 126 patients. J Heart Valve Dis 2001;10:717–723.
161. Kjaergard HK, Tingleff J, Abildgaard U, Pettersson G. Recurrent endocarditis in silver-coated heart valve prosthesis. J Heart Valve Dis 1999;8:140–142.
162. Ionescu A, Payne N, Fraser AG, et al. Incidence of embolism and paravalvar leak after St. Jude Silzone valve implantation: Experience from the Cardiff Embolic Risk Factor Study. Heart 2003;89:1055–1061.
163. Dávila-Román VG, Waggoner AD, Kennard ED, et al; Artificial Valve Endocarditis Reduction Trial Echocardiography Study. Prevalence and severity of paravalvular regurgitation in the Artificial Valve Endocarditis Reduction Trial (AVERT) Echocardiography Study. J Am Coll Cardiol 2004;44:1467–1472.
164. Schaff HV, Carrel TP, Jamieson WR, et al; Artificial Valve Endocarditis Reduction Trial. Paravalvular leak and other

events in Silzone-coated mechanical heart valves: A report from AVERT. Ann Thorac Surg 2002;73:785–792.
165. Jamieson WR, Fradet GJ, Abel JG, et al. Seven-year results with the St. Jude Medical Silzone mechanical prosthesis. J Thorac Cardiovasc Surg 2009;137:1109–1115.
166. Grunkemeier GL, Jin R, Im K, et al. Time-related risk of the St. Jude Silzone heart valve. Eur J Cardiothorac Surg 2006;30:20–27.
167. Herijgers P, Herregods MC, Vandeplas A, et al. Silzone coating and paravalvular leak: An independent, randomized study. J Heart Valve Dis 2001;10:712–715.
168. Stalenhoef JE, Mellema EC, Veeger NJ, Ebels T. Thrombogenicity and reoperation of the St. Jude Medical Silzone valve: A comparison with the conventional St. Jude Medical valve. J Heart Valve Dis 2003;12:635–639.
169. Dandekar UP, Baghai M, Kalkat M, Ridley PD. Silzone-coated St. Jude Medical valves: Six-year experience in 46 patients. J Heart Valve Dis 2007;16:37–41.
170. Butany J, Leask RL, Desai ND, et al. Pathologic analysis of 19 heart valves with silver-coated sewing rings. J Card Surg 2006;21:530–538.
171. Seipelt RG, Vazquez-Jimenez JF, Seipelt IM, et al. The St. Jude "Silzone" valve: Midterm results in treatment of active endocarditis. Ann Thorac Surg 2001;72:758–762.
172. Rosenman KD, Moss A, Kon S. Argyria: Clinical implications of exposure to silver nitrate and silver oxide. J Occup Med 1979;21:430–435.
173. Fuller FW. The side effects of silver sulfadiazine. J Burn Care Res 2009;30:464–470.
174. Coombs CJ, Wan AT, Masterton JP, et al. Do burn patients have a silver lining? Burns 1992;18:179–184.
175. Bader KF. Organ deposition of silver following silver nitrate therapy of burns. Plast Reconstr Surg 1966;37:550–551.
176. Wan AT, Conyers RA, Coombs CJ, Masterton JP. Determination of silver in blood, urine, and tissues of volunteers and burn patients. Clin Chem 1991;37:1683–1687.
177. Iwasaki S, Yoshimura A, Ideura T, et al. Elimination study of silver in a hemodialyzed burn patient treated with silver sulfadiazine cream. Am J Kidney Dis 1997;30:287–290.
178. Lansdown AB. Critical observations on the neurotoxicity of silver. Crit Rev Toxicol 2007;37:237–250.
179. Trop M, Novak M, Rodl S, et al. Silver-coated dressing Acticoat caused raised liver enzymes and argyria-like symptoms in burn patient. J Trauma 2006;60:648–652.
180. Vlachou E, Chipp E, Shale E, et al. The safety of nanocrystalline silver dressings on burns: A study of systemic silver absorption. Burns 2007;33:979–985.
181. Eldad A, Neuman A, Weinberg A, et al. Silver sulphadiazine-induced haemolytic anaemia in a glucose-6-phosphate dehydrogenase-deficient burn patient. Burns 1991;17: 430–432.
182. Choban PS, Marshall WJ. Leukopenia secondary to silver sulfadiazine: Frequency, characteristics and clinical consequences. Am Surg 1987;53:515–517.
183. Fuller FW, Engler PE. Leukopenia in non-septic burn patients receiving topical 1% silver sulfadiazine cream therapy: A survey. J Burn Care Rehabil 1988;9:606–609.
184. Gamelli RL, Paxton TP, O'Reilly M. Bone marrow toxicity by silver sulfadiazine. Surg Gynecol Obstet 1993;177: 115–120.
185. Fraser-Moodie A. Sensitivity to silver in a patient treated with silver sulphadiazine (Flamazine). Burns 1992;18: 74–75.
186. Poon VK, Burd A. In vitro cytotoxity of silver: Implication for clinical wound care. Burns 2004;30:140–147.
187. Cortese-Krott MM, Münchow M, Pirev E, et al. Silver ions induce oxidative stress and intracellular zinc release in human skin fibroblasts. Free Radic Biol Med 2009;47:1570–1577.
188. Asharani PV, Hande MP, Valiyaveettil S. Anti-proliferative activity of silver nanoparticles. BMC Cell Biol 2009;10:65.

Address correspondence to:
Dr. Amani D. Politano
Department of Surgery
University of Virginia Health System
P.O. Box 800709
Charlottesville, VA 22908

E-mail: ADP2Q@hscmail.mcc.virginia.edu