

STATE-OF-THE-ART CLINICAL ARTICLE

Anti-Infective Efficacy of Silver-Coated Medical Prostheses**Rabih O. Darouiche**

From the Center for Prostheses Infection, Department of Physical Medicine and Rehabilitation, and Infectious Disease Section, Department of Medicine, Baylor College of Medicine and Veterans Affairs Medical Center, Houston, Texas

Medical prostheses constitute an indispensable component of modern health care. Like other approaches of medical intervention, the insertion of medical prostheses can be associated with serious complications. The ongoing advances in the mechanical properties of medical prostheses have not necessarily resulted in lower rates of prosthesis-related infection. Infection remains the most common serious complication of medical prostheses. For instance, vascular catheters account for most cases of nosocomial bloodstream infection [1], and catheter-related urinary tract infection is the most frequent nosocomial infection [2]. Two decades ago, infections associated with medical prostheses accounted for about half of all nosocomial infections [2]. Today, with their increasing use, medical prostheses are expected to cause a larger portion of cases of nosocomial infections, particularly in the subpopulations of immunocompromised, chronically ill, and elderly subjects.

Infections associated with medical prostheses result in major morbidity and can be life-threatening. For instance, the mortality associated with prosthetic valve endocarditis ranges from 30% to 80% in patients with early-onset infection and from 20% to 40% in patients with late-onset endocarditis [3]. Often, infections associated with medical prostheses are very expensive to manage, and their cure requires removal of the infected prosthesis. For example, findings from the Dutch Trauma Trial indicated a mean cost of \$22,000 (in 1991 dollars) to treat a patient who developed a deep wound infection after internal fixation of a closed fracture [4].

The difficulty and expense associated with the treatment of prosthesis-related infections have led to heightened interest in prevention. Because colonization of the prosthesis is a prelude to clinical infection, one important approach has been to coat the surface of the prosthetic devices with an antimicrobial substance. Although many such substances have been suggested to guard against prosthesis-related infection, only a very few have been demonstrated in prospective, randomized clinical trials to be clinically protective. A highly debated issue is the potential benefit of using silver-coated medical prostheses. Silver exhibits a rather broad-spectrum antimicrobial activity in vitro by binding both to microbial DNA, preventing bacterial replication, and to the sulfhydryl groups of the metabolic enzymes of the bacterial electron transport chain, causing their inactivation [5, 6]. In one form or another, silver molecules have been incorporated into the surfaces of a large variety of medical devices, including vascular, urinary, and peritoneal catheters, vascular grafts, prosthetic heart valve sewing rings, sutures, and fracture fixation devices. Despite the plethora of such silver-coated medical prostheses, their anti-infective efficacy has not been collectively addressed. The 2 main objectives of this comprehensive article are to review the in vitro, animal, and clinical experience with a variety of silver-coated medical prostheses (table 1) and to analyze the scientific reasoning for the anti-infective properties, or lack thereof, of silver-coated medical prostheses.

Silver-Coated Bladder Catheters

Unfortunately, all clinical trials of the efficacy of silver-coated bladder catheters studied catheter-associated bacteriuria rather than true clinical outcomes, such as symptomatic catheter-related urinary tract infection and bacteremia. Although the presence of bacteriuria is mandatory for the evolution of symptomatic urinary tract infection, bacteriuria remains asymptomatic in most cases. Furthermore, the various clinical trials used different definitions of catheter-associated bacteriuria, with concentrations ranging from $\geq 10^2$ cfu/mL [7, 8] to $\geq 10^5$ cfu/mL [9–12]. Such factors augment our inability to clearly assess the clinical impact of silver-coated bladder catheters.

Bladder catheters coated with silver alone. Two earlier clinical trials conducted at the same institution had indicated that

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The author reports that he has invented or consulted on approaches related to coating of metallic and nonmetallic medical prostheses with antimicrobial agents that do not include silver.

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Reprints or correspondence: Dr. Rabih O. Darouiche, Center for Prostheses Infection, Baylor College of Medicine, 1333 Moursund Avenue, Suite A221, Houston, TX 77030 (darouiche.rabih.o@houston.va.gov).

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Table 1. In vivo efficacy of silver-coated medical prostheses.

| Type of prosthesis | Efficacy in animals | Efficacy in humans |
|---|---------------------|--|
| Bladder catheters | | |
| Coated with silver alone | Unknown | Controversial |
| Coated with silver hydrogel | Unknown | Moderately effective |
| Central venous catheters | | |
| Affixed with silver-chelated cuff | Unknown | Effective with short-term but not long-term cuffed catheters |
| Coated with silver alone | Unknown | Ineffective |
| Silver iontophoretic catheter | Effective | Unknown |
| Coated with silver sulfadiazine-chlorhexidine | Effective | Moderately effective for short-term but not long-term access |
| Coated with silver sulfadiazine | Not effective | Unknown |
| Coated with silver-benzalkonium chloride | Unknown | Unknown |
| Peritoneal catheters | | |
| Coated with silver alone | Effective | Unknown |
| Equipped with a silver ring | Unknown | Not effective |
| Vascular grafts coated with silver-antibiotic | | |
| Silver-coated prosthetic heart valve sewing rings | Not effective | Unknown |
| Silver-coated external fixation pins | Not effective | Unknown |
| Silver-coated sutures | Unknown | Unknown |

bladder catheters coated with silver alloy on both the external and internal surfaces significantly reduce the rate of catheter-associated bacteriuria, compared with uncoated catheters (10% vs. 37%–50%) [10, 11]. However, those 2 clinical trials were relatively small and offered no explicit description of the characteristics of enrolled patients. A recent meta-analysis also showed a significant benefit (the OR for developing catheter-associated bacteriuria was 0.24) from using bladder catheters with silver alloy coating on both the external and internal surfaces [13]. However, that meta-analysis was based on a total of 4 clinical trials, all conducted by the same group of investigators, including the 2 clinical trials mentioned above [10, 11] and 2 others reported in the form of a letter [7] and an abstract [12]. More recent, well-conducted, larger clinical trials demonstrated similar overall rates of bacteriuria in patients who received uncoated bladder catheters versus bladder catheters with silver-oxide coating either on the external surface alone (13% vs. 11%) [14] or on both the external and internal surfaces (10% vs. 9%) [8]. Although another prospective, randomized clinical trial demonstrated that bladder catheters with silver-oxide coating on the external surface were associated with significantly lower rates of catheter-associated bacteriuria than were control uncoated catheters (27% vs. 55%), the conclusions of that study were limited by the fact that the experimental group of patients also had trichloroisocyanuric acid instilled into the urinary drainage bag [9]. For yet unclear reasons, bladder catheters coated with silver oxide were more protective against catheter-associated bacteriuria in women than in men [8, 14].

Silver hydrogel-coated bladder catheters. Because bacteria are better absorbed onto hydrophobic surfaces, rendering the catheter surface hydrophilic can potentially decrease bacterial colonization of the catheter in vitro [15]. A recent preliminary report from a prospective, randomized, double-blinded study indicated that after 1 week, the incidence of bacteriuria was reduced by 30% in patients who received silver hydrogel-coated

versus uncoated bladder catheters, largely because of protection from gram-positive bacteria and, to a lesser extent, yeast [16].

Silver-Coated Vascular Catheters

Silver-chelated collagen cuff. In an attempt to prevent bacterial migration along the external surface of the indwelling central venous catheter, a silver-chelated collagen cuff was designed for subcutaneous placement. In initial prospective, randomized clinical trials of short-term catheter use (mean duration of placement, 6–9 days) in critically ill patients, catheters that had a silver-chelated subcutaneous cuff were 3-fold less likely to be colonized and nearly 4-fold less likely to cause bloodstream infection than were uncuffed catheters [17, 18]. However, a prospective, randomized clinical trial of long-term (median duration of placement, 143 days), tunneled, cuffed Silastic catheters compared with the same catheter affixed with an additional more proximal silver-chelated cuff showed no differences in the rates of catheter-related bloodstream or tunnel infections between the 2 groups [19]. Three reasons may help explain why the silver-chelated subcutaneous cuff appears to reduce infection with short-term, but not long-term, tunneled, cuffed catheters. First, the antimicrobial activity of the silver-chelated subcutaneous cuff lasts only several days, owing to the biodegradable nature of the collagen cuff to which the silver ions are chelated. Second, the silver-chelated subcutaneous cuff can potentially resist bacterial migration along only the external surface but not the internal surface of the catheter and, therefore, is unlikely to be protective when used with long-term catheters that are commonly infected secondary to contamination of the catheter hub. Finally, the mechanical barrier generated by tunneling of catheters and/or subcutaneous placement of a collagen cuff may be more important in protecting against catheter-related infection than is the antimicrobial shield provided by the silver coating.

Vascular catheters coated with silver alone. In vitro testing

has yielded conflicting results, with some showing reduced bacterial adherence to the surfaces of silver-coated polyurethane catheters [20] and others failing to demonstrate the efficacy of silver-coated silicone catheters [21]. Studies of the efficacy of silver-coated catheters in animals have been inconclusive [22]. Although the results of 1 prospective small (total of 72 catheters) clinical trial [23] suggested that silver-coated vascular catheters protect against catheter-related infection, this study suffered from a number of limitations: patients were not randomized, and the silver-coated catheters were made of silicone or polyurethane, whereas the uncoated ones were Teflon, polypropylene, or polyurethane. Another larger (total of 156 central venous catheters) prospective, but nonrandomized, clinical trial by the same group of investigators, which disclosed neither the materials of the catheters nor the protocol for insertion of the silver-coated versus uncoated central venous catheters, indicated a nearly 3-fold lower incidence of colonization in the silver-coated catheter group [24]. A preliminary report of a prospective, randomized, similarly sized (total of 165 evaluable catheters with a mean duration of placement of 10 days) clinical trial indicated that silver-coated central venous catheters reduce the incidence of catheter colonization (14% vs. 22.8%) and catheter-related bloodstream infection (5.1% vs. 18.3%) compared with uncoated catheters [25].

However, a recently published, prospective, randomized clinical trial of 91 tunneled hemodialysis catheters (mean duration of placement, 92 days) demonstrated a nonsignificant trend for higher rates of catheter colonization (0.28 vs. 0.13 cases per 100 catheter-days) and catheter-related infection (0.18 vs. 0.11 cases per 100 catheter-days) in patients receiving silver-coated versus uncoated catheters [26]. In addition to being clinically ineffective, the silver-coated hemodialysis catheters were removed from 2 (4%) of 47 patients because of the development of chronic hyperpigmented skin lesions at the site of catheter insertion, thereby contributing to the decision to remove that particular silver-coated catheter from the market [26]. Another recently published, prospective, randomized clinical trial of 67 central venous catheters demonstrated similar rates of catheter colonization (26% vs. 21%) and catheter-related bloodstream infection (6% vs. 6%) in critically ill patients receiving silver-coated versus uncoated catheters [27]. Although, in general, clinical studies of silver-coated vascular catheters have yielded conflicting results, the recent reports of the 2 well-conducted, prospective, randomized clinical trials strongly indicate that vascular catheters coated with silver alone are clinically ineffective.

Silver iontophoretic vascular catheters. When low grade currents (20–75 μ A) are conducted through heavy metals, such as silver, ions with antimicrobial activity are generated. This principle was used to construct the silver iontophoretic catheter, which consists of silver wires that helically surround the external circumference of a silicone vascular catheter and are connected to a power source [28]. The silver iontophoretic catheter allows

leaching of silver ions off the surface of the catheter, thereby producing zones of inhibition in vitro against most potential pathogens [28]. By means of an established rabbit model for infection of percutaneously implanted catheter segments, the silver iontophoretic catheter was shown to protect in vivo against infection by *Staphylococcus aureus* [28]. However, the clinical efficacy of this device has yet to be examined.

Catheters coated with chlorhexidine and silver sulfadiazine. Vascular catheters coated with the combination of chlorhexidine and silver sulfadiazine were shown in both in vitro and animal studies to reduce bacterial adherence [29]. The first conducted prospective, randomized, large (403 catheters) clinical trial concluded that short-term (mean duration of placement, 6 days) polyurethane central venous catheters coated with chlorhexidine and silver sulfadiazine were 2-fold less likely to be colonized and about 4-fold less likely to cause bloodstream infection than were uncoated catheters [30]. A few other prospective, randomized clinical trials [31–33] did not demonstrate the clinical efficacy of such antimicrobial-coated central venous catheters; none, however, had sufficient power to examine differences in the rates of catheter-related bloodstream infection. A meta-analysis of 12 clinical trials showed an OR of 0.56 for developing bloodstream infection in association with short-term central venous catheters coated with chlorhexidine and silver sulfadiazine versus uncoated catheters [34]. Because catheters coated with chlorhexidine and silver sulfadiazine provide short-lived (for ~1 week) antimicrobial activity only along the external surface of the catheter [33], they are unlikely to protect against infection in use as long-term catheters, which often become colonized with bacteria that migrate from a contaminated catheter hub along the internal surface of the catheter. A large prospective, randomized clinical trial of 680 central venous catheters that were placed in patients with hematologic malignancy for a mean of 20 days showed no differences in the rates of bloodstream infection associated with catheters coated with chlorhexidine and silver sulfadiazine versus uncoated catheters [35].

Catheters coated with silver sulfadiazine. A preliminary report indicated that catheters coated with chlorhexidine and silver sulfadiazine and those coated with chlorhexidine alone are equally effective in reducing catheter-related infection in a rabbit model of *S. aureus* infection of subcutaneously placed catheters [36]. In the same animal model, catheters coated with silver sulfadiazine did not protect against catheter-related infection. The clinical efficacy of central venous catheters coated with silver sulfadiazine has not been evaluated.

Catheters coated with silver chloride and benzalkonium chloride. When tested in vitro against a broad variety of pathogens, polyurethane catheters coated with silver chloride and benzalkonium chloride produced zones of inhibition that were comparable in size to those observed around catheters coated with chlorhexidine and silver sulfadiazine [37]. Although elution studies in serum suggested that catheters coated with silver

chloride and benzalkonium chloride provide more durable antimicrobial activity against staphylococci than do catheters coated with chlorhexidine and silver sulfadiazine [37], the clinical efficacy of the former catheters has not been examined.

Silver-Coated Peritoneal Catheters

A preliminary report from an experimental study in rabbits indicated that silver-coated peritoneal catheters significantly reduced *S. aureus* counts in fluid samples taken aseptically from the internal segments of the catheters, compared with samples taken from uncoated catheters (1.9×10^2 cfu/mL vs. 7.5×10^7 cfu/mL) [38]. The clinical efficacy of peritoneal catheters with silver coating along the length of the catheter has not been reported. However, a recently completed prospective, controlled multicenter clinical trial that compared peritoneal catheters that have a silver ring mounted onto the catheter at the skin exit site with control catheters demonstrated no significant differences in the rates of exit site infection (24% vs. 16%), sinus tract or tunnel infection (12% vs. 12%), and peritonitis (16% vs. 18%) between the 2 groups [39].

Silver-Coated Vascular Grafts

The complexing of silver with antibiotics on the coated surfaces of vascular polytetrafluoroethylene (PTFE) grafts has been examined in a number of studies. A complex of silver and ciprofloxacin increased the elution and prolonged the duration of ciprofloxacin release from the coated surfaces, compared with grafts coated with ciprofloxacin alone [40]. In a dog model of *S. aureus* infection of abdominal aortic PTFE grafts, the mean concentrations of bacteria retrieved from grafts coated with either silver and oxacillin (1.7×10^2 cfu) or silver and amikacin (2.0×10^2 cfu) were significantly lower than those recovered from uncoated grafts (1.3×10^6 cfu) [41]. Because grafts coated with silver alone or an antibiotic alone were not examined in that study, it is not clear whether the anti-infective efficacy of grafts coated with silver and antibiotics was primarily due to silver, the antibiotic, or the combination [41]. However, the production of large zones of inhibition in vitro (a phenomenon usually seen with antibiotic-coated vascular prostheses) by the grafts coated with the silver-antibiotic combinations suggests that the coating antibiotics were largely responsible for their anti-infective efficacy in vivo [41].

Silver-Coated Prosthetic Heart Valve Sewing Rings

Silver coating of polyethylene tetraphthalate polyester that is used to construct prosthetic heart valve sewing cuffs was shown to significantly reduce microbial adhesion in vitro [42, 43]. Although silver coating of polyester fabric was shown to reduce inflammation of the polyester fabric implanted subdermally in guinea pigs [6], silver-coated polyester fabric inserted

intramuscularly in rabbits displayed signs of inflammation that were comparable with those seen with uncoated polyester fabric [44]. On the basis of the unproven assumption that reduction in the degree of acute inflammation is associated with resistance to infection, the former animal study [6] suggested that silver-coated polyester fabric was anti-infective in vivo, despite the study's findings that bacteria were extracted from all explanted fabric samples (both silver-coated and uncoated) that had been inoculated with *Staphylococcus epidermidis*. When infection was directly assessed in vivo by use of a rabbit model of *S. aureus* infection of subcutaneously implanted polyester fabric, the silver-coated fabric was ineffective in reducing prosthesis colonization and prosthesis-related infection, compared with those seen with uncoated fabric (40% vs. 39% and 32% vs. 22%, respectively) [45]. At present, clinical experience with silver-coated prosthetic heart valve sewing rings is limited to a few case reports with conflicting results. For instance, 1 report communicated the cure of recurrent prosthetic valve endocarditis in 1 patient by use of a silver-coated prosthetic heart valve sewing ring [46], whereas another described recurrent endocarditis in 1 patient who had received a silver-coated prosthetic heart valve sewing ring on 2 occasions [47]. The clinical efficacy of silver-coated prosthetic heart valve sewing rings is being properly examined by the ongoing large, prospective, randomized, multicenter clinical trial [48].

Silver-Coated Sutures

Immersing catgut, Dacron, silk, or chromic sutures for 24 h in a 5% or 50% aqueous solution of silver nitrate did not appreciably reduce adherence of *S. aureus*, compared with that to unsoaked sutures [49]. Dacron and silk sutures coated with a silver-zinc-allantoin complex did, however, reduce the number of adherent *S. aureus* colonies by 88% and 99%, respectively [49]. The investigators attributed the differences in in vitro efficacies of the differently coated sutures to the fact that silver nitrate firmly binds to the suture material, whereas the silver-zinc-allantoin complex provides slow release of silver ions sufficient to inhibit bacterial adherence.

Silver-Coated Fracture Fixation Devices

A preliminary report indicated that silver-coated fracture fixation devices uniformly inhibit bacterial adherence in vitro [50]. Another in vitro study, however, showed that silver-coated external fixation pins reduce adherence of *Escherichia coli*, *Pseudomonas aeruginosa*, and *S. aureus* but enhance adherence of *Staphylococcus haemolyticus* [51]. Moreover, the insertion of silver-coated stainless steel external fixation pins into the iliac crests of sheep inoculated with *S. aureus* was associated with a nonsignificant decrease in the rate of pin tract infection, compared with that associated with uncoated pins (62% vs. 84%) [52]. The lack of efficacy in vivo of silver-coated stainless steel

external fixation pins was confirmed recently in a preliminary report of a caprine model of *S. aureus* infection demonstrating similar rates of infection associated with silver-coated (83%) and uncoated (92%) pins [53].

Conclusion

Despite promising in vitro results, implanted medical prostheses that are coated with silver alone have not been proven to be infection-resistant in the majority of studies. The discrepant results of in vitro and in vivo testing can be attributed to the following factors: minimal leaching or nonleaching silver-coated surfaces and limitations imposed by potential silver toxicity.

A number of approaches can be used to incorporate silver alone onto the surfaces of medical prostheses; generally, a rather tight adherence of silver molecules is achieved. Whereas a potential advantage of a minimally leaching or nonleaching antimicrobial surface is the long durability of the antimicrobial coating on the surface, a major disadvantage appears to be the inability to produce zones of inhibition around the coated surfaces. The production of an effective zone of inhibition by an antimicrobial-coated surface may serve to inhibit adherence of organisms, not only to the coated surface but also to a variety of host-derived adhesins, such as fibronectin, fibrinogen, fibrin, and laminin, that exist within the biofilm layer surrounding the indwelling prosthesis [54, 55]. The size of the zone of inhibition in vitro around a coated medical prosthesis may correlate with efficacy in vivo [56]. For instance, antimicrobial-coated vascular catheters that produce large zones of inhibition in vitro were demonstrated to protect clinically against catheter-related infection [30], whereas those that produce small zones of inhibition in vitro proved to be clinically ineffective [57]. Taken together, these factors help explain why, despite encouraging antimicrobial properties in vitro, coating of medical prostheses with silver alone has generally not been clinically protective. However, when silver is incorporated onto the surfaces of medical prostheses in a manner that allows leaching of silver off the coated surfaces (e.g., the silver iontophoretic vascular catheter) or is complexed with other antimicrobial agents on the surfaces of vascular prostheses, zones of inhibition are produced, and the resulting coated prostheses are more likely to be infection-resistant in vivo.

Silver-containing compounds, such as silver sulfadiazine and silver nitrate, are usually applied cutaneously rather than administered systemically. Silver toxicity has been reported to occur at serum levels as low as 0.3 $\mu\text{g}/\text{mL}$ and manifests as argyria, leukopenia, and alterations in renal, hepatic, and neural tissues [42, 58]. Therefore, it is prudent while constructing a silver-coated medical prosthesis to incorporate silver onto the surfaces of the prostheses in concentrations that are adequate to reduce bacterial adherence to the indwelling prosthesis but not high enough to cause systemic silver toxicity in humans. The specific

design of a minimally leaching or nonleaching silver-coated surface can further reduce the likelihood of causing toxic silver concentrations in serum, albeit at the expense of anti-infective efficacy. For instance, the conscientious effort to design a minimally leaching or nonleaching silver-coated prosthetic heart valve sewing ring that does not cause toxic silver concentrations in serum [59] and/or damage to organs with high uptake of silver, particularly the liver [60], has resulted an antimicrobial-coated medical prosthesis of unproven anti-infective efficacy in vivo.

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