Silver: Fact... or Fiction
Utilizing the Antibacterial Mechanisms of Silver in Wound Care
Continuing Education Info

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Learning Objectives: At the conclusion of this activity, the participant should be able to:
• Decide when to use topical antimicrobial treatment in wound management
• Differentiate the need for using topical versus systemic treatment or both
• Explain the mechanism of action for silver’s antibacterial effects
• Describe two methods to increase the aqueous solubility of silver
• Differentiate in vivo and in vitro issues in evaluating antimicrobial efficacy in wound care
• Discuss how combining therapies may allow for greater healing potential

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The Truth about Silver

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Interest in silver as a topical agent in wound healing is undergoing a renaissance. Having basic information regarding silver’s chemical properties and potential actions in the wound bed is important to its appropriate clinical use. Such information is also relevant to the interpretation of silver’s in vitro antimicrobial (antiseptic) effects, which in turn relate to issues involved in the evaluation of the clinical effects of silver in vivo. Gaining an understanding of the basic science of silver products and the different challenges inherent to in vitro versus in vivo antimicrobial evaluations will allow clinicians to address several key questions inherent when considering the use of silver as a topical antimicrobial: 1) Are there different forms of silver? 2) How does the amount of silver released into the wound environment correlate with clinical benefit? 3) How does the rate of silver release correlate with clinical benefit?

After studying this article, the reader should be able to:

- Decide when to use topical antimicrobial treatment in wound management
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Why the Current Resurgence of Interest in Silver?

Clinicians are interested in silver products because they are interested in controlling bacteria. Humans wage a constant battle with bacteria in general and in wound care specifically. Bioburden — the concept of the biological burden that is placed on the wound not only by the bacterial cells but also by the chemicals that are produced by bacteria in the wound — has received a great deal of attention recently in wound management. Bacterial cells produce and secrete a variety of different enzymes and toxins in the wound that can impede the healing process through direct detrimental effects on cells and tissue as well as by interference with endogenous biochemical balances in the local wound environment.1,2 The resurgence of interest in silver products stems from concerns about these deleterious effects of bacteria in wounds coupled with the fact that adequate management of wound bioburden is becoming increasingly critical to the effectiveness of advanced wound care therapies, such as topical exogenous growth factors and bioengineered tissues.

In terms of managing bacteria in wounds, a number of different approaches are available. Physically reducing bacterial levels or preventing the entry of bacteria into the wound is one strategy. Sharp debridement is a mainstay in reducing bacteria levels in wounds because it removes not only the bacteria, but also the environment that they tend to populate — ie, superficial necrotic tissues. A wide variety of advanced wound care dressings also can provide a physical barrier to the entry of exogenous bacteria into the wound.3 Using this type of dressing can result in decreased wound infection rates as compared to gauze dressings, which are incapable of preventing bacterial entry.4,5 Debridement and barrier dressing strategies do not render the wounds free of bacteria but provide incremental approaches to managing wound bioburden.

In addition to these physical methods, clinicians also can use chemical methods — waging...
the battle against bacteria by using “chemical warfare,” so to speak. Chemical agents for battling bacteria in open wounds include topical antibiotics and topical antiseptics. Systemic antibiotics are used to treat or protect the patient from systemic bacterial infection; however, it has been determined that systemic antibiotics rarely reach adequate levels in the granulation tissue of chronic wounds to effectively control superficial proliferating bacteria. Therefore, some method of topical management of the bacteria at the wound surface is warranted in addition to systemic coverage.

**Topical antibiotics.** Topical antibiotics have been used for many years in wound care because they are selectively cytotoxic, attacking only the foreign (bacterial) cells in the wound and having very little effect on host cells. This selective cytotoxicity derives from their mechanism of action, which comprises the antibiotic binding to chemical targets that exist in bacterial cell walls and not in human cell membranes. However, topical antibiotics have some drawbacks. Many are narrow spectrum in terms of the bacterial species they are effective against, and in the wound environment — especially chronic wounds — polymicrobial colonization occurs. Two or more topical antibiotics are usually necessary to cover the range of bacterial species found colonizing chronic wounds. Also, the delivery systems of some of topical antibiotics are not necessarily effective for managing other aspects of the wound environment such as drainage; solutions, creams, and ointments do not have the ability to absorb or otherwise manage the elevated wound drainage often associated with bacterial colonization of a wound. In addition, because of concern about increasing incidence of bacterial resistance associated with the overuse of antibiotics, they are often reserved for systemic use.

**Topical antiseptics.** The other category of chemical agent is topical antiseptics. The benefits of topical antiseptics for bioburden management include the fact that they are broad spectrum agents and can address almost all the types of bacteria found in the wound environment including Gram-positive, Gram-negative, and even antibiotic-resistant strains. Topical antiseptics also are not commonly associated with promoting significant bacterial resistance despite widespread, long-term clinical use. However, some clinicians consider the broad-spectrum activity or non-selective cytotoxicity of topical antiseptics a drawback to their use in wounds. Because antiseptics do not discriminate between foreign cells and host cells, they can potentially damage host cells essential for wound healing. Most data cited to support the detrimental effects of antiseptics on wound healing are based on *in vitro* studies of the effects of antiseptic solutions on cells in test tubes, not on cells in their natural environment (e.g., tissue). The potential detrimental effects of antiseptics on wound healing may be more a factor of their delivery system than their chemical action. A recent *in vivo* study demonstrated that common antiseptics do not inherently delay wound healing. The study evaluated the effects of five different antiseptic solutions versus saline controls on the healing of partial-thickness wounds in swine. The wounds were treated topically with gauze soaked in and remoistened every 8 hours with one of five common antiseptics: 5% mafenide acetate (Sulfamylon® solution, Bertek Pharmaceuticals, Morgantown, WV), 10% povidone with 1% free iodine (Betadine, The Purdue Frederick Company, Norwalk, Conn.), 0.25% sodium hypochlorite (“half-strength” Dakin’s solution), 3% hydrogen peroxide, and 0.25% acetic acid. Because the gauze was kept continuously moist with the antiseptic solution, any delays in healing would be attributable to the chemical agent as opposed to wound dehydration. Re-epithelialization, angiogenesis, neodermal regeneration, fibroblast proliferation, collagen production, and bacterial colony counts were analyzed at 4 and 7 days after wounding. Interestingly, for the parameter of wound re-epithelialization — the point at which wounds are commonly judged to be clinically healed — none of the antiseptic agents had any negative effect compared to saline controls. In fact, some of the antiseptic agents actually improved angiogenesis and fibroblast proliferation.

The typical delivery system for antiseptics in wounds consists of gauze soaked in an aqueous solution of the antiseptic, packed into the wound, and changed once or twice daily. However, because they bind to proteins, antiseptics have a short duration of action (only a minute or two) in the wound bed. In the wound environment, the antiseptic can quickly bind to multiple, alternate sources of proteins (blood, sera, extracellular matrix) and therefore be unavailable for killing cells. In addition, the gauze does not main-
tain an optimally moist wound environment nor does it provide a physical barrier to the entry of additional bacteria into the wound.12

In summary, both types of topical antimicrobial agent have their benefits and drawbacks. Topical antibiotics are selectively cytotoxic, but possess a narrow spectrum of activity and may promote microbial resistance,13 while topical antiseptics are broad spectrum and much less likely to promote resistance but are not selectively cytotoxic and suffer from a very short duration of action and poor delivery systems. However, while antibiotic resistance is still an ongoing problem, the drawbacks of topical antiseptics are being successfully addressed. Advances in biomaterial sciences have produced delivery systems for some antiseptics that can provide an ongoing release of the antiseptic agent from a reservoir over longer periods of time (the antiseptic is still short-acting once released) for a longer duration of action in the wound bed. In addition, the carrier or vehicle of these antiseptics sustains a moist environment in the wound bed so the wound will not dry out.

Silver is one of the antiseptics for which a variety of sustained release delivery systems have recently been developed. These delivery systems include various silver salts, silver complexes, and silver coatings and have been incorporated into a array of moisture-retentive dressing vehicles, such as foams, films, alginites, hydrocolloids, hydrofibers, hydrogels, fabrics, and wound contact layers. These dressings may differ in terms of how the silver is incorporated into the dressing material, how much silver they contain, and the kinetics of the release. This paper considers whether these factors make a clinical difference in terms of selecting one silver product versus another for wound management.

The Chemistry of Silver

In some regards, silver exists in only one form — it is an element. An element is a unique form of matter whose identity is determined solely by the number of protons in its atomic nucleus. If the number of protons in the nucleus changes, the identity of the element changes. Silver is the element having 47 protons and all forms of silver will contain 47 protons in the atomic nucleus. However, the silver atom, or any atom, contains other types of particles in addition to the protons. Atoms also contain neutrons in the nucleus and electrons that orbit the nucleus.14 The number of electrons can change the electrical charge on the atom without changing the identity of the atom — atoms with more electrons than protons develop a negative charge, those with fewer electrons than protons develop a positive charge, and atoms with equivalent numbers of electrons and protons are neutral. Silver in particular can exist as a neutral atom with 47 electrons and 47 protons or as a positively charged atom with 46 electrons and 47 protons.15 The version of the silver atom that has no electrical charge is called elemental silver or metallic silver, often abbreviated as Ag (0) and is the material commonly used to make eating utensils and jewelry. This version of the silver atom is not antimicrobial. However, the version of the silver atom that has lost an electron and therefore has a positive charge is antimicrobial. Silver with a positive charge is also referred to as ionic silver or more specifically the silver cation, and may be abbreviated as Ag (I) or Ag+.

All silver-based antimicrobial dressings, whether alginites, hydrofibers, foams, films, or other materials, achieve their antimicrobial action by somehow generating and releasing this silver cation. In other words, all silver dressings employ the same active ingredient, the silver cation.

The silver cation, Ag+, is a potent antimicrobial agent because it can bind to and damage bacterial cells at multiple sites. The mechanism of action for Ag+ is that it attaches to specific chemical sites (thiol groups containing sulfur and hydrogen) found on a wide variety of proteins that play structural and functional roles in the bacterial cell.16 Once the silver cation attaches to these sites on the proteins, it alters their structure, resulting in consequent structural and functional changes in the cell. For example, when Ag+ binds to proteins in the cell wall, the wall can rupture and the internal cell contents may leak out, resulting in the death of the bacterial cell. Ag+ also may bind to bacterial enzymes (proteins) and prevent them from performing their function, resulting in the inability of the bacterial cell to carry out processes necessary for respiration or to take in or process nutrients and the like, resulting in subsequent death of the bacterial cell. Ag+ also may bind to bacterial cell DNA and interfere with cell division and the replication process. The existence of multiple binding sites for silver is one of the reasons...
that bacterial resistance is rare to silver and to antiseptics in general. Most antiseptics have this type of multi-pronged attack on a cell as opposed to most antibiotics that have a single-pronged attack; hence, multiple mutations would be necessary in order for most cells to become resistant to silver, which while not impossible is not common.

**Getting Silver into a Wound Dressing**

Silver-based antimicrobial dressings may differ in the way they incorporate the active ingredient or how they create the reservoir from which the silver cation is released over time. These reservoirs can be metallic (elemental) silver or a silver compound (a chemical combination of silver and another atom or molecule). Pure silver metal is relatively insoluble in most fluids and will release Ag+ only in very small amounts on contact with moisture through an oxidation process. A basic strategy to derive more silver cation from silver metal is to increase the surface area of that metal, exposing more of the metallic silver atoms to the aqueous interface so the oxidation process can take place more rapidly. Many dressings employ this method of using metallic silver, coating it over a carrier with a large surface area, so when placed in the aqueous environment of the wound, the oxidation process takes place and silver cations are generated and released. This is the mechanism behind nanocrystalline coatings of silver — very, very small particles silver-coated onto polymers or fibers to increase the surface area of the silver so more of the metallic atoms are at the interface of the aqueous environment. Another method of creating a reservoir for silver cation release from a dressing involves formation of a silver complex or compound where the silver cation is ionically bound to an anion or negatively charged species. These silver complexes can be incorporated into materials like hydrocolloids, hydrogels, or foams. When the materials contact an aqueous environment, the silver complex contained in them dissociates and releases the silver cation. Depending on the identity of the anion, these silver complexes will dissociate in water at different rates. The bottom line is that silver dressings may use different methods of creating and incorporating a reservoir for silver cation release but they are all releasing the same active ingredient, Ag+.

**Differences in Silver Dressings**

All antimicrobial silver dressings release the same active ingredient, so are all antimicrobial silver dressings equivalent or are there performance differences? Differences certainly exist in the identity or composition of the dressing vehicle — eg, is it a film, a foam, an alginate, a hydrocolloid, a hydrogel? The dressing vehicle will affect the overall performance of the product in terms of its effects on moisture maintenance or exudate management in the wound. Antimicrobial silver dressings also may differ in the amount of silver they contain as well as the rate at which they release the silver cation. Specific dressings may contain higher amounts of silver per surface area or per volume than others, may release different overall amounts of silver into the wound environment, or may have different rates of silver release.

But do any of these diversifications make a clinical difference? Is one silver dressing superior to another silver dressing in clinical use? A conclusive answer to these questions is not known because clinical evaluations comparing one silver dressing to the others are not yet available in the literature. What are available are *in vitro* comparisons of these dressings’ performance in laboratory tests. In the absence of *in vivo* comparative data, clinicians are left to make assumptions about the potential clinical superiority of one dressing versus another based only on *in vitro* data.

**In vitro Antimicrobial Evaluations**

Two major types of *in vitro* antimicrobial evaluations are commonly conducted to evaluate the antimicrobial performance of silver dressings. One is called a *zone of inhibition study*. For this test, an agar plate is uniformly and aseptically inoculated with a single species of bacteria and then a moistened sample of the silver dressing is placed in the middle of the plate. The plate is then incubated and the bacteria will grow on the agar plate while the silver dressing releases its cations. If the bacterial cells are killed by the silver cations diffusing away from the dressing material, no growth or a clear area around the dressing sample will be visible. This is called the *zone of inhibition*. Researchers measure the distance of the zone of inhibition around the dressing sample placed in the middle. The other type of common *in vitro* antimicrobial study
is a log₁₀ reduction of bacterial counts in a solution. In these studies, a sample of the antimicrobial dressing is added to a test tube containing a solution of a specific concentration of a single species of bacteria. The test tube is placed into a shaking water bath and aliquots of the solution are removed from the test tube at different time points and analyzed to see if the numbers of bacteria are decreasing — ie, is the antimicrobial agent in the dressing killing the bacteria in the solution? The rate of bacterial killing is reported as log reductions in bacterial counts over time. These studies elicit several questions: Does this type of data predict in vivo performance? Does killing a single species of bacteria on an agar surface or in a liquid solution predict what effect the antimicrobial agent might have in the superficial tissue environment of the wound?

The in vitro conditions used in the laboratory are very different from those encountered in a wound. Typically, an antimicrobial product is tested in vitro on a single species of bacteria at a time, but wounds rarely contain only one species of bacteria. If only one species of bacteria is present, no bacterial synergies such as quorum sensing and polymicrobial biofilm formation can occur. In the in vivo environment of a wound, multiple species of bacteria — Gram-positive, Gram-negative, aerobic, anaerobic — exist simultaneously. They are all “talking” to each other, creating issues of quorum sensing and the formation of biofilms. The in vitro conditions include no complicating factors that could interfere with or quench the antimicrobial agent. The wound environment contains not only the bacteria as targets, but also other cells such as fibroblasts, macrophages, and epithelial cells, as well as a wide array of extracellular matrix proteins, blood, serum, multiple anions, and other chemical species such as free radicals. From both a cellular and biochemical standpoint, the in vivo wound environment is a much more difficult setting in which to kill bacteria.

The antimicrobial agent could have multiple targets depending on its mode of action. For an antimicrobial such as silver, which works by nonspecific binding to protein, numerous distractions (other proteins and anions) are present in the wound environment that do not exist in vitro. The in vitro environment offers a
best-case scenario for killing bacteria. For these reasons, *in vitro* antimicrobial efficacy data may not be reliable for predicting clinical performance. Additionally, *in vitro* evaluations of antimicrobials measure only the impact of the agent on reducing bacterial counts and do not consider or measure the potential effects — positive or negative — of the agent on other parameters of healing. *In vitro* antimicrobial evaluations are useful to demonstrate that a product contains and releases an antimicrobial agent and to determine which organisms are susceptible to that agent.

**The Amount of Silver**

Is the amount of silver in one dressing a reason to preferentially select it — ie, does a higher amount of silver necessarily correlate to better clinical performance? More important than the total amount of silver a dressing contains is the amount of silver it releases. Various commercially available silver-containing dressings were analyzed *in vitro* under the same test conditions to determine how much silver they released into simulated wound fluid. It was found that the different dressing products contained and released different amounts of silver over time (see Figure 1). But are these differences significant and will they make a difference in the clinical effect of that product in the wound bed?

The overall clinical effect of a particular dose of silver cations in a particular wound may be related to the relative amount of bacteria present. If the bacterial numbers are low, other cells may be affected and potential delays in healing can occur if the silver cation binds to host cells such as fibroblasts and epithelial cells. A recent study examined the effects of silver cations on fibroblasts and epithelial cells under different conditions. Fibroblast and epithelial cells were tested in individual monolayer cultures and in a bilayered esterified hyaluronic acid matrix of fibroblast and epithelial cells that had been allowed to differentiate into keratinocytes. Fibroblasts in a three-dimensional contracted collagen lattice also were tested. In each of these situations, the cells were exposed to silver nitrate solution or to a nanocrystalline silver dressing, (demonstrating the release of silver cations from different reservoirs). Both silver-releasing agents were toxic to the cells, regardless of the situation. However, the toxic dose differed depending on whether the cells were in monolayer or in one of the three-dimensional constructs. Cells in monolayer required the lowest dose

![Figure 2: Log reductions in Pseudomonas aeruginosa.](image)
of silver cations to be toxic. When the cells were in a three-dimensional environment, more silver cations or a higher dose was required to be toxic to them; hence, the three-dimensional association offers a measure of protection for the cells. However, even the lowest toxic dose of silver for these mammalian cells was similar to the toxic dose for bacterial cells. Because epithelial cells resurface the wound by moving in a monolayer, silver dressings should be used cautiously on epithelializing wounds. At least one case in the literature supports this caveat. It has been shown that the use of a silver dressing in a wound with a low bioburden can delay epithelialization. Innes et al\textsuperscript{20} compared the effects of a non-antimicrobial foam dressing to a nanocrystalline silver dressing in a controlled, matched pair skin graft donor sites. They found that re-epithelialization was significantly slower in the wounds treated with the silver dressing (14.5+/−6.7 days versus 9.1+/−1.6 days; \(P = 0.004\)). No differences in bacterial counts between treatment groups were found, indicating that the silver may have delayed healing.

**Rate of Silver Cation Release**

Does a faster release of silver cations into the wound environment necessarily correlate to an improved clinical outcome? When in vitro log reduction data are compared for various silver dressings, the results may show that a particular dressing kills 99.9% of the bacteria (a 3-log reduction) within minutes because it releases large amounts of silver cations quickly and other dressings which release the silver cations more slowly do not achieve that similar log reductions until later time points. For example, an in vitro log reduction study of *Pseudomonas aeruginosa* was performed using five different commercially available silver-releasing antimicrobial dressings.\textsuperscript{17,18} Only one of the dressings achieved a 3-log reduction of the bacteria at the 15 minute time point, yet by the 2-hour time point, all of the dressings had achieved a 5-log reduction (a 99.999% decrease) of the bacteria (see Figure 2). Similar data are available for a log reduction test of *Escherichia coli* (see Figure 3). Would the faster-releasing dressing be a better choice for bioburden management in a colonized or infected...
wound? Would it actually make a clinical difference, especially when dressings are typically changed not after 15 minutes but after 24 or 48 hours? All the dressings tested achieved the same reductions in bacterial counts within 2 hours — still less than the typical period between dressing changes.

**Biofilms**

Biofilms may significantly impact the effectiveness of antimicrobials like silver in the wound environment, further complicating the translation of *in vitro* data to *in vivo* clinical performance. Biofilms refer to a three-dimensional association of multiple species of bacteria that live in an adhered extracellular polysaccharide matrix as opposed to free-floating bacteria, which are called planktonic bacteria.21 One way to think about biofilms is to consider the analogy of fruit in a gelatin mold where the fruit is the bacteria and the gelatin is the exopolysaccharide matrix. Bacteria in a biofilm can be of multiple types, including Gram-positive, Gram-negative, anaerobic, and aerobic. Channels in the polysaccharide matrix allow the flow of nutrients and communication chemicals. Bacteria in a biofilm have been shown to be less susceptible to antimicrobial therapies than planktonic bacteria due to the protective nature of the surrounding polysaccharide matrix.21 For this reason, the effectiveness of antimicrobial agents in an *in vitro* test, which does not contain biofilms, may not be achieved in the wound environment, which can contain biofilms.

Mertz and Davis developed a swine model for studying biofilms and the antimicrobial efficacy of various agents on biofilm bacteria versus planktonic bacteria.23 Recently, they used the model to examine the effects of two silver dressings — a silver-containing hydrocolloid and a nanocrystalline silver coated contact layer — on both planktonic and biofilm phenotypes of *P. aeruginosa* in second-degree burn wounds and compared results to untreated controls.24 The silver hydrocolloid dressing reduced planktonic bacterial counts by approximately 2 logs in the planktonic infection groups cultured at 24, 48, and 72 hours when compared to the untreated control group and the bacterial baseline counts. The nanocrystalline silver-coated dressing only slightly reduced planktonic bacterial counts at 24 and 48 hours but not at the 72-hour time point (see Figure 4). However, when the effects of these dressings on biofilm-associated bacteria were measured, both dressings demonstrated limited, if any, antimicrobial effect when compared to the untreated groups at all time points (see Figure 5). It appears that the association of bacteria in this three-dimensional structure seems to offer them some protection from attack by the silver cations being released from both of
these dressings. Again, silver binds to proteins and biofilm bacteria are surrounded with a non-proteinaceous material, offering them a level of protection against the antimicrobial.

**Caveats Regarding Antimicrobial Silver Dressing Use**

In addition to the potential toxicity of silver cations to host cells previously discussed, another potential adverse effect of using silver dressings in wounds might be bacterial resistance. Antiseptic resistance in bacteria is rare but not impossible, and while the silver dressings have not been on the market very long, silver compounds have been used in wounds, in particular burn wounds, for many years. Throughout the literature, a variety of resistant species of bacteria have developed in burn patients whose wounds were treated with either silver sulfadiazine or silver nitrate. Although nothing has yet appeared in the literature about resistant strains growing beneath wounds treated with silver dressings, Canadian clinicians have cultured resistant strains of *Pseudomonas* from wounds that were treated with nanocrystalline silver dressing. However, even though silver-resistant bacteria have been cultured from beneath various silver products, it does not seem to be a resistance mechanism that has spread rapidly through the bacterial population. In fact, some silver-resistant bacteria can be cultured and then in vitro, after several growth cycles, become sensitive to silver again.

**Conclusion**

Are there different forms of silver? Yes and no. Only one element is known as silver; only one atom is known as silver based on the number of protons in its nucleus. However, the silver atom may exist in different oxidation states, which means that it may have variable numbers of electrons that affect its overall electrical charge. The silver atom in different oxidation states may be either positively charged or neutral. Although silver can be incorporated into or onto various dressing materials by different methods, all of the dressings release the same form of antimicrobial silver at the wound surface, the positively charged silver cation.

Does a higher amount of silver or a faster release of silver cations in a dressing necessarily equate to an improved clinical benefit in wound management? While in vitro studies show differential performance of dressings with higher amounts of silver or faster release rates, it is not clear that these differences are relevant.
clinically. No in vivo evidence exists to support the supposition that dressings with higher levels or faster rates of silver cations perform better than others.

To truly evaluate and compare antimicrobial dressings, ideally they must be tested in infected or heavily colonized wounds in either humans or animal models. Evidence of comparative efficacy and performance must be based in the complex in vivo tissue environment, not in the best-case scenario of an in vitro environment. The wide variety of silver-releasing antimicrobial dressings currently available should be considered as valuable tools in bioburden management and should be selected based on their overall clinical performance rather than on in vitro antimicrobial performance. Silver dressings may never achieve the kill rates in vivo that are seen in vitro due to complicating factors like biofilms, mixed bacterial populations, tissue proteins and anions. However, it may not be necessary to achieve a 99.99% kill rate in the wound environment. Wounds heal with bacteria present and it may be enough to bring the bioburden into a balance that the host can handle. Silver, especially the sustained release of silver from delivery systems in vehicles that maintain wound moisture levels, is a valuable tool to achieving that goal.

References
29. Personal communication to the author.
Silver has a long and colorful history. The increasing level of bacterial resistance to traditional antibiotics and the isolation of organisms with minimal antibiotic sensitivity are driving the current interest in silver products for chronic wound care. For example, methicillin-resistant Staphylococcus aureus (MRSA) has shown a five-fold increase from 1985 to 1995. The Centers for Disease Control (CDC) recently reported that nearly 70% of the nosocomial infections among ICU patients in the US involve MRSA. Resistance to vancomycin — the antibiotic most commonly used against MRSA — is also increasing. Because silver cations do not incur resistance, they have been proven effective in controlling a broad range of microorganisms, including aerobic, anaerobic, Gram-negative and Gram-positive bacteria, yeast, filamentous fungi, and viruses.

Wound Evaluation

Healthcare providers need to determine if and when to use topical or systemic treatments and whether topical antibiotics or antiseptics are indicated. Clinicians start with the basic tenets of evaluating an infected wound with broad strokes by noting such factors as an increase in white blood cell count, pain, heat, and swelling. The stage of the infection continuum is assessed by signs and symptoms. A quantitative biopsy can help identify the infecting organism. However, it should be noted that many wounds are cultured without clinical evidence of infection, forcing the clinician to immediately begin treatment and possibly contribute to resistant organisms. Another consideration is that high-risk patients often will present with few or no clinical symptoms of infection, even though infection is present. Potentially masked symptoms include purulence, erythema, elevated white blood count, or systemic manifestations — the only clue to a problem is that the wound healing has become static or the wound has worsened; blood glucose (in patients with diabetes) has remained elevated; and abnormal erythrocyte sedimentation values or osseous distinction are evident on plain film. Clinical signs or a high index of suspicion on a high-risk patient are reasons to perform a deep tissue culture. It should be noted that curettage/sampling technique is important in obtaining useful culture results to ensure surface colonies do not
confound results.⁷ Also, wounds must be constantly monitored for bacterial colonization.

Quantitative biopsy results >10⁵ to 10⁶ colony-forming units (cfu)/gram of tissue along with nonhealing can be used to indicate the need for antibiotic therapy.⁸ Trengrove et al⁹ found that the presence of multiple species (four or more) slows wound healing. The presence of critically or heavily colonized bacteria can upset the delicate balance in the wound, increase the inflammatory response, delay healing, release bacterial endotoxins that damage growth factors, and increase the level of matrix metalloproteases (MMPs). Excessive MMP activity may result in destruction of growth factors. Cell receptor destruction can result in a chronic nonhealing wound.¹⁰⁻¹⁴

Another important factor is host resistance. This function can be expressed as:

\[
\text{Infection} = \text{Number of bacteria} \times \text{virulence}
\]

Host resistance

Patient factors involved in host resistance include vascular status, edema, malnutrition, immunodeficiency, alcoholism, and history of diabetes mellitus, among others.¹⁵ Of note: infected diabetic foot wounds are often less symptomatic than nondiabetic wounds, exhibiting only subtle or even a complete absence of signs.¹⁶⁻¹⁷ In fact, recalcitrant hyperglycemia may be the only clinical finding indicating a severe infection of a diabetic foot wound.¹⁸ Kingsley¹⁹ proposed a five-stage wound infection continuum (sterility, contamination, colonization, critical colonization, and infection) with suggested actions to address each stage. Antiseptics are recommended for use at the critical colonization state and possibly earlier for diabetic foot wounds, and antibiotics are reserved for the final infection stage.

**Treatment**

After a thorough assessment of the wound and after reviewing the patient’s medical history and current conditions, local wound care can be initiated, utilizing debridement, moisture balance, and control of bacterial bioburden (assuming osteomyelitis and deep tissue infection are ruled out).¹⁹ As the wound is debrided, the clinician should carefully assess for tunneling, fistulas, or areas that probe to bone. Deep infection must not being overlooked.
The Clinical Role for Silver Dressings

Wound clinicians know that silver dressings are not a silver bullet, so to speak — they do not cure infections. However, if used proactively, silver dressings can inhibit the progression of bacterial penetration and can be effective against MRSA and most other superficial pathogens. A number of technologies are available that release various concentrations of silver cations to wounds: silver salts, adsorbed or trapped ionic silver used in silver charcoal metallic silver products, and nanocrystalline silver coatings that use silver vapor sprayed onto the backing of a dressing material. But how does the clinician know which dressing to select?

All of the dressing characteristics appropriate for the specific wound being managed must be considered. For example, if a patient presents with a highly exudative wound, an alginate might be considered. If bacterial toxin loading is a concern, a dressing with activated charcoal is an option. Some caveats with regard to dressing selection and silver include avoiding use of saline — it will react with the silver cation and form silver chloride crystals, consequently reducing the release of ionic silver — and avoiding use of a papain-urea debriding ointment, which can be inactivated by silver salts.

Clinical Cases

Case 1. A 70-year-old man with insulin-dependent diabetes, diabetic neuropathy, peripheral vascular disease, hypertension, and high cholesterol presented with an injury to the lateral aspect of his left foot. He presented to the Emergency Department 8 days post-trauma with a limb-threatening infection evidenced by purulent wound drainage, wound probing to bone, cellulitis to the knee, and systemic signs of infection. A vascular consultation determined that the patient had biphasic wave forms and adequate perfusion to heal the amputation site. He was immediately taken to the operating room for incision and drainage with resection of the fifth ray, deep cultures, and pulsed lavage and placed on intravenous antibiotics. His wound was packed open to drain with a plan to return to the operating room in 7 to 10 days for a definitive procedure.
Approximately 10 days after the first debridement, the patient had a myocardial infarction and underwent a quadruple bypass. The second surgical debridement of his foot wound was not performed because of his poor cardiac status and his inability to return to the operating room. In the interim, a silver dressing with alginate was used to pack the foot wound to help decrease the critical bacterial load that was accumulating until the patient could be taken back to the operating room. The patient went on to recover from his cardiac episode and was taken to the operating room for the final debridement. This patient’s outcome was successful due to a combination of therapies that included surgical decompression of the infection, intravenous antibiotics, and topical silver dressings.

Case 2. In another case, a 51-year-old morbidly obese woman with insulin-dependent diabetes presented with a full-thickness right foot neuropathic plantar ulceration. This patient was familiar to staff because of previous treatment for bilateral, rocker-bottom Charcot foot and dislocation. The etiology of her ulcer was determined to be pressure related due to a bony prominence. A resection of the prominence was performed without complications. One week postoperatively, the patient presented with a right foot, limb-threatening infection stemming from the surgical site that included purulent exudate, cellulitis to the tibial tuberosity, and three-plus pitting edema. The patient’s white blood cell count was 26 and she was experiencing systemic manifestations consisting of fever, chills, and malaise.

The patient was admitted to the hospital, placed on intravenous antibiotics, and taken to the operating room for incision and drainage. After grossly infected soft tissue and bone were removed, the wound was pulse-lavaged, cultured, and a negative pressure wound therapy device was placed intraoperatively to help manage the high level of exudate. The infection responded to this treatment regimen; however, the large amounts of exudate continued, mostly due to the significant edema. The periwound tissue became macerated because of the dependent position of the wound and the high level of fluid discharge (see Figure 1). Silver with alginate was placed under the negative pressure wound therapy dressing to absorb the excessive fluid; thereby, decreasing tissue maceration and bacterial burden (see Figure 2).
Case 3. The third case involves a 66-year-old insulin-dependent man with peripheral vascular disease, history of bilateral vascular reconstruction and who years before had bilateral partial foot amputation secondary to limb threatening infections. This patient had been ambulatory and able to carry out his activities of daily living for more than 5 years, living alone and adamant about remaining mobile. He presented most recently with a right anterior tibial ulcer with tibial bone exposed at the proximal margin that resulted in the placement of a full-thickness skin graft, which minimally “took” in the central wound area. The wound was surgically debrided with maintenance debridement weekly, followed by PDGF-bb growth factor applied daily for approximately 3 weeks. This method of treatment allowed for proliferation of granulation tissue in the wound bed in preparation for cadaver graft placement. One week post graft placement, the graft showed signs of fluid accumulation and began to lift from the wound bed. The graft was fenestrated to allow for drainage of the exudate and a topical silver dressing was placed over the wound to address the high bacterial load. The expedient clinical assessment and treatment of wound exudate and bacterial colonization contributed to the success of the graft (see Figure 3).

Implications for Practice

Table 1 and Table 2 outline indications, concerns, and recommendations for using silver products in clinical practice.

Conclusion

The presence of bacteria in the wound is not necessarily an indication of infection. Even when bacteria are present in sufficient quantity and combination to cause infection and/or compromise the host, clinicians must be cautious about avoiding “overkill” with regard to chronic wounds, in part due to the presence of treatment-resistant organisms. Silver is an important component in this prudent approach to chronic wound care. Its characteristics and capabilities as an antiseptic, as well the variety of dressings in which it can be incorporated, make it a valuable consideration during wound management.

References

1. Silver is nontoxic to which type of cells?
   A. Gram-positive bacteria
   B. Fungi
   C. Mammalian cells
   D. None of the above

2. The antimicrobial form of silver is known as
   A. Metallic silver
   B. Elemental silver
   C. Cationic silver
   D. Anionic silver

3. The antimicrobial activity of silver is due to:
   A. Binding to polysaccharides
   B. Binding to proteins
   C. Binding to chloride ions
   D. Binding to toxins

4. Biofilm bacteria can be described as:
   A. Surrounded by a protein matrix
   B. Surrounded by a polysaccharide matrix
   C. Free floating
   D. Actively migrating

5. Antimicrobial agents are least effective in killing which type of bacteria?
   A. Biofilm bacteria
   B. Planktonic bacteria
   C. Anaerobic bacteria
   D. Aerobic bacteria

6. When might a topical antimicrobial be used for a chronic wound?
   A. High bacterial burden
   B. Malodorous
   C. Increased inflammatory state
   D. All of the above

7. How do excessive MMPs affect wound healing?
   A. Control critical bacterial colonization
   B. Destruction of growth factors and cell surface receptors
   C. Promote new tissue growth
   D. Prevent bacterial infection

8. What are the benefits of silver dressings?
   A. They provide a sustained release of silver ions at the wound surface
   B. They effectively kill a wide range of microorganisms (including resistant strains) in colonized and infected wounds
   C. They control critical bacterial colonization
   D. All of the above

9. What other kinds of treatments can silver dressings be combined with?
   A. Negative pressure wound therapy
   B. Moist wound healing
   C. Compression hose
   D. All of the above

10. What is the proper technique for obtaining a wound culture?
    A. Cleanse and debride the ulcer bed, then obtain tissue with sterile curette
    B. Cleanse the ulcer bed, then obtain tissue with sterile curette
    C. Cleanse the ulcer bed, then superficially swab the wound bed
    D. Cleanse the ulcer bed, then obtain tissue with sterile curette and debride thoroughly

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**Quiz and Answer Form**

Silver: Separating Fact from Fiction
Supplement to the September 2004 Ostomy/Wound Management

From the choices offered for each question, select the one best response.

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**Answers:** Circle one letter for each answer:

1. A B C D
2. A B C D
3. A B C D
4. A B C D
5. A B C D
6. A B C D
7. A B C D
8. A B C D
9. A B C D
10. A B C D

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**Evaluation**

1. Content was current and relevant. ——
2. Content will have a positive impact on my professional effectiveness. ——
3. Home study was an appropriate format —— for the content.
4. The content met my educational needs. ——
5. Now that I have read this supplement, I have achieved the objectives listed in each section. ——

**Scale**

5- Strongly agree; 4- Agree; 3- Neither agree nor disagree; 2- Disagree; 1- Strongly disagree

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**What questions do you still have?**

**How will you use what you’ve learned in this activity?**

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All tests must be received by 9/14/05
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