Antiseptics on Wounds: An Area of Controversy

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### Abstract and Introduction

#### Abstract

Antiseptics have long and commonly been used on wounds to prevent or treat infection. However, citing cytotoxicity data, many authors have advised against their use on open wounds. This article discusses antiseptics and their use on open wounds, as well reviews relevant animal studies and clinical trials examining the effects of commonly used antiseptics, including iodine compounds (povidone iodine and cadexomer iodine), chlorhexidine, hydrogen peroxide, acetic acid, and silver compounds. This article examines their effects on wound healing and reepithelization and their efficacy on reducing bacterial number in wounds and incidence of wound infections. The authors found despite cytotoxicty data, most antiseptics have not been shown to clearly impede healing, especially newer formulations like cadexomer iodine (which speeds healing) and novel silver delivery systems. These compounds appear to be relatively safe and efficient in preventing infection in human wounds. Given this review, the role of antiseptics on wounds and their role in wound care management should be reconsidered.

#### Introduction

Antiseptics are agents that destroy or inhibit the growth and development of microorganisms in or on living tissue. Unlike antibiotics that act selectively on a specific target, antiseptics have multiple targets and a broader spectrum of activity, which include bacteria, fungi, viruses, protozoa, and even prions.[1,2] Several antiseptic categories exist, including alcohols (ethanol), anilides (triclocarban), biguanides (chlorhexidine), bisphenols (triclosan), chlorine compounds, iodine compounds, silver compounds, peroxygens, and quaternary ammonium compounds.[1] The most commonly used products in clinical practice today include povidone iodine, chlorhexidine, alcohol, acetate, hydrogen peroxide, boric acid, silver nitrate, silver sulfadiazine, and sodium hypochlorite.

Antiseptic uses and indications vary. Several antiseptic agents mainly focus on cleansing intact skin and are used for prepping patients preoperatively and prior to intramuscular injections or venous punctures, pre- and postoperative scrubbing in the operating room, and hand washing by medical personnel. Some also contain detergents, which render them too harsh for use on nonintact skin.[3] The usefulness of antiseptics on intact skin is well established and broadly accepted. However, the use of antiseptics as prophylactic anti-infective agents for open wounds, such as lacerations, abrasions, burns, and chronic ulcers, has been an area of intense controversy for several years.

Two official guidelines have been released recently concerning antiseptic use on wounds. Povidone iodine has been Food and Drug Administration (FDA)-approved for short-term treatment of superficial and acute wounds.[4] The statement includes that povidone iodine has not been found to either promote or inhibit wound healing. On the other hand, guidelines for the treatment of pressure ulcers by the US Department of Health and Human Services strongly discourage the use of antiseptics and promote the use of normal saline for cleansing pressure ulcers.[5]

In clinical practice, antiseptics are broadly used for both intact skin and wounds, although concerns are raised based upon their effect on human cells and wound healing. Opinions are conflicting. Some authors strongly disapprove the use of antiseptics in open wounds.[6-8] On the other hand, others believe antiseptics have a role in wound care, and their use may favor wound healing clinically.[9,10]

#### Reasons to Use Antiseptics on Wounds

The main rationale for using antiseptics on open wounds is prevention and treatment of infection and, therefore, increased rate of the healing process. It is established that infections may delay healing, cause failure of healing, and even cause wound deterioration.[11] Microbial pathogens delay wound healing through several different mechanisms, such as persistent production of inflammatory mediators, metabolic wastes, and toxins, and maintenance of the activated state of neutrophils, which produce cytolytic enzymes and free oxygen radicals.[12] This prolonged inflammatory response contributes to host injury and delays healing. Moreover, bacteria compete with host cells for nutrients and oxygen necessary for wound healing.[13] Wound infection can also lead to tissue hypoxia, render the granulation tissue hemorrhagic and fragile, reduce fibroblast number and collagen production, and damage reepithelization.[7,14-16] Consequently, although creation of an optimal environment for the wound healing process is currently the primary objective of wound care, addressing infection still plays a critical role in wound management.

Despite the universal acceptance of the detrimental role of infection on wound healing, the exact significance of increased bacterial load on wounds is still an area of debate. All chronic wounds are colonized by bacteria population, and it is known colonized wounds can heal.[17,18] However, in addition to clinical infection, it seems that bacterial number above a critical concentration can decrease the wound healing rate and may have deleterious effects on the wound healing process. The role of bacteria in the chronicity of nonhealing wounds is under investigation. Likely, a state of bacterial contamination that can produce subclinical tissue damage exists.[19] This may be caused by shear number or by other properties of the bacterial process. Increased bacterial numbers in pressure ulcers have been implicated as significant participants of chronic ulceration.[20] Several studies have demonstrated that bacterial number above 105 or 106 organisms per gram can cause local disease to skin or can delay wound healing.[21-24] Quantification of bacteria within wounds is not the sole predictor of the risk of infection, since several individualized factors, such as presence of foreign material and concomitant diseases, can decrease the ability of the hosts to defend themselves. Moreover, the nature of the wound and the virulence of microbes involved are important.[25] In addition to use of antiseptics to reduce bacterial load of a wound, several other approaches have been developed, including debridement, cleansing and pulsating jet lavage for removal of the devitalized tissue, and application of topical antibiotics.

Another argument for the use of antiseptics on wounds to prevent wound infection is that antiseptics may be preferable to topical antibiotics with regard to development of bacterial resistance. Antibiotic resistance of skin wound flora has emerged as a significant problem, and measures to prevent it should be taken.[26] Generally, antiseptics aim at eliminating all pathogenic bacteria of the wound, while antibiotics are effective only to certain bacteria that are sensitive to them. Although resistance toward antiseptics has been reported, it is to a significantly lesser degree than reported with antibiotic usage.[18] According to McDonnell, et al., some acquired mechanisms of resistance (especially to heavy metals) are clinically significant, but in most cases the results have been speculative.[1] Moreover, development of resistance against povidone iodine, which is the most commonly used antiseptic today, does not exist.[27] Payne, et al., state that the sensible use of antiseptics could help decrease the usage of antibiotics, preserving their advantage for clinically critical situations.[28]

Antiseptics are also considered superior to topical antibiotics when their rates of causing contact sensitization are compared. Aminoglycosides, especially neomycin, have a much higher sensitization rate compared to povidone iodine.[3] Moreover, patients allergic to one antibiotic may acquire cross-allergy to other antibiotics, as well. The sensitization rate to povidone iodine, the most commonly used antiseptic, has been found to be only 0.73 percent.[3]

#### Arguments Against Antiseptics

A main concern for clinicians prior to applying a topical agent on an open wound is safety. Agents that are cytotoxic or cause delay in wound healing are used with reservation. The strongest argument against the use of antiseptics on wounds is that antiseptics have been found, primarily using *in-vitro* models, to be cytotoxic to cells essential to the wound healing process, such as fibroblasts, keratinocytes, and leukocytes.[29-31] However, this cytotoxicity appears to be concentration dependent, as several antiseptics in low concentrations are not cytotoxic, although they retain their antibacterial activity *in vitro.*[27] Since the *in-vitro* results are not always predictive of what may happen *in vivo,* numerous studies have been conducted on animal and human models. The results of these studies are conflicting and will be presented later in the article.

A second reason against the use of antiseptics on open wounds, as first stated by Fleming in 1919,[32] is that antiseptics are not as effective against bacteria that reside in wounds as they are against bacteria *in vitro.* The presence of exudate, serum, or blood seems to decrease their activity. However, in practice, several bacteriological studies have shown that antiseptics can decrease bacterial counts within wounds.[33,34]

In order to draw conclusions regarding the appropriateness and usefulness of antiseptic use on wounds, the authors have chosen to review the results of animal and human studies of the most common antiseptics used currently.

### Iodine Compounds

Since the first discovery of the natural element iodine in 1811 by the chemist Bernard Courtois, iodine and its compounds have been broadly used for prevention of infection and treatment of wounds.[35] However, molecular iodine can be very toxic for tissues, so formulations composed by combination of iodine with a carrier that decreases iodine availability were developed. Povidone iodine (PVP-I) results from the combination of molecular iodine and polyvinylpyrrolidone. Povidone iodine is available in several forms (solution, cream, ointment, scrub). The scrub form contains detergent and should be used only on intact skin. Cadexomer iodine consists of spherical hydrophilic beads of cadexomer-starch, which contain iodine, is highly absorbent, and releases iodine slowly in the wound area. It is available as an ointment and as a dressing. Numerous studies have been conducted in order to determine the safety and efficacy of iodine compounds on wound healing.

#### Effects of Iodine Compounds on the Bacterial Load of Wounds

**Povidone iodine.** Several animal studies have examined the effects of povidone iodine on the bacterial load of wounds ([Table 1](http://www.medscape.com/content/2003/00/45/63/456300/456300_tab.html" \l "Table 1.)). These results have not proven the efficacy of povidone iodine; however, the results of numerous clinical trials show that it is effective in reducing the bacterial load of wounds. Rodeheaver, et al.,[36] studied the bactericidal activity of povidone iodine solution in contaminated wounds in Hartley guinea pigs and the potential therapeutic benefit. Although they found that it can significantly reduce bacterial load 10 minutes after the application of the antiseptic, this effect did not persist. Four days after a single PVP-I application, there was no decreased rate of infection or decreased bacteria number. Another study[37] that evaluated contaminated 12-hour old lacerations in a guinea pig model failed to find any decrease of wound bacterial counts after irrigation with PVP-I in comparison to normal saline. However, the authors mention that this may be due to the formation of a proteinaceous wound coagulum and point out that even parenteral antimicrobials are ineffective in preventing infection in animal models if administered alone more than three hours after wounding.

However, most of the human trials performed prove the efficacy of povidone iodine in clinical situations. Georgiade, et al.,[38] applied PVP-I ointment on burn wounds in 50 patients and showed that control of bacterial growth was effective. There was not a control group in this study; however, the control of bacterial growth showed a significant correlation to the frequency of PVP-I application.

Gravett, et al.,[39] studied the effect of one-percent PVP-I solution in the prevention of infection in sutured lacerations in 395 patients. Their data suggest that use of one-percent PVP-I solution prior to suturing reduces the incidence of wound infection.

In a recent study[40] on clinically noninfected venous leg ulcers, the combination of PVP-I with hydrocolloid dressing was shown to reduce bacterial clumps, neutrophilic vasculitis, and phagocytic infiltration and increase the healing rate in comparison to the hydrocolloid dressing alone.

One of the most cited studies is the one conducted by Viljanto[41] in surgical wounds in 294 pediatric patients. He found that a five-percent PVP-I aerosol, which contained some excipients (glycerol, citrate-phosphate buffer, polyoxyethylated nonylphenol), increased the infection rate. In order to explain these results, he used the cellstic method, which consists of placing a cellulose sponge inside a silicone-rubber tube between the wound edges. Wound exudate fills the sponge, and cells migrate into the sponge. He found that the five-percent aerosol caused pronounced leukocyte migration, a five-percent solution without excipients caused slighter inhibition, while the one-percent solution was practically no different to the control (saline). Subsequently, spraying wounds with a one-percent PVP-I solution had no effect on wound healing while it significantly decreased infection rate. Interestingly, povidone iodine has been found to have increased bactericidal activity in lower concentrations.[42]

Conversely, some studies have not confirmed those previously mentioned results. PVP-I soaking was not found to significantly decrease bacterial counts in acute, traumatic, contaminated wounds that required debridement, while saline soaking caused increased counts. PVP-I solution was not found to be an effective substitute to wound cleaning and debridement.[43] However, PVP-I irrigation has been shown to be effective in several other studies,[44-46] so it is not obvious if the lack of effect of PVP-I in this study should be attributed to the antiseptic itself or to the method used. In another study with infected chronic pressure ulcers, PVP-I solution was found to reduce bacterial levels but was no more effective than saline.[47]

**Cadexomer iodine.** The efficacy of cadexomer iodine has been shown in both animal and human models ([Table 2](http://www.medscape.com/content/2003/00/45/63/456300/456300_tab.html" \l "Table 2.)). Mertz, et al.,[48] examined the effect of cadexomer iodine dressing on partial-thickness wounds in specific pathogen-free pigs contaminated with or without methicillin-resistant *Staphylococcus aureus* (MRSA). Applied daily, cadexomer iodine was found to significantly reduce MRSA and total bacteria in the wounds in comparison to no treatment control and vehicle (cadexomer) at all time points studied (1, 2, and 3 days after inoculation). The reduction was most pronounced at day 3.

In an uncontrolled small study series (*n* = 19), Danielsen, et al.,[49] used cadexomer iodine in ulcers colonized with *Pseudomonas aeruginosa* and found negative cultures in 65 percent and 75 percent of patients after 1 and 12 weeks of treatment, respectively.

#### Effects of Iodine Compounds on the Wound Healing Process

**Povidone iodine.** Literature regarding the effect of povidone iodine on wound healing in animal wound models is conflicting. Reasons for this discrepancy may be differences in the parameters of wound healing evaluated, the variety of assessment times, iodine concentrations and control groups, and the diversity of animal wound models (partial thickness, full thickness, burn wounds, ischemic wounds, etc.). The type of animal used appears to be of importance, as different animals show different healing responses. Loose-skinned animals (mice, rabbits, guinea pigs) heal mainly through contraction, while the primary mechanism of healing in tight-skinned animals (pigs) is epithelization, and healing in tight-skinned animals more closely resembles the human healing response.[50] It should be emphasized that none of the animal studies examined the effect of povidone iodine in chronic wound models, as an animal model equivalent to human chronic wounds does not exist. Briefly, in some studies povidone iodine was found to cause no inhibition on wound re-epithelization,[51,52] while in others it retarded healing.[53] As far as the tensile strength of the wound is concerned, PVP-I has been reported to cause increase,[54] reduction,[56] have no effect,[55] and cause either reduction or no effect depending on the assessment time.[29] It has also been found to have no effect on collagen[56] and granulation tissue production or nonsignificant reduction.[57] Moreover, it has been shown to increase revascularization.[53] In another study measuring the corneal toxicity of antiseptics, povidone iodine was found to be nontoxic in rabbit corneas.[58]

Clinical studies evaluating the influence of PVP-I in wound healing are numerous. Most of them have shown no decrease of the wound healing rate from the use of povidone iodine. The aforementioned study by Viljanto[41] found no effect on wound healing when a one-percent solution is used. Niedner[59] reviewed the cytotoxicity of PVP-I and concluded that "the normal course of wound healing (suction blister[60]) as well as the disturbed one (Mohs therapy[61] and burns[62]) is not negatively influenced by PVP-I."

Piérard-Franchimont, et al.,[40] examined the effect of PVP-I in combination with hydrocolloid dressing on venous leg ulcers. The control group was treated with compression hydrocolloid dressings alone. Using planimetric evaluation, they showed that the rate of leg ulcer healing was accelerated in the PVP-I-treated group in comparison to control, especially the first four weeks of treatment.

Lee, et al., in a noncontrolled study found reduction of infection and promotion of healing in patients with long-standing (6 months to 16 years) decubitus and stasis ulcerations.[63]

Knutson, et al.,[64] reported their five-year experience and concluded that the combination of sugar and PVP-I enhanced healing of burns, wounds, and ulcers and reduced the requirements for skin grafting, antibiotics, and the hospital costs. However, they do not mention what "standard care" thecontrol group received; neither is it clear if this improvement is due to PVP-I, to sugar, or to the combination.

Mayer, et al.,[9] reviewed the *in-vivo* studies examining the effects of the various PVP-I formulations on wound healing. They reported five human studies using PVP-I solution, three with PVP-I ointment, and three with PVP-I cream. In all these studies, PVP-I was not found to negatively influence wound healing in comparison to the control group or to other treatments.

Burn wounds are, in many ways, different than the other acute wounds, and they have a higher risk of infection that not only can delay wound healing but also can cause a significant risk for the patient’s life. Steen[65] reviewed the use of PVP-I in the treatment of burns. After reviewing *in-vitro* animal and human studies, he concluded that PVP-I has concentration-dependent cytotoxicity. The higher the complexity of the system studied (*in-vivo* > *ex-vivo* > *in-vitro* studies) the less detectable the effects are. He did not exclude the possibility that PVP-I may cause slight retardation in wound healing but believed the benefits of the microbicidal effects of PVP-I should not be ignored. Since large areas usually need to be treated in burn patients, risks of systemic toxicity of increased PVP-I absorption were reviewed, as well.

For several more reviews of PVP-I use on wounds, see references 9, 10, 27, 66, and 67.

**Cadexomer iodine.** In animal models, cadexomer iodine has been reported to increase epidermal regeneration and epithelialization in both partial-thickness and full-thickness wounds.[33,68] However, cadexomer iodine appears to have no effect on granulation tissue formation, neovascularization, or wound contraction.[59]

Cadexomer iodine has also been the subject of many clinical studies. In these studies, cadexomer iodine has been found to be effective and beneficial to wound healing. Nine clinical trials comparing the effects of cadexomer iodine with other treatments on chronic venous ulcers showed enhancement of wound healing. The other treatments that were compared to cadexomer iodine included various "standard treatment" (cleansing with diluted hydrogen peroxide or dilute potassium permanganate baths and covering with either zinc paste dressings or nonadherent dressings, mainly paraffin-impregnated or saline dressings, or saline wet-to-dry compressive dressings, or gentian violet and polymyxin-bacitracin ointment, or support bandaging/stocking and a dry dressing),[69-74] dextranomer,[75] and hydrocolloid dressing or paraffin gauze dressings.[76] In one study, no control group was used, since the main purpose of the study was to examine the safety of cadexomer iodine with regard to development of sensitivity.[77] In several studies, the ulcers had been recalcitrant to previous treatments. All studies found cadexomer iodine not only to cause no inhibition on wound healing but to accelerate it. Moreover, observations of reduction of pain, removal of pus, debris, and exudate, and stimulation of granulation tissue formation were made.[71] The reduction of exudate could be considered an expected action of cadexomer iodine, since cadexomer iodine is designed to absorb large quantities of exudate (each gram can absorb 3mL of fluid) and then results in slow release of iodine.

Apelqvist, et al.,[78] examined the effects of cadexomer iodine in cavity foot ulcers in diabetic patients and found no clinical difference in comparison to other treatments (gentamicin solution, streptodornase/streptokinase, or dry saline gauze) but considerable less costs.

In a randomized trial, Moberg, et al.,[79] compared cadexomer iodine (*n* = 16) with standard treatment (*n* = 18) in patients with decubitus ulcers. Cadexomer iodine significantly reduced pus, debris, and pain of the ulcers and accelerated the healing rate. After eight weeks of treatment, the ulcer areas were reduced by 76 and 57 percent in the cadoxemer iodine and standard treatment group, respectively. Six ulcers treated with cadexomer iodine were completely healed, while only one with standard treatment was healed.

Summarizing the review of numerous *in-vivo* studies of iodine compounds the authors can conclude that in humans PVP-I and cadexomer iodine do not have a negative influence on wound healing, while cadexomer iodine causes an acceleration of healing in chronic human wounds. Both can be effective in reducing bacteria number and decreasing infections. Results from animal studies depend on many variables and should be interpreted with cautiousness. Studies of PVP-I have more conflicting results, especially with animal models, and have caused concern on many clinicians. Nevertheless, the results from the studies evaluating cadexomer iodine are clear and leave no doubt that this newer iodine compound is effective without having any negative influence on wound healing rate. Inversely, an acceleration of wound healing has been observed.

### Hydrogen Peroxide

A three-percent solution of hydrogen peroxide is commonly used as a wound antiseptic. The three-percent solution demonstrates *in-vitro* broad-spectrum efficacy. Its greatest activity is towards Gram-positive bacteria, but the presence of catalase in these bacteria makes dilutions below three percent less effective.[1] In a similar fashion, catalases present in tissues can render hydrogen peroxide even less bactericidal *in vivo.*[6] Although hydrogen peroxide is very commonly used, surprisingly few studies have been conducted to examine its effect on the wound healing process and its efficacy as a wound antiseptic ([Table 3](http://www.medscape.com/content/2003/00/45/63/456300/456300_tab.html" \l "Table 3.)).

Animal and human studies have shown hydrogen peroxide to have no negative effect on wound healing. Lineaweaver, et al.,[29] did not find retardation of reepithelization in a rat model after irrigation of the wound with three-percent hydrogen peroxide. However, at the *in-vitro* component of the same study, he found minimal bactericidal effect of hydrogen peroxide. Gruber, et al.,[52] found acceleration of reepithelization in a rat model and in a clinical trial. However, bullae were formed on or about the day of healing in most of the patients, suggesting possibly that hydrogen peroxide should not be used in newly formed epithelium.

In another study by Tur, et al.,[80] hydrogen peroxide was found to significantly increase the blood flow in ischemic ulcers in a guinea pig model. The increased blood flow may be due to new vessel formation through activation of metalloproteinases. Interestingly, the blood flow was increased even in places distant to the local application of hydrogen peroxide. No explanation was given for this finding. However, the authors found no difference in the wound-healing rate. This may be due to the limited sensitivity of the method they used to evaluate the clinical response (visual determination of the non-necrotic area).

In a clinical study evaluating the effectiveness of hydrogen peroxide on reducing the infection rate of appendectomy wounds, no toxic effects were found, but it was found to be ineffective.[81] Similarly, in another clinical study in human blister wounds contaminated with *Staphylococcus aureus,* hydrogen peroxide was found not to retard the healing but neither did it decrease bacterial load.[82]

In conclusion, hydrogen peroxide appears not to negatively influence wound healing, but it is also ineffective in reducing the bacterial count. However, it may be useful as a chemical debriding agent. The American Medical Association concluded that the effervescence of hydrogen peroxide might provide some mechanical benefit in loosening debris and necrotic tissue of the wound.[13]

### Acetic Acid

Acetic acid is frequently used in wounds as a 0.25-percent or 0.5-percent solution. It is bactericidal against many Gram-positive and Gram-negative organisms, especially *Pseudomonas aeruginosa.* No delay of reepithelization has been found in animal and human models.[52] Although one study found that acetic acid initially delayed reepithelization, after the eighth day, this effect did not persist. In the same study, it was not shown to influence tensile wound strength.[29] In two human uncontrolled studies, acetic acid was found to be beneficial in wounds infected with *Pseudomonas aeruginosa.*[83,84] In a study with patients with venous leg ulcers,[85] gauze dressings wetted with acetic acid were shown to effectively decrease the number of *Staphylococcus aureus* and Gram-negative rods. Pseudomonas was not reduced significantly.

Although several *in-vitro* studies found acetic acid to be cytotoxic,[31,86] the *in-vivo* studies do not confirm these findings. The authors believe that acetic acid can continue being used topically in contaminated wounds where an agent is needed in order to eliminate the chances of infection ([Table 4](http://www.medscape.com/content/2003/00/45/63/456300/456300_tab.html" \l "Table 4.)).

### Chlorhexidine

Chlorhexidine has been commonly used in disinfectant and antiseptic solutions. Chlorhexidine antiseptic solutions are used mainly in urology, gynecology, dentistry, and in the treatment of wounds. It is highly bactericidal.

Several animal studies have tested the efficacy and safety of chlorhexidine on wounds ([Table 5](http://www.medscape.com/content/2003/00/45/63/456300/456300_tab.html" \l "Table 5.)). It has been found to have mild inhibitory effects on wound healing in guinea pigs.[87] Chlorhexidine diacetate was found to accelerate wound healing in full-thickness wounds in beagles.[88] Chlorhexidine was also found to be relatively safe for use as a surgical wound irrigation solution, since only the higher concentrations tested (0.05%) caused slight tissue toxicity in rats.[89] Lower concentrations (0.02%) are recommended for wound irrigation. In other studies, it was found to cause inhibition of granulation tissue in guinea pigs[57] and decreased tensile strength of wounds in rats.[90] However, Brennan, et al., found no decrease in collagen production in a rat model,[91] and Shahan, et al., also in a rat model, found decreased tensile strength 48 hours after the treatment and significantly increased strength at 96 hours, since chlorhexidine decreased the healing time.[92]

In human studies, chlorhexidine rinses were shown effective in reducing microbial complications when used perioperatively in patients that received dental implants.[93] Conversely, in another study, it was found to be ineffective to reduce wound sepsis rate and length of hospital stay in patients that had undergone appendicectomy.[94] The authors speculate that reinfection from within as an explanation for the lack of chlorhexidine efficiency.

Chlorhexidine appears to be relatively safe with little effect on the wound healing process, and its use may favor healing of open wounds in risk for infection. However, the results from studies to date are insufficient to draw conclusions about the use of chlorhexidine on open wounds. More human trials need be performed to assess its efficacy and safety.

### Silver Compounds

Silver compounds have widely been used as wound antiseptics, mainly in burns. Silver sulfadiazine (SSD) and silver nitrate (AgNO3) are among the most commonly used. Silver sulfadiazine is the most broadly used treatment for the prevention of infection in patients with burn wounds.[95,96] Combinations of SSD with cerium nitrate[97] and nanocrystalline silver releasing systems (Acticoat®, Westaim Biomedical, Exeter, New Hanover)[98] have been developed in order to increase its efficacy and/or reduce its toxicity. Newer silver formulations appear to increase the rate and degree of microbial killing, decrease exudate formation, and can remain active for days.[99]

Animal studies examining the effects of SSD and AgNO3 on wounds have showed no significant effect[53] on epithelization rate ([Table 6](http://www.medscape.com/content/2003/00/45/63/456300/456300_tab.html" \l "Table 6.)). SSD was also found to increase the rate of neovascularization.[53] In another study in rats, silver compounds were found to promote wound healing, reduce the inflammatory and granulation phases of healing, and influence metal ion binding.[100] Moreover, Geronemus, et al.,[51] found increased reepithelization rate in domestic pigs with the use of SSD.

Yet, Leitch, et al.,[101] found SSD to cause inhibition of wound contraction in an acute wound rat model. Likewise, Niedner, et al.,[57] found a slight, nonsignificant reduction of granulation tissue formation with the use of AgNO3.

Among human studies, the authors present only those on patients suffering from wounds other than burns, as there is currently no controversy for the use of silver compounds on burn patients, as mentioned above. Kucan, et al.,[47] examined the effects of SSD on bacterial counts in patients with infected chronic pressure ulcers. He found SSD to be effective in decreasing the bacteria below 105/gr tissue in all the ulcers treated. In a randomized trial with venous ulcers, SSD one-percent cream was proved to statistically reduce the ulcer size compared to the placebo,[102] while in another study it was found to be well tolerated and effective on wound cleansing and granulation tissue formation.[103] Livingstone, et al.,[104] studied the effect of AgNO3 and an antibiotic solution (neomycin plus bacitracin) on reducing autogenous skin graft loss due to infection in patients with thermal injury. They found both medications to be effective in comparison to the control group (Ringer’s lactate solution), but the antibiotic solution was associated with the rapid emergence of drug-resistant organisms, while AgNO3 was not. Nanocrystalline silver compounds have been found to increase the reepithelization rate of meshed autografts[105] and appear to be promising for the treatment of other chronic wounds as well. The anti-inflammatory effects of silver could be associated with the vehicle, which reduces wound drying, reducing therefore inflammation (moist wounds have been found to be significantly less likely to be infected).[111] More clinical trials are needed for the evaluation of nanocrystalline silver.

Summarizing, it appears that silver compounds do not have a negative effect on wounds and maybe accelerate wound healing clinically. Their *in-vivo* antimicrobial activity is not in question.

### Discussion

The use of antiseptics on wounds is currently being viewed with skepticism. Results from *in-vitro* studies have shown that antiseptics are toxic not only against bacteria and other microorganisms but also against human cells essential to the wound healing response. These findings resulted in a series of animal and human studies in order to evaluate the *in-vivo* activity of antiseptics. However, it seems that in human subjects, pronounced cytotoxicity, found *in vitro,* was not confirmed. In the majority of clinical trials, antiseptics appear to be safe and were not found to negatively influence wound healing. Their antimicrobial efficiency, with the exception of hydrogen peroxide, seems satisfactory as well. Randomized controlled studies to evaluate the effect of each antiseptic on the different kinds of wounds (acute, venous, diabetic, or pressure ulcers) are indicated to provide greater evidence regarding the benefits of antiseptic use on wounds. Efforts to develop superior antiseptic formulations are likely to and should continue. Development of cadexomer iodine, which not only does not negatively influence wound healing but also accelerates healing even in noninfected wounds, and development of improved silver delivery systems, which release silver more efficiently than previous formulations while enhancing re-epithelization, are paradigms of the therapeutic potential of antiseptics. Vehicles that contribute to the maintenance of an optimal moist environment may be more appropriate as delivery systems of antiseptics than the current ones, since moist environments result in both increased wound healing rate and enhancement of antimicrobial penetration to wounds.

Antiseptics need not be omitted from the therapeutic armamentarium of wound care. In patients and wound types with high risk of infection, antiseptics may be used to prevent wound infection that would have deleterious effects on wound healing. Antiseptics present advantages over topical antibiotics, since they do not cause the emergence of drug-resistant bacteria and have broader antimicrobial spectrum and lower sensitization rates.

In conclusion, after review of the literature, most antiseptics, especially newer formulations, appear to be relatively safe and efficient in preventing infection in human wounds. The advantages of antiseptics on wounds may outweigh possible disadvantages, and their position in wound care management should be reconsidered.

### Tables

### Table 1. Povidone iodine

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| --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Wound Type** | **Species** | **Number of Wounds Treated** | **Control/Comparator** | **Effect on Healing** | **Effect on Infection** |
| Bennett, et al.[107] | Partial thickness | Pigs | 48 (8 wounds for each group) | Mafenide acetate; sodium hypochlorite; hydrogen peroxide; acetic acid; no treatment | No effect (81% reepithelialization, with 1% PI, after 4 days vs. 69% for the no treatment group, nonsignificant difference) | Slightly decreased bacterial counts, (yet still >105, statistical difference from control not calculated) |
| Fumal, et al.[110] | Leg ulcers | Humans | 34 (17 patients) | No treatment; silver sulfadiazine; chlorhexidine (all groups treated with hydrocolloid dressing) | Increase (4-18% improvement of healing rate, 2-9 weeks faster vs. untreated, p < 0.01) | N/A |
| Howell, et al.[37] | Contaminated lacerations (with *S. aureus*) | Guinea pigs | 48 (12 animals) | Saline; cefazolin; no treatment | N/A | No effect (4.63 log S. aureus recovered from wounds 2 h after irrigation vs. 5.47, 6.13, and 6.37 for no treatment, cefazolin, and saline groups, respectively; nonsignificant difference) |
| Georgiades, et al.[38] | Burns | Humans | 50 | N/A | N/A | Decrease (77% of wound cultures did not have bacterial growth after QID application vs. 42% and 33% for the BID/TID and QOD/QD application groups, p < 0.001) |
| Geronimus, et al.[51] | Partial thickness | Pigs | 600 wounds (in 4 animals, 300 for each group) | No treatment | No influence (4.55 days needed for 50% of wounds to reepithelialize with pharmadine [9-12% PI solution] vs. 4.6 for control, relative rate of healing +1%; nonsignificant difference) | N/A |
| Gravett, et al.[39] | Sutured lacerations | Humans | 395 | No treatment (all wounds were initially irrigated with saline) | N/A | Decrease (1% rate of purulent wounds and 5.47% wound sepsis rate vs. 6.19% and 15.4% at the control group) |
| Gruber, et al.[52] | Partial and full thickness | Rats | 40 (20 for each group) | Saline | No effect (12.2 and 9.3 days mean healing time for betadine vs. 12.4 and 9.5 for saline in partial-thickness wounds in rats and humans; 19.2 vs. 19.5 in full-thickness wounds in rats, nonsignificant difference) | N/A |
| Humans | 20 (10 for each group) |
| Kashayap, et al.[56] | Incisional | Mice | 120 (2 animals) | Vehicle; steroids; no treatment | Decreased strength/no effect on collagen (334gr bursting strength vs. 404, 439, and 322 at the vehicle, no treatment, and steroid groups, respectively; p < 0.05 vs. no treatment group) | N/A |
| Kjolseth, et al.[53] | Full thickness | Mice | 23 (13 control, 10 PI) | No treatment | Decrease (11.8 days for complete reepithelization vs. 7.2 for control, p < 0.01) | N/A |
| Knutson, et al.[64] | Burns, chronic wounds | Humans | 759 (90 PI solution and sugar, 515 PI solution, PI ointment and sugar, 154 standard treatment) | Standard therapy | Increase (0% need for skin graft for the triple combination group, 4.5% for the PI sol/sugar group vs. 40.3% for the control group) | Decrease |
| Kucan, et al.[47] | Pressure ulcers | Humans | 40 (15 SSD, 15 PVP-I, 14 saline) | Saline; PVP-I | N/A | No effect (60% of patients responded to treatment after 14 days vs. 60% and 90% at the saline and SSD groups) |
| Lammers, et al.[43] | Acute heavily contaminated | Humans | 33 | Saline; no treatment | N/A | No effect (bacterial counts similar to no treatment group after 10 min; saline soaking increased bacterial counts, p < .0001) |
| Lee, et al.[63] | Decubitus ulcers; stasis ulcers | Humans | 18 | N/A | Increase (67% of ulcers cured after 6 wks, 33% of ulcers improved) | Decrease (2 out of 14 infected lesions continued being infected after 6 wks, p < 0.001) |
| Menton, et al.[54] | Incisional | Guinea pigs | 120 (60 animals) | Saline; Shur-Clens; DPS 89009 | Decrease (betadine surgical scrub significantly delayed epidermal and dermal healing vs. all groups, but increased significantly tensile strength after 21 days vs. all groups) | N/A |
| Mertz, et al.[108] | Partial thickness | Pigs | 54 (9 animals) | Distilled water; alcohol 70% | N/A | Decrease (5.94 log bacterial counts after 24 hr vs. 7.53 and 7.28 at the water and alcohol groups, p < 0.05) |
| Mulliken, et al.[55] | Incisional | Rats | 341 | Ringer's solution | No effect on strength (17.52 gm/mm2 tensile strength after 1 wk vs. 17.90 at the Ringer's solution group; nonsignificant difference) | N/A |
| Niedner[57] | Full thickness | Guinea pigs | 10 for each group | No treatment | No effect (nonsignificant decrease by 19% of thickness of the granulation layer in comparison to control) | N/A |
| Pierard-Frachimont, et al.[40] | Venous ulcers | Humans | 30 (15 patients) | No treatment (both groups treated with hydrocolloid dressings) | Increase (increased healing rate with PVP-I treatment, especially during the first 4 weeks of treatment, p < 0.05) | Decrease (less neutrophilic vasculitis, and bacterial clumps in PVP-I treated group, significance not calculated) |
| Rodeheaver, et al.[36] | Contaminated | Guinea pigs |  | Saline | N/A | Decrease (?) (1.31 log reduction of bacteria 10 min after, p < 0.001; no effect 4 days after a single application; no effect on infection rate) |
| Severyns, et al.[89] | Femoral vessels section | Rats | 150 animals | Saline, chlorhexidine | Toxicity (marked difference of 10% PI solutions on histological assessment, damage to vascular endothelium and thrombosis, vs. saline, and chlorhexidine) | N/A |
| Sindelar, et al.[46] | Surgical | Humans | 500 (242 PI, 258 control) | Saline | N/A | Decrease (2.9% wound sepsis rate vs. 15.1% in the control group, p < 0.001) |
| Viljando[41] | Surgical | Humans | 294 | Saline | No effect (cell morphology similar to saline-impeded control) | Decrease (2.6% infection rate with 1% PI solution after appendectomy vs. 8.5% at the control group; however, 19% infection rate with 5% PI solution vs. 8% at the control group) |

### Table 2. Cadexomer iodine

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Wound Type** | **Species** | **Number of Wounds Treated** | **Control** | **Effect on Healing** | **Effect on Infection** |
| Apelqvist, et al.[78] | Diabetic ulcers | Humans | 25 (12 CI, 13 control) | Standard treatment | No difference between groups | N/A |
| Danielsen, et al.[49] | Venous ulcers with *P. aeruginosa* | Humans | 17 | N/A | N/A | Decrease bacterial counts (65% of pt had negative P. aeruginosa cultures after 1 wk) |
| Floyer, et al.[77] | Venous ulcers | Humans | 30 (ulcers deteriorating or static in their existing treatment) | N/A | Increase (15 out of 18 ulcers healed or reduced in size, while 3 increased) | (Decrease\*) (erythema, exudate, pus, and debris were reduced from baseline) |
| Hansson, et al.[76] | Venous ulcers | Humans | 153 | Hydrocolloid dressing or paraffin gauze | Increase (62% mean reduction of ulcer area vs. 41% and 24% in the hydrocolloid and paraffin gauze groups) | N/A |
| Harcup, et al.[74] | Venous ulcers | Humans | 72 | Standard treatment (dry dressing ± topical antibacterial cleanser) | Increase (36% decrease of ulcer size after 4 wks vs. 10% in the standard treatment group, p < 0.01) | (Decrease\*) (decrease of edema, erythema, exudate, pus, debris, pain, p < 0.05-p < 0.001) |
| Holloway, et al.[72] | Venous ulcers | Humans | 75 (38 CI, 37 control) | Standard treatment (wet-to-dry dressings) | Increase (0.95±0.12cm2/wk ulcer healing vs. 0.41±0.13 in the standard treatment, p < 0.0025) | (No effect-decrease\*) (not statistically significant) |
| Lamme et, al.[68] | Full thickness | Pigs | 36 (12 CI, 12 cadexomer, 12 saline) | Cadexomer and Saline | Increase (increase in reepithelialization 6 and 9 days after treatment, p < 0.05) | N/A |
| Laudanska, et al.[69] | Venous ulcers | Humans | 60 (30 CI, 30 control) | Standard treatment (cleansing with dilute hydrogen peroxide and covering with a zinc paste dressing) | Increase (74% mean reduction of ulcer area after 6 wks vs. 54% in the standard treatment, p < 0.01) | (Decrease\*) (decreased debris, exudate, erythema, and edema, p < 0.05-p < 0.001) |
| Mertz, et al.[33] | Partial thickness | Pigs | 120 (for the epithelialization study; 40 in each group) | Air exposed and ointment base control | Increase (4.6 days for complete epithelialization of 50% of the wounds vs. 4.9 and 5.7 days for ointment base control and air exposed wounds, significant) | Decrease bacterial counts (significant reduction of S. aureus counts at 24, 48, and 72 hours and of P. aeruginosa at 48 hours) |
| 18 (*S. aureus* or *P. aeruginosa* inoculated wounds for the bacteriological study; 6 in each group) |
| Moberg, et al.[79] | Decubitus ulcers | Humans | 34 (18 CI, 16 control) | Standard treatment (saline dressings, debriding agents or non adhesive dressings) | Increase (76% decrease in ulcer size after 8 weeks of treatment, vs. 57% decrease in the standard treatment group, p < 0.05) | (Decrease\*) (Decrease of pain, pus, and debris, p < 0.005) |
| Ormiston, et al.[73] | Venous ulcers | Humans | 60 (30 CI, 30 control) | Standard treatment (gentian violet and polymyxin-bacitracin ointment) | Increase (0.89cm2/wk ulcer healing vs. 0.46 in the standard treatment, p < 0.0001) | (Nonsignificant decrease\*) |
| Skog, et al.[71] | Venous ulcers | Humans | 74 (36 CI, 38 control) | Standard treatment (most commonly paraffin-impregnated dressings) | Increase (34% decrease in ulcer size after 6 weeks of treatment, vs. 5% increase in the standard treatment group) | Decrease (in 16 out of 23 pt infection was cleared in comparison to 0 out of 18 in the standard treatment group) |
| Tarvainen, et al.[75] | Venous ulcers | Humans | 27 (14 CI, 13 control) | Dextranomer | Increase (64% of pt healed after 8 wks vs. 50% in the dextranomer group) | (No effect) (reduction of erythema, exudate, and pus from baseline, nonsignificant difference between groups) |

|  |  |  |
| --- | --- | --- |
|  | \* | Cadexomer iodine decreased one or more of pus and debris, exudate, pain, and erythema, which are considered as clinical indicators of infection. |

### Table 3. Hydrogen peroxide

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Wound Type** | **Species** | **Number of Wounds Treated** | **Control** | **Effect on Healing** | **Effect on Infection** |
| Bennett, et al.[107] | Partial thickness | Pigs | 48 (8 wounds for each group) | Mafenide acetate; sodium hypochlorite; povidone iodine; acetic acid; no treatment | No effect (69% reepithelialization after 4 days vs. 69% for the no treatment group) | Decreased bacterial counts, (<105 vs. >105 at the control group, statistical difference not calculated) |
| Gruber, et al.[52] | Partial and full thickness | Rats | 40 (20 for each group) | Saline | Increase (10.2 and 8.4 days mean healing time vs. 12.4 and 9.5 for saline in partial-thickness wounds in rats and humans; 17 vs. 19.5 in full-thickness wounds in rats, *p* < 0.05 for the animal study, nonsignificant difference for the human study) | N/A |
| Humans | 20 (10 for each group) |
| Lau, et al.[81] | Appendectomy | Humans | 217 (109 HP, 108 control) | No treatment | N/A | No effect (21 pt developed infection vs. 26 of the control group) |
| Leyden, et al.[82] | Blister wounds (contaminated) | Humans | 144 (24 volunteers with 3 wounds per forearm) | No treatment, triple antibiotic | No effect (14.3 days for healing vs. 13.2 and 9.4 in the no treatment and triple antibiotic group) | No effect (6.7 log *S. aureus* counts vs. 7.1 and 0.4 in the no treatment and triple antibiotic group) |
| Tur, et al.[80] | Ischemic ulcers | Guinea pigs | 34 | Placebo cream | No effect (visual evaluation of percent nonnecrotic wound surface showed no difference between groups); increased blood flow (vascular perfusion measured with laser Doppler velocimeter was increased, *p* < 0.01) | N/A |

### Table 4. Acetic acid

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Wound Type** | **Species** | **Number of Wounds Treated** | **Control/Comparator** | **Effect on Healing** | **Effect on Infection** |
| Bennett, et al.[107] | Partial thickness | Pigs | 48 (8 wounds for each group) | Mafenide acetate; sodium hypochlorite; hydrogen peroxide; povidone iodine; no treatment | No effect (77% reepithelialization after 4 days vs. 69% for the no treatment group, nonsignificant difference) | No effect (>105, statistical difference from control not calculated) |
| Gruber, et al.[52] | Partial and full thickness | Rats | 40 (20 for each group) | Saline | No effect (12 and 9.3 days mean healing time vs. 12.4 and 9.5 for saline in partial-thickness wounds in rats and humans; 18.6 vs. 19.5 in full-thickness wounds in rats, nonsignificant difference) | N/A |
| Humans | 20 (10 for each group) |
| Hansson, et al.[85] | Venous ulcers | Humans | 45 | Aluminum acetotartrate; potassium permanganate; chloramine | N/A | Decrease (acetic acid 0.25% reduced both *S. aureus* and Gram-negative rods, *p* < 0.002 and *p* < 0.03. Pseudomonas, Proteus, *S. epidermidis*, and *S. hemolyticus* were not significantly reduced, *p* > 0.05) |
| Sloss, et al.[84] | Burns or soft tissue wounds | Humans | 16 | N/A | N/A | Decrease (eliminated *P. aeruginosa* counts in 14 out of 16 patient within 2 weeks) |
| Phillips, et al.[83] | Superficial | Humans | 20 (10 acetic acid, 10 control) | Chlorhexidine or hypochlorite | N/A | Decrease (mean growth fell from 4.1 to 0.7 after 7 days vs. 3.3 to 3.4 in the control group) |

### Table 5. Chlorhexidine

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Wound Type** | **Species** | **Number of Wounds Treated** | **Control/Comparator** | **Effect on Healing** | **Effect on Infection** |
| Brennan, et al.[91] | Full thickness | Rats | 540 (45 animals with 4 wounds each, for each group: chlorhexidine, saline, chloramine T) | Saline, chloramine | No effect (no difference from saline on collagen production and on histologic examination) | N/A |
| Crossfill, et al.[94] | Appendicectomy wounds | Humans | 288 (97 chlorhexidine, 97 saline, 92 no treatment) | Saline, no treatment | No effect on hospital stay (average stay of 8.2 days for noninflamed appendices vs. 8.3 and 8.8 for saline and no treatment groups, nonsignificant difference) | No effect (overall sepsis rate 13.2% vs. 12.2% and 14.1% for saline and no treatment groups, nonsignificant difference) |
| Fumal, et al.[110] | Leg ulcers | Humans | 34 | No treatment; silver sulfadiazine; povidone iodine (all groups treated with hydrocolloid dressing) | No effect (mild improvement of healing rate vs. untreated, -1-5%, non significant) | N/A |
| Lambert, et al.[93] | Dental implants | Humans | 2641 (595 patients) | Saline | N/A | Decrease (4.1% infectious complications vs. 8.7% in the control group) |
| Saatman, et al.[87] | Incisional wounds, abrasions | Guinea pigs | 175 | Saline vehicle (4% CHL skin cleanser, tincture 0.5% CHL in 70% isopropanolol, 0.5% CHL in water, 4% CHL in water, saline, skin cleanser, tincture) | Mild decrease (4% chlorhexidine groups mildly decreased healing rate at days 6 and 9 at incisional wounds and at all time points at abrasions vs. saline; no difference between chlorhexidine and vehicles; no differences among groups after 21 days of treatment) | N/A |
| Mobacken, et al.[90] | Incisional wounds | Rats | 130 (65 rats, each with 1 wound for treatment and 1 for control) | Saline, vehicle | Decrease tensile strength (significant decrease vs. both saline and vehicle, after 7 days, *p* < 0.001 and *p* < 0.01 for 0.1% and 0.02 % chlorhexidine solutions) | N/A |
| Niedner, et al.[57] | Full thickness | Guinea pigs | 10 for each group | No treatment | Decreased granulation (66% decrease of thickness of the granulation layer in comparison to control, *p* < 0.001) | N/A |
| Sanchez, et al.[88] | Full thickness | Beagle dogs |  | Saline, povidone iodine | Increase (larger healed wound area on days 7 and 14, increased contraction on days 7, 14 and 21 vs. saline) | Decrease bacterial counts (0.05% chlorhexidine solution significantly reduced bacterial counts vs. PI and saline) |
| Severyns, et al.[89] | Femoral vessels section | Rats | 150 animals | Saline, povidone iodine | No toxicity (no difference of 0.02% and 0.001% chlorhexidine solutions on histological assessment of collagen and elastic fibers, vs. saline. Nonsignificant toxicity of 0.05% solution) | N/A |
| Shahan, et al.[92] | Full thickness | Rats | 80 (40 animals) | Saline | Increase (reduced tensile wound strength with 0.12% chlorhexidine solution at 48h, 127 vs. 150; increased at 96h, 202 vs. 183, resulting in shorter healing time, *p* < 0.05) | N/A |

### Table 6. Silver compounds

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Wound Type** | **Species** | **Number of Wounds Treated** | **Control/Comparator** | **Effect on Healing** | **Effect on Infection** |
| Bishop, et al.[102] | Venous stasis ulcers | Humans | 86 (28 SSD 1% cream, 29 copper tripeptide copper, 29 placebo) | Placebo, copper tripeptide complex | Increase (44% decrease in lesion size vs. 18.7 and 22.5 for the other groups, p < 0.05) | N/A |
| Fumal, et al.[110] | Leg ulcers | Humans | 34 | No treatment; chlorhexidine; povidone iodine (all groups treated with hydrocolloid dressing) | No effect (mild improvement of healing rate vs. untreated, 2-7%, nonsignificant difference ) | N/A |
| Geronimus, et al.[51] | Partial thickness | Pigs | 600 wounds (in 4 animals, 200 for each group) | No treatment; vehicle | Increase (3.1 days needed for 50% of wounds to reepithelialize with Silvadine (1% sulfadiazine silver) vs. 4.3 for untreated control and 3.4 for vehicle, relative rate of healing +25%) | N/A |
| Kjolseth, et al.[53] | Full thickness | Mice | 46 (13 control, 18 silver sulfadiazine, 15 silver nitrate) | No treatment | No effect (7.1and 8.9 days for complete reepithelization with silver sulfadiazine and silver nitrate vs. 7.2 for control, nonsignificant difference) | N/A |
| Kucan, et al.[47] | Pressure ulcers | Humans | 40 (15 SSD, 15 PVP-I, 14 saline) | Saline, PVP-I | N/A | Decrease (90% of patients responded to treatment after 14 days vs. 60% at the saline and PVP-I groups, p < 0.022) |
| Lansdown, et al.[100] | Incisional | Rat | 50 (10 wounds for each group) | Deionized water (silver nitrate 0.01%, 0.1%, 1%, SSD 0.5g, deionized water) | Increase (all wounds completely closed by day 8 for 1%, 0.1% silver nitrate and SSD vs. half wounds closed for the 0.01% silver nitrate and water groups, significance not calculated) | N/A |
| Leitch, et al.[101] | Full thickness | Rats | 40 (10 for each group: Silver sulfadiazine, Silvazine, air exposed, mafenide acetate) | Air exposed; mafenide acetate | Decrease (decreased wound contraction with silver compounds in comparison to control, especially the first 10 days of treatment, p < 0.05) | Decrease (decreased bacterial counts in treatment groups, statistical significance not given) |
| Livingstone, et al.[104] | Grafting after burn injury | Humans | 52 (19 silver nitrate, 18 neomycin + bacitracin, 15 ringer's lactate) | Ringer's lactate, Neomycin plus bacitracin | N/A | Decrease (16% graft failure, mostly due to infection, vs. 33% and 53% for topical antibiotics and Ringer's lactate groups, p = 0.02; 1 out of 3 infection cases of emergence of antibiotic-resistant bacteria at the silver nitrate group vs. 6 out of 6 and 4 out of 8 for the other groups, p < 0.05) |
| Niedner, et al.[57] | Full thickness | Guinea pigs | 10 for each group | No treatment | No effect (nonsignificant decrease by 25% of thickness of the granulation layer with AgNO3 solution in comparison to control) | N/A |
| Olson, et al.[106] | Partial thickness | Pigs | 72 (24 for each group: silver coated dressing moistened once, daily, and petrolatum gauze) | Petrolatum gauze | Increase (100% and 96% of wounds reepithelialized by day 7 on silver-treated groups vs. 33% for petrolatum gauze group, p < 0.0001) | N/A |
| Ouvry[103] | Venous ulcers | Humans | 71 | N/A | Increase (40 ulcers healed, 25 improved, 4 remained stable and 1 worsened after 45 days with sulfadiazine treatment) | N/A (no infections observed) |
| Tredget, et al.[98] | Burns | Humans | 30 | Silver nitrate vs. Acticoat® | N/A | Decrease (5 wounds with >105 counts in Acticoat-treated wounds vs. 16 in silver nitrate group and 1 secondary bacteremia vs. 5) |

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