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Antimicrobial Silver Dressings: Emerging Issues for Modern Burn Care

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Mesh terms

"Wounds and injuries", burns, silver, dressings, antimicrobial stewardship

Abstract

Skin is an important barrier to pathogenic microorganisms and plays a critical role in activation of innate immune responses. When the skin barrier is breached following wounding or burn injury, pathogens can invade and complicate healing with infection resulting in delayed healing and symptomatic scarring. Wound infection is a significant problem after burn injury and also post operatively at the surgical site. Antimicrobial silver has had a significant role in wound antisepsis throughout history and, given the rise in community acquired antibiotic resistance, silver dressings are now commonly used to combat burn wound infection. The multi-modal mechanism of action, low potential for toxicity and the formation of microbial resistance makes silver dressings suitable tools against a wide array of clinically important microbes. There are, however, a number of issues with silver dressings including a conflicting evidence base, the important environmental consideration of nanoparticle manufacture, and the significant cost of these products. One solution may be to adopt an “opened-but-unused” means of wound care whereby bulk dressing materials are used piecemeal and stored in between dressing changes to increase the cost-effectiveness and reduced wastage of silver dressings during wound care. There is, however, little literature on this topic and so more research must be performed to consider the efficacy of active ingredient dressings in burn wound care including silver dressings once opened and stored.

Introduction

The skin is the largest organ in the human body and an effective primary defence against infection.(1) Skin acts as a physical barrier to pathogens and also as a means for surveillance and reactive response by both the innate and adaptive immune system. When the skin is disrupted by a burn injury the barrier function is impaired and the immune response compromised. Although microbial colonisation of burn wounds can be normal, the immune system is critical in preventing the progression to active infection. Large wounds including major burns are particularly susceptible to microbial infection and resulting biofilm formation.(2) Despite major advances in burn wound management and supportive care, infection still

remains a significant issue for burns patients due to complications including sepsis, delayed healing, systemic inflammatory response syndrome, burns contracture, symptomatic scars and skin graft loss.(3) The clinically significant microbiome of major burns include *Pseudomonas aeruginosa* and *Staphylococcus aureus* as primary infective pathogens.(4, 5) Conversely, chronic wounds including diabetic foot ulcers are polymicrobial in nature.(6) Systemic antibiotic therapy is often of limited use in these cases due to associated peripheral vascular disease and resulting difficulty of antibiotic diffusion through inflamed wound tissue.(7) Increasingly, there are emerging antimicrobial stewardship concerns with the rise of acquired resistance to commonly prescribed systemic antimicrobial therapies.(8, 9) As a result, dressings including those containing silver are now widely used. Silver dressings inhibit microbial growth in wounds via many different modes of action and may facilitate faster healing.(10-12) There are, however, several issues with silver dressings including a conflicting evidence base with a lack of high-quality clinical trials, an important environmental consideration of silver nanoparticle manufacture, and a significant fiscal expense without clearly demonstrated cost-effectiveness. In this article we review these issues and explore a potential solution to minimise them by using an "opened-but-unused" model of burn wound care.

A Short History of Silver

There is a substantial historical evidence to suggest that silver has been used for its antimicrobial properties in wound care since ancient times. The use of silver in making water potable dates back to as early as 1000 BC (13) and silver was used in the middle ages as an alternative to hot iron wound cauterisation.(14) Topical preparations of silver nitrate and silver sulfadiazine were extensively used in the prophylaxis and treatment of wound infection in the 1960s.(15) These topical preparations were, however, considered inconvenient and their use declined with the discovery of penicillin and the emergence of the antibiotic era. The incorporation of silver into wound dressings has been implemented more recently with several dosage and silver composition forms developed to improve silver stability and delivery to wounds while reducing cytotoxicity to human cells. After the realisation in the 1980s that commonly applied topical disinfectants and antiseptic agents could be toxic to host cells (16), and with

increasing concern regarding the rise in microbial resistance, silver dressings are once again widely used in burn wound care. (12, 17)

Mechanism of Action

Despite being used for thousands of years, the pharmacological mechanisms by which silver exerts its antimicrobial effects are still not well understood. Current main concepts of silver mechanism of action governing its antimicrobial properties are summarised in Fig 1.

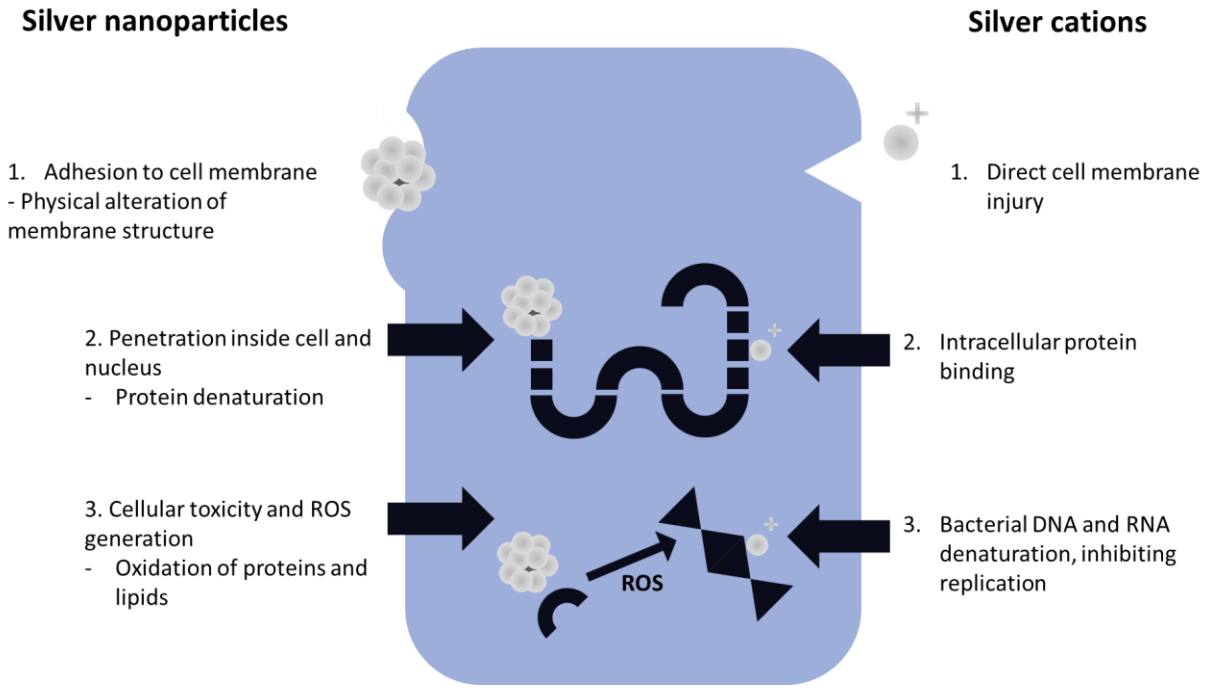


Figure 1: Antimicrobial mechanism of action for silver (adapted from Fong et al.(18) and Dakal et al.(19))

Silver in its metallic state is inert, however interaction with moisture from the skin and fluid from a wound bed result in dissolution and ionisation. Silver ions (Ag+) are highly reactive, binding to tissue proteins and causing structural changes in bacterial cell walls and intracellular and nuclear membranes, ultimately leading to cell lysis.(20, 21) Additionally, silver ions exhibit bacteriostatic properties by binding to and denaturing bacterial DNA and RNA, thereby inhibiting protein synthesis and replication.(20, 22) Given that wound exudate often contains a high level of debris and electrolytes, silver ions are sequestered and inactivated in the wound bed by proteins and chloride. The antimicrobial effects of silver products are therefore directly related to the amount and rate of silver released from the dressing, replenishing the

concentration of free ions for antimicrobial activity.(20) The more recent use of nanotechnology to package silver into nanoparticles increases the surface area available for silver dissolution and enhances its antimicrobial activity. (20, 23) The silver nanoparticles induce an oxidative stress in the wound and interfere with the bacterial cell wall by means of aggregation, especially for Gram negative organisms.(24) Additionally, silver nanoparticles have been shown to have anti-inflammatory effects on wound healing resulting in decreased neutrophil infiltration and increased numbers of M2 pro-healing macrophages.(22, 23, 25) The mechanism of action of silver ions and silver nanoparticles are multiple, resulting in antimicrobial effects against the wide spectrum of clinically important aerobic and anaerobic organisms encountered in burn wounds.(26)

Silver Toxicity

Given that silver dressings are applied directly to wounds that are inherently deficient in the skin's defensive barrier capabilities, there is a potential for significant absorption and therefore the risk of toxicity is a concern that needs consideration. Long term exposure to high levels of silver causes argyria, which is the permanent grey discolouration of the skin, conjunctiva and internal organs from deposition of silver particles. This is rare and should be distinguished from the short-term hyperpigmentation of wound area skin by topical silver dressings and products. On review of the literature there are no reported cases of argyria from modern silver dressings however high serum silver levels have been reported with currently available silver dressings, and their prolonged use for infants under one or patients with large surface wounds is strongly discouraged.(27) Additionally, rare adverse effects of silver dressings described include renal toxicity and hepatotoxicity, however these have been associated with the traditional silver nitrate or sulfadiazine preparations.(28) Our experience is that silver dressings used in clinical practice have a generally low risk profile with these exceptions.

Clinical Applications and Evidence for Today

The efficacy of silver dressings has been evaluated using both *in vitro* and *in vivo* pre-clinical studies. Early studies by Yin et al. tested Acticoat® dressings against topical silver nitrate or silver sulfadiazine topical preparation (29). The authors hypothesised that silver ions were consumed by chloride anions and bacterial proteins *in vitro* and therefore a mechanism for sustained release of silver ions from an inert

dressing would result in a continuous supply of ions available for prolonged antimicrobial activity. This was reflected in Zone of Inhibition and Minimum Inhibitory Concentration testing, where pathogens showed increased susceptibility to Acticoat®.(29) Aramwit et al. compared several commercially available dressings using Zone of Inhibition assays against multiple clinically significant pathogens and found that nanocrystalline silver had superior antimicrobial activity compared to silver sulfadiazine impregnated dressings.(1)

Animal models of scald wound infections have also been used for antimicrobial efficacy testing.(30) Wright et al. applied nanocrystalline silver dressings in a contaminated porcine wound model and found faster healing compared with a plain dressing product.(31) Additionally, silver sulfadiazine application was compared with silver dressings in a rat burn model showing that Acticoat® and Silvalon® products were superior in reducing the microbial burden in these wounds.(32)

Clinical evidence has been somewhat less convincing for use of silver dressings in wound care. A Cochrane review conducted in 2010 found that there was insufficient evidence to support the use of silver dressings to prevent infection and improve healing time, remarking on the low quality of evidence.(33) A more recent systematic review examining silver dressing use in venous leg ulcers reached the same conclusion.(34) Most chronic wounds host mixed bacterial populations and silver might be considered as an ideal candidate for these applications as a broad-spectrum agent. A study by Sibbald et al. showed a decrease in the wound microflora after applying a silver based dressing to chronic wounds.(35) Jude et al. studied non-ischaemic diabetic foot ulcers and found that a silver containing hydrofiber dressing provided an improved ulcer depth and a reduced rate of superficial infection requiring antibiotics when compared to alginate dressings.(36) In contrast, the VULCAN trial found no advantage in wound healing for silver dressings when used for venous ulcers.(37) A recently published (2021), retrospective study sponsored by Smith and Nephew did show a significant improvement of approximately 50% in healing time for chronic wounds treated with silver dressings.(11) Additionally, a clinical trial in burns patients who were randomised to receive silver nanoparticle dressings or topical silver nitrate found that silver dressings have a role in the prophylaxis of infection.(38) The rate of both local wound infection and also systemic bacteraemia was significantly improved with the use Acticoat®.(28) Moreover, Demling et al. compared time to epithelialisation between 20 grafted burns wounds and found a 40% improvement for Acticoat® than dressings without silver.(39) While there remains no universal, high level, evidence-based

recommendation, silver dressings appear to have a positive role in preventing infection and improving healing in certain wounds including burns.

Resistance

Microorganisms have a low tendency to develop silver resistance due to its multi modal mechanism of action and potency at low concentration.(40) There have, however, been several silver resistance genes described in the literature (28) and a single clinical case of a resistant salmonella species has been reported.(41) Acknowledging the increasing recognition and importance of antimicrobial resistance in the world, silver resistance remains rarely encountered and silver is still highly effective against a wide variety of clinically important bacteria and fungi.

Health Economics

There are, however, several important considerations to balance against potential benefits of silver dressing use. Modern silver dressings come with an important economic consideration. The financial burden of chronic wounds has an impact of an estimated A$3 billion per year. A recent Australian report identified high cost as a primary barrier to wound management.(42) Silver dressings are expensive products and increase health expenditure for health institutions. For patients purchasing ongoing dressing supply this cost may create a disparity in access. Scanlon et al. studied multiple dressing options for the treatment of leg ulcers and estimated cost effectiveness using a cost per percentage reduction and found that a silver-containing Aquacel Ag® regimen was the least cost effective among different wound dressing protocols. Conversely, Hurd et al. recently published a retrospective study that showed a significant reduction in cost of wound care with silver dressings related to the decreased number of dressing changes required and therefore lower overall nursing costs.(11) Silver dressings are costly and with a yet to be proven cost-benefit ratio in both hospital and community settings.

Environmental Impact

Healthcare is the largest consumer of metal nanoparticles. On an industrial scale, the global consumption of silver nanoparticles has more than doubled since 2014.(43) The manufacture of commercial nanoparticle silver dressings currently involves either high energy physical or hazardous chemical production methods and the consequences of environmental nanoparticle pollution is not known.(21, 43) New, plant based methods have been described that may reduce the environmental burden of manufacture.(44, 45) However, with increasing usage and demand for silver dressings in wound care the global consumption of silver may consequently increase rare earth metal wastage in landfill which is a significant problem. The environmental cost of silver dressings has not been formally reviewed, at this point, to our knowledge.

Open-But-Unused Dressings

One way of maximising the cost effectiveness of silver wound dressings may be by reducing wastage. The concept of open-but-unused dressings is one where large sheets of dressing material are used piecemeal for each dressing change and the unused portion stored in between changes. Purchasing dressings in larger sizes are often less expensive per square unit area and therefore may improve the cost per dressing change. Table 1 describes the results of an online search performed on 29/06/2021 for retailers with silver dressings for purchase in Australia.

Table 1: Average cost per unit area of commonly used silver dressings

	Cost (AUD per cm^2 of dressing material)	
	Small dressing size	Large dressing size
Acticoat®	0.84 (5x5cm)	0.37 (10x120cm)

Acticoat 7®	1.50 (5x5cm)	0.80 (15x15cm)
Aquacel Ag®	0.63 (5x5cm)	0.19 (15x15cm)
Mepilex Ag®	0.28 (10x10cm)	0.24 (20x20cm)

The average cost was calculated for the smallest and largest dressing size per unit area. Commonly used silver dressings in Australian hospitals were used as examples. In most cases, the cost savings per unit area for larger dressings is more than half of the smaller.

The Wounds Australia Consensus 2017 (46) states that open-but-unused dressing material may only be used in the following cases:

- When smaller dressing sizes are not available
- Where storage has been within its original packaging plus an additional sealable plastic bag
- An opened dressing must be used for the same patient.

And should not be used in:

- Immunocompromised patients
- Hospital inpatient scenarios
- Recently skin grafted wound beds.
- Cases where dressings have been opened for four weeks or longer.

In our experience, surgical burn units in public hospitals practice a single use dressings model. There are two main issues regarding the use of open-but-unused dressing materials:

Microbial contamination

Templeton et al. showed that there was low risk of contamination of stored plain dressings by performing serial culture swabs in the home setting.(47) There is, however, no documented literature addressing risk of contamination of stored dressings specifically for currently available commercial silver dressings or in their use hospital settings. Inherently antimicrobial dressings including silver dressings might be resistant to contamination during handling and storage.(45)

Dressing deactivation

Silver may oxidise over time and therefore silver wound dressings may lose antimicrobial efficacy after opening. The use of nanoparticles in silver dressings maximises the surface area available for dissolution of silver ions in the wound and this is commonly done in dressing design.(21) This may also result in an increased surface area for silver oxidisation and degradation once dressings are opened and stored. Because there are no published investigations on this topic, it is not known if silver retains its antimicrobial activity over time in storage.

Conclusion

The antimicrobial use of silver is historically important and current research indicates that silver dressings remain a useful component of the management of the bioburden of burn wounds in practice. There is an environmental challenge in the industrial upscaling of silver dressing manufacturing and wastage as well as an economic challenge due to the high cost of currently available silver dressings. Unnecessary wastage compounds these costs as excess dressing material is discarded in the single use packet model of dressing care. The concept of "open-but-unused" wound care could provide significant increases to the cost-effectiveness of silver dressings, however there is a paucity of laboratory and clinical research to support the this practice. No studies to date have evaluated the antimicrobial efficacy of silver dressings after packaging is opened and whether opened silver dressings are vulnerable to microbial contamination during storage. More research is required to advise clinicians suitability of an "open-but-unused" model of wound care to reduce financial and environmental impact of silver dressings in burn wound management.

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