Silver dressings: Healing is a matter of time, and sometimes opportunity

Ewan Masson

ARTICLE POINTS

1 Micro-organisms existing in 'biofilm' colonies may be highly resistant to antibacterials to which they would normally be susceptible.

2 Silver ions are highly toxic to a large variety of microbes through a variety of mechanisms and so microbial resistance is unlikely.

3 Various types and quantities of silver have been added to all types of advanced wound management products.

4 There is little evidence base from which to direct choice of silver dressing – literature consists mainly of case studies and observational data.

5 Sustained-release silver is almost certainly a more appropriate antibacterial for surface wounds than most other commonly used substances.

KEY WORDS
- **Silver dressings**
- **Bacteria**
- **Bioburden**
- **Anti-microbial**
- **Evidence base**

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Introduction

One of the developing product ranges in wound care recently has been the introduction of silver to many types of wound dressing. It has been advocated to control bioburden and to act as a barrier to bacterial ingress. It is possible that early infection might be treatable topically by such products. The aim of this article is to explain the background to the concepts and examine the rationale for product choice in this bewildering field.

Hippocrates said that: *'Healing is a matter of time, but it is sometimes also a matter of opportunity.' Hippocrates (460 BC – 377 BC), Precepts.* This is a very relevant concept when applied to the diabetic foot.

What is 'bioburden'?

It is increasingly accepted that chronic wounds of all types may have a critical level of bacterial contamination above which healing is unlikely (Sibbald, 2001). Furthermore, there is a developing understanding that the behaviour of bacteria on surfaces, including wounds, may not be as straightforward as many clinicians have previously understood (Wysocki, 2002).

Many bacteria and other micro-organisms exist in communities, which may be of varied species in a matrix of extracellular polysaccharide. These colonies are known as biofilms and may have a role in wound healing or its prevention. Their role in most medical conditions is at present uncertain, but their presence has been demonstrated in animal wounds (Serralta et al, 2001).

In the context of biofilms, organisms may be highly resistant to the effects of antibacterials to which they would normally be susceptible. However, colonisation of this nature may represent a stable state that could prevent clinical infection depending on the species involved.

Various methods of bacterial sampling, including tissue fluid collection, conventional swabs and wound-bed biopsies have yielded different quantities and counts of viable commensal and pathogenic bacteria from wounds of all types and poor consensus exists on the interpretation of the results (personal communication with McCulloch, 2004). Total eradication of bacteria is probably neither essential nor indeed possible, and colonisation by skin flora may provide protection against pathogenic colonisation.

Few would argue against bacteria in excessive numbers being generally undesirable in wounds and the concept of wound bed preparation is increasingly popular – generally taken to mean creating a healthy-looking pink granulating surface by one method or another. It follows that this state should then be maintained and one strategy that may help is topical antisepsis. This has been a controversial issue in wound management over the years, as various commonly-used antiseptic agents have been shown to be cytotoxic, at least in vitro (Hellewell, 1997) and some that used to be commonplace (notably EUSOL [Edinburgh University Solution Of Lime]; sodium hypochlorite) have fallen out of favour.

Why add silver?

The antimicrobial properties of silver (or more accurately silver ions, Ag^+) were exploited long before microbes were discovered. They have been exploited in

Figure 1. Silver ions selectively bind to thiol groups, which are widely distributed in bacterial cell wall proteins, and may also bind to bacterial DNA.

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1 Antibacterial effect depends on the available concentration of silver ions.

2 Silver ions are highly toxic to a large variety of microbes and due to having a variety of mechanisms of toxicity are unlikely to provoke bacterial resistance.

3 Silver in advanced wound management products is added in forms designed to make the cations more readily available.

4 No head-to-head trials have been undertaken on the various silver-containing products, so it is difficult to chose products based on evidence.

5 Manufacturers focus their claims on the dressing 'device' rather than the silver as a medicinal substance, which may be considered a 'pharmaceutical' product and therefore require radically different approval process.

wound management for many years. Ricketts et al (1970) demonstrated both that the antibacterial effect depended on the available concentration of silver ions and that antibacterial concentrations did not appear to be toxic to mammalian tissue. Silver nitrate solutions and silver sulfadiazine have been popular for the management of burns (Modak et al, 1986). For less extensive injury, such as diabetic foot wounds, physical occlusion to prevent bacterial ingress has been a much more common philosophy.

Silver ions are highly toxic to a large variety of microbes, and except in special circumstances they are unlikely to provoke much bacterial resistance as they have a variety of mechanisms of toxicity (Silver, 2003). They selectively bind to thiol groups, which are widely distributed in bacterial cell wall proteins, and may also bind to bacterial DNA (Lansdown, 2002; see *Figure 1*). However, silver ions are highly reactive and need to be released continuously for a sustained antibacterial effect. Metallic silver does not oxidise quickly and, although simple silver foils have been used in burns management, the silver added to advanced wound management products (AWMP) is added in forms designed to make the cations more readily available. This can be done by exposing a high surface area to wound fluid by making the particles of metallic silver very small (the so called 'nanocrystalline' technology; see *Figure 2*) or by incorporating a variety of silver compounds that may release silver cations more easily than metallic silver (Lansdown, 2002).

What type of wound care product?

Silver in varying quantities and types has been added to all types of AWMP – hydrogels, hydrofibres, hydrocolloids, films, foams and others. No head-to-head testing has been done of one versus another in conventional clinical trials, therefore the choice of a silver-containing product must depend on other factors.

Clearly the clinician's preference for the type of material used to treat a particular type of wound may be one factor, but what other evidence is there for a choice? It stands to reason that the volume and speed of silver cation release may also be important, but how can one judge this? Interestingly, perusal of manufacturers' literature is not always as useful as one might think in this regard. Many references are made to the antibacterial barrier provided by silver products, but few, if any, to the release of silver cations into the wound.

One of the reasons for this is the nature of medical device regulation, which varies throughout the world but has some important principles common to most systems. For example, in Europe, a product specifically designed to deliver a medicinal substance either systemically or topically would be considered a 'pharmaceutical' product rather than a 'medical device'. Thus, it would have to go through a radically different efficacy and safety approval process whereas a device fundamentally has to be proven to be safe and usually does not have to undergo large double-blind clinical trials to prove efficacy – a process which is notoriously difficult in the field of wound care anyway.

A device, however, may contain a medicinal substance whose action is ancillary to the main purpose of the device (European Economic Union, 1993). Silver has been widely used as a medicinal substance for many years, so can be incorporated into AWMP. Therefore, although it is tacitly acknowledged that silver does come from at least some of these AWMP into wounds it is not the basis of manufacturers' primary claims, which have to be based on the regulatory data submitted. Thus manufacturers tend to concentrate on silver effects within the device, on the wound surface and in vitro.

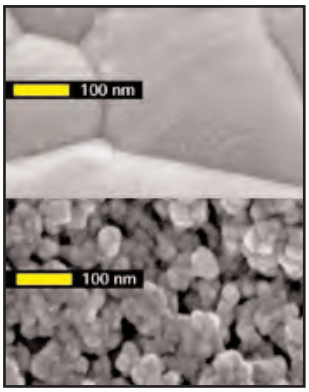


Figure 2. The magnification of normal silver (top) compared with nanocrystalline silver (bottom).

PAGE POINTS

1 The use of different in vitro microbiological techniques may lead to different conclusions and so demonstrate how controversial the issue of treatment efficacy can be.

2 A wide range of performance was shown across a range of dressings when a variety of laboratory tests were carried out by Thomas and McCubbin (2003b).

3 Broadly speaking, the antibacterial activity reflected the silver content, however as the dressings had different incomparable properties, no firm conclusions concerning acceptability or clinical performance were drawn.

4 There are virtually no published clinical trials comprehensively comparing types of dressings – silver-containing dressings included – for any aspect of wound care.

In vitro assessments

Most websites and product literature list the species of microbes against which AWMP have been tested in the process of product regulation. A number of other authors have published comparative data on one or another 'silver dressing', which allows limited data for comparisons to be made.

Ovington (2004) describes a series of comparisons of time to killing suspended planktonic bacteria of various types: *Pseudomonas aeruginosa* and *Escherichia coli*. Superior reductions are seen at very early timepoints with some products, but similar bacterial killing is achieved within hours by all products tested. Ovington goes on to suggest, therefore, that as dressings are seldom changed more than once a day this difference may not matter, and shows other data suggesting that sliver dressings may be ineffective against biofilms. Speed of killing has relevance to the possibility of resistance emergence, however, as several generations of bacterial reproduction can occur in a matter of hours.

Other reports using different in vitro microbiological techniques may lead one to different conclusions. A series of articles and attendant correspondence (Thomas and McCubbin, 2003a,b,c,d; Lansdown, 2003; Nielsen, 2003) demonstrate how controversial these issues can be.

A series of experiments were performed on a wide range of products from a variety of manufacturers (Thomas and McCubbin, 2003b). A challenge test of a planktonic suspension, similar to that described above, was carried out using three organisms: *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* (respectively Gram-positive and -negative bacteria, and a yeast). Further testing involved the determination of a 'zone of inhibition' around a portion of dressing placed on agar plates that had been evenly inoculated with the test organism. If a zone was detected it was measured, and the dressing was removed. The test was repeated up to seven times, in order to give an idea of the duration of antibacterial action. The third test was a 'microbial transmission test' in which a piece of dressing bridged a gap between a sterile and an inoculated block of agar, thus testing the ability of the test organism to migrate across the dressing surface. The group went on to assay the extractable silver content of a sample of each dressing.

In short, this variety of tests in the laboratory showed a wide range of performance across the range of dressings in terms of antibacterial activity and silver content, and broadly speaking the antibacterial activity reflected the silver content. The caveat is that these results cannot be extrapolated directly into clinical practice – the dressings tested had various physical properties which are not comparable in this context and not all have identical indications. Thus, no firm conclusions concerning acceptability or clinical performance were drawn.

In vivo

There are virtually no published clinical trials comparing types of dressings in a comprehensive manner for any aspect of wound care, and particularly for the diabetic foot (Jeffcoate and Harding, 2003). This is also true for silver-containing dressings. Limited conclusions can be drawn from some small studies, but even then they are difficult to generalise. For example, Innes et al (2001) compared a silver dressing to a foam for graft donor sites and concluded that the silver product could not be recommended. Demling and DeSanti (2002), however, reached the opposite conclusion, their comparator being an antibiotic-moistened gauze. In their hands the silver product seemed to out-perform the foam used in their predecessors' trial. The earlier report suggested there could have been inappropriate handling of the silver product, but it is easy to imagine other methodological confounders.

There is a huge volume of literature consisting of case studies and observational data of many aspects of wound care but no 'scientific' evidence for many of the techniques used in the sense normally associated with pharmaceutical 'evidence-based' practice. A randomised, double-blind, controlled trial is extremely difficult to devise for the comparison of medical devices such as advanced wound-care products. Even the selection of appropriately comparable patients is fraught with difficulty. The financial side of this is also important. There are many fairly large wound care

companies but they are minnows compared to pharmaceutical giants, whose research budgets reflect the enormous cost of drug development and potential market size. That is not a model of product development that would be sustainable in the current relatively low-margin medical device market.

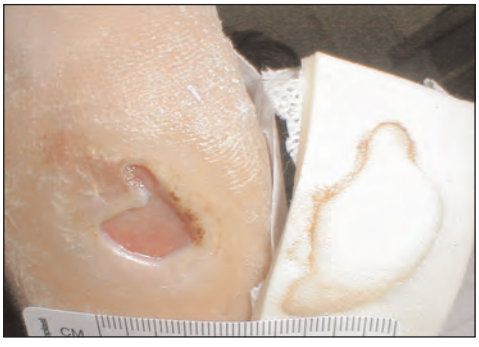
Experience can also be valid evidence and there are many strongly held beliefs among practitioners of wound care which are rarely challenged – for example 'moist wound healing'.

Is silver safe?

Yes, probably. Although there are various reports of in vitro cytotoxicity (Poon and Burd, 2004) and theoretical concerns over potential toxicity of systemically-absorbed silver (Lansdown and Williams, 2004). The most commonly seen complication of prolonged use of silver is argyria – a cosmetically distressing discolouration of the skin that does not usually cause any other harm. Although it is possible that enough silver could be absorbed through very extensive wounds treated with silver products to produce argyria, in every day terms (at least with respect to the foot) they are as safe as other wound management products.

Conclusions

There are differences between the silver-containing AWMPs, which may be important in dressing selection (*Figure 3*). Those with higher silver content show greater antibacterial action in the laboratory. The physical characteristics of the dressing may also be important depending on the wound type. Sustained-release silver is almost certainly a more appropriate antibacterial for surface wounds than most other commonly used substances, e.g. iodine, which is rapidly inactivated. ■



Conflict of interest: Dr Masson is medical consultant to Smith & Nephew Medical Ltd who market a silver wound dressing. The views expressed in this review are, however, entirely those of the author alone.

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Figure 3. An example of one of the many silver-containing dressings. Differences between the products available may be important in dressing selection.

PAGE POINTS

1 The most commonly seen complication of prolonged use of silver is argyria, which discolours the skin but does not usually cause any other harm.

2 In every day terms, silver-containing dressings are as safe as other wound management products.

3 Differences between silver-containing dressings and a dressing's physical characteristics may be important in dressing selection.

4 Sustained-release silver is almost certainly a more appropriate antibacterial for surface wounds than most other commonly used substances.

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