Silver dressings: their role in wound management

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ABSTRACT

Dressings have a part to play in the management of wounds; whether they are sutured or open, usually chronic wounds of many aetiologies which are healing by secondary intention. They traditionally provide a moist wound environment, but this property has been extended through simple to complex, active dressings which can handle excessive exudate, aid in debridement, and promote disorganised, stalled healing. The control of infection remains a major challenge. Inappropriate antibiotic use risks allergy, toxicity and most importantly resistance, which is much reduced by the use of topical antiseptics (such as povidone iodine and chlorhexidine). The definition of what is an antimicrobial and the recognition of infection has proven difficult. Although silver has been recognised for centuries to inhibit infection its use in wound care is relatively recent. Evidence of the efficacy of the growing number of silver dressings in clinical trials, judged by the criteria of the Cochrane Collaboration, is lacking, but there are good indications for the use of silver dressings, to remove or reduce an increasing bioburden in burns and open wounds healing by secondary intention, or to act as a barrier against cross contamination of resistant organisms such as MRSA. More laboratory, and clinical data in particular, are needed to prove the value of the many silver dressings which are now available. Some confusion persists over the measurement of toxicity and antibacterial activity but all dressings provide an antibacterial action, involving several methods of delivery. Nanocrystalline technology appears to give the highest, sustained release of silver to a wound without clear risk of toxicity.

Key words: Antiseptics • Chronic wounds • Silver • Silver Dressings • Wound Healing • Wound Infection

Key Points

- dressings have a major part to play in the modern management of wounds
- progress has been considerable during the subsequent 40 years from the introduction of passive through to active dressings with sophisticated additional therapies
- a major factor common to all wound care is the prevention of infection
- infection control is a contentious issue, particularly against a background of the continuous and expanding number of resistant organisms

INTRODUCTION

Dressings have a major part to play in the modern management of wounds, whether they are closed, sutured wounds of surgical or traumatic origin or open, usually chronic wounds of many aetiologies, healing by secondary intention. Since George Winter described the value of the prevention of scab formation to promote the epithelialisation of experimental superficial wounds by using a moist wound environment (1), there has been a progressive exponential increase in the numbers and types of dressings available in clinical practice.

Progress and development has been considerable during the subsequent 40 years from the introduction of passive through to active dressings with sophisticated additional therapies (2,3). Hydrocolloids, polyurethane films and foams and hydrogels were introduced for their exudate handling and ability to promote autodebridement, and alginates and collagen-based dressings for an alleged promotion of granulation tissue (4). Active biological dressings, such as skin substitutes, purport to orchestrate the disorganised stalled healing often found in chronic wounds (5,6) (e.g. Dermagraft and Apligraf), and the addition of growth factors (7) or removal of cytokines and proteases, most effectively by topic negative-pressure (vacuum assisted closure (V.A.C.)) therapy (8), has also found a niche in wound management.

The basic tenet of keeping open wounds moist by use of dressings has not been challenged clinically and is still widely observed, but wounds should be kept neither too moist nor too dry (9). This has been reviewed for the management of split thickness skin donor site care (10). Disappointingly, the research in this field is lacking in convincing evidence-based medicine (11,12). There is no panacean dressing, nor will there ever be, and it is difficult to offer

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convincing guidelines for open-wound management, which have to be based on changing expert opinion. Management of wounds with dressings must be combined with optimal local wound care, such as adequate compression in venous leg ulcers, appropriate arterial bypass surgery or angioplasty in vascular ulcers, and systemic care, such as attention to holistic medicine and general nutrition, although the value of the latter is also unproven.

A major factor, common to all wound care, is the prevention of infection. However, infection control is a contentious issue, particularly against a background of the continuous and expanding number of resistant organisms. Systemically administered antibiotics should be reserved for treating invasive infection, and topical antibacterials used for superficial, local management of an open wound surface (13). There are several dressings still available that are impregnated with broad-spectrum antibiotics, such as neomycin, polymyxin and mupirocin. They risk allergy and resistance (14), particularly if narrow-spectrum antibiotics are used, give poor topical delivery of the antimicrobial they contain, and do not work well in the presence of biofilms (15).

By contrast, topical antibacterials have been used for centuries and are still in widespread practice. Concerns about toxicity, or development of resistance to their antimicrobial qualities, have limited the use of some, but povidone–iodine, for example, is available in many different presentations for use as a topical antimicrobial (16). Its active iodine component is still the principal alternative antiseptic to the introduction, and current trend to the widespread use, of silver-impregnated dressings.

NEED FOR DEFINITIONS

Infection is the main cause of delayed healing in primarily closed (surgical) wounds, traumatic and burn wounds, and chronic skin ulcers. The recognition of a surgical site infection (SSI) is relatively easy when an incised wound presents with an extended, raised inflammatory margin (cellulitis) around the wound, sometimes associated with lymphangitis, raised local or systemic temperature and local pain (the Celsian signs of tumour, rubor, calor and dolor). It is not so easy to define in open, chronic wounds healing by secondary intention (17–20) (and has been the topic of a recent position document from the European Wound Management Association) (21). Even in the definition of SSI, there is a need for careful grading and assessment by a trained, validated, ideally blinded observer, particularly in research evaluation (22).

This overexpressed, inappropriate and uncoordinated inflammatory response relates to invasion of microorganisms through the normally intact resistant skin barrier. The bacteria release toxins and proteases, depending on their pathogenicity, which facilitates their spread. The host response, locally and systemically, may be overwhelmed, particularly in immunosuppressed patients, leading to bacteraemia, systemic inflammatory response syndrome, sepsis, organ failure or death. Infection may also be contained, as suppuration, or completely resolved depending on host response, bacterial load and virulence.

The measurement of the numbers of bacteria present in tissue (greater than 10^5/g of tissue) has been used to define burn wound infection (23). This needs to be substantiated further, for example a 10^3/g yield of *Streptococcus pyogenes* would probably justify therapy, and this definition of infection has not worked so convincingly in chronic wounds where biopsies, often serial, are needed. When there are clear clinical signs of invasive infection, systemic antibiotics are required. In the treatment of a diabetic foot, for example with osteomyelitis, treatment with systemic antibiotics may need to be intravenous and prolonged. Surrogates of wound infection include increasing pain, smell and level of wound exudate, which may indicate the need for antibiotics. When there are large numbers of multiple pathogens, and particularly when they increase in numbers, antibiotics should be considered (24–26). Certain pathogens when found in wounds, particularly the Lancefield Group A, β-haemolytic *S. pyogenes*, should always have antibiotic therapy prescribed to control them. The presence of a pseudomonad in an infected diabetic foot should also represent a firm consideration for systemic antimicrobial therapy. However, it is recognised that a sterile wound surface is not needed for the healing of a chronic ulcer. It is important that the definitions of the different antibacterials are agreed:

- An antiseptic is a broad-spectrum, antimicrobial, topical agent that ideally is not

Key Points

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- the recognition of a surgical site infection (SSI) is relatively easy when a incised wound presents with an extended raised inflammatory margin (cellulitis) around the wound, sometimes associated with lymphangitis, raised local or systemic temperature and local pain
- this overexpressed, inappropriate and uncoordinated inflammatory response relates to invasion of microorganisms through the normal intact resistant skin barrier
- when there are clear clinical signs of invasive infection, systemic antibiotics are required

Key Points

- because of cross contamination and the risk of MRSA (meticillin resistant *Staphylococcus aureus*) reservoirs developing in chronic wound beds, such as pressure sores, control of MRSA has become a major feature of wound care
- in relation to this some new definitions, although not accepted by all wound care practitioners, are appearing and leading to confusion
- all these terms need clear definition in any trial or in any guideline and are relevant in the evaluation of any new antimicrobial product
- the field of wound care and use of dressings have proved to be difficult in providing level 1 evidence, although, some progress is being made particularly with the newer types of advanced therapies
- the introduction of silver into wound care as an antibacterial, particularly in burns is relatively recent
- there is a growing number of silver dressings available and each preparation claims different advantages, the common effect to all perhaps being the antibacterial action of silver

toxic to tissues and may have the effect of promoting healing, but has a rapid, sustained effect on surface bacteria. Most antiseptics, such as chlorhexidine, povidone–iodine and silver, are rapidly deactivated by contact with tissues or body fluids and need to be used as a frequent wound or ulcer irrigant, or to have sustained release at bactericidal levels, in order to be effective in reducing surface bioburden of chronic wounds.

- A disinfectant has a broad-spectrum effect on all vegetative forms of microorganisms, including spores, but is usually toxic to tissues. Disinfectants are used therefore for sterilising surfaces, lavatories and feeding bottles. Some, the hypochlorites, have been used in wound care and effective chronic wound bed preparation prior to skin grafting but are mostly rejected for routine wound care. Fleming stated almost 90 years ago that antiseptics should preserve the host response, destroy bacteria, but should not be toxic to tissues (27). Disinfectants, the most well known being Eusol (Edinburgh University Solution of Lyme), should not be regarded as antiseptics.
- The definition of a chronic open-wound healing by secondary intention is more difficult to agree on, but a less than 20–40% reduction in wound area after 2–4 weeks of optimal treatment (28), an open wound that has not healed after 6 weeks, or a poor response to a treatment change is as good as any.

THE NEED FOR TOPICAL ANTISEPTIC THERAPY

In chronic wounds healing by secondary intention, there are always bacteria to be found colonising the surface. Some may be potential pathogens and their presence, and certainly their numbers, needs to be controlled. Clear examples are the β-haemolytic streptococcus already mentioned, and *Pseudomonas* spp., particularly in ulcers involving the diabetic foot. In addition to this is the inexorable rise in resistant pathogens, the major current concern being that of meticillin-resistant *Staphylococcus aureus* (MRSA) with its risks of bacteraemia, hospital or ward epidemics and their huge cost potential, and patient death if uncontrolled. Because of cross-contamination and the risk of MRSA reservoirs developing in chronic wound beds, such as pressure sores, control of MRSA has become a major feature of wound care. The UK has a much larger prevalence of MRSA than other Northern European countries, probably relating to management of surgical targets and ward work load, large numbers of acute admissions, and a relative lack of facilities for patient isolation or ward closures to aid eradication of colonisation, cross-contamination and infections ('search and destroy' techniques).

In relation to this, some new definitions, although not accepted by all wound care practitioners, are appearing and leading to confusion. The concept of bioburden has been introduced to describe the increased metabolic load imposed by multiplying bacteria in the wound bed, which are often present as multiple strains, and an ability to spread in tissues and produce toxins (15,29). Critical colonisation describes the bioburden as being at a level just below that which causes invasive infection (18,20,29). Critical colonisation is clearly more than superficial contamination or colonisation although all these terms are difficult to accurately define. The definition of infection by biopsy in burns has not translated well into chronic wound care.

In plastic surgery, wound bed preparation has traditionally meant the cleansing of an open wound for optimal take of a skin graft. This term has been borrowed to also imply preparation of a chronic wound by cleansing, antimicrobial therapy and debridement to an optimal state to facilitate its rapid successful closure by secondary intention (epithelialisation and contraction) (30–32). Hypochlorites are topical antimicrobials, some would say disinfectants as described earlier, which are used to prepare wound beds for grafting, but these have been rejected for routine chronic wound care (33).

Clearly, all these terms need clear definition in any trial or in any guideline and are relevant in the evaluation of any new antimicrobial product. There are many antibacterial-containing products already available, and to prove superiority for any product, randomised controlled trials are needed for evidence-based medicine. The field of wound care and use of dressings have proved to be difficult in providing level 1 evidence, although some progress is being made particularly with the newer

types of advanced therapies. Nevertheless, topical antibacterial therapy is an established part of chronic ulcer care and has an obvious advantage over topical antibiotics, which are difficult to deliver, have poor activity in biofilms, and often have a narrow spectrum and selectivity, as well as risks of allergy and the promotion of resistance (14,15).

THE INTRODUCTION OF SILVER DRESSINGS INTO WOUND CARE

Although silver has been used for centuries in water recycling and sanitisation, in complementary health care and to inhibit bacteria in food, the introduction of silver into wound care as an antibacterial, particularly in burns, is relatively recent. These historical issues have been well reviewed elsewhere (34–37). The use of silver nitrate to promote skin graft survival and the use in silver sulphadiazine (SSD) in the 1960s has also been previously reviewed (38,39). It is almost certainly the silver that is the antibacterial, as the attached sulphonamide has a narrow spectrum, which risks the development of resistance and allergy.

There is a growing number of silver dressings, which are already available and are presented as creams, foams, hydrogels, hydrocolloids and polymeric films and meshes. Each preparation claims different advantages, the common effect to all perhaps being the antibacterial action of silver. This latter characteristic is also being exploited in other medical devices (40). So is there a superior quality for each of these silver-containing dressings? Is silver an effective, safe antimicrobial, with perhaps even a stimulative effect on healing, or is it an elitist name for an ingredient in a new range of products?

THE ACTION OF SILVER

Elemental silver (Ag^o) appears to have no antibacterial action or ionic charge, whereas its cation (Ag^+) is highly reactive (34,41–42), particularly at a concentration between 5 and 40 mg/l (43), and its low concentration component means it retains efficacy even when dilute. Unlike antibiotics, silver is toxic to multiple components of bacterial cell metabolism. These include damage to the bacterial cell wall, and membrane permeability leads to gross cellular structural changes, blockage of transport and enzyme systems such as the respiratory cytochromes, alteration of proteins and binding of microbial deoxyribonucleic acid and ribonucleic acid to prevent transcription and division. Like other antiseptics, silver is soon inactivated by protein binding, but this inactivation can also be caused by tissues and anions such as chloride, phosphate and sulphide. It is probable that the presentation of an immediate large bolus of silver with sustained release promotes the speed of bacterial kill (37) and that rapid or sustained release of silver ions gives a wide spectrum of activity (44,45). Dressings that can sustain release of silver do not need to be changed so often, thereby representing a nursing management time benefit. A reduced number of dressing changes could affect positively a patient's quality of life, particularly in burn management.

Organisms do vary in their susceptibility to silver, but there is good evidence that silver has activity against the common pathogens, *S. aureus* and *Pseudomonas* spp., which are commonly encountered in chronic wound care. The newer dressings present silver ions differently from silver nitrate and SSD (46). These include forming unique Ag^+/Ag^o complexes by the use of nanocrystalline technology, or a high silver availability (Ag^+) through other means, to give a large and effective sustained bolus delivery (47,48). The development of resistance is unlikely, as it is with other antibacterials such as povidone–iodine, as the antiseptic actions affect at least three bacterial cell systems (37,49). Repeated exposure to low levels of silver may make resistance possible (29), and there is some in vitro evidence that this can occur (50). Certainly, resistance to some antiseptics has been described, for example to chlorhexidine (51), possibly through plasmid mediation. A risk of false resistance should be considered when there is prolonged wound contact time (52). Clinical evidence of bacterial resistance to silver ions, involving organisms cultured from chronic wounds, is awaited, but it would be inappropriate to discount that the possibility could occur.

Local staining by silver dressings does not appear to be a major complication and is usually temporary. This probably relates to sustained release and high bioavailability, which is furnished by many of the new dressings. Although the level of staining relates to the silver concentration presented by dressings

Key Points

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- organisms do vary in their susceptibility to silver, but there is good evidence that silver has activity against the common pathogens, *S. aureus* and *Pseudomonas* spp., which are commonly encountered in chronic wound care
- clinical evidence of bacterial resistance to silver ions, involving organisms cultured from chronic wounds is awaited but it would be inappropriate to discount that the possibility could occur
- there have been no consistent reports of silver allergy, unlike the use of topical antibiotics

Key Points

- evidence of the efficacy of silver contained dressings in clinical trials, judged by the criteria of the Cochrane Collaboration is lacking
- the choice of silver dressing still mainly relies for the most part on in vitro evidence and small clinical series
- some evidence exists that nanocrystalline technology can lead to the removal of or reduction in an increasing bioburden, critical colonisation, an infection in an open wound and burns, and has the potential to reduce reservoirs of resistant organisms or act as a barrier to cross contamination, for example in pressure sores colonised by MRSA
- there is a need for quantitative microbial counting in clinical practice
- industry led trials have used different organisms and methodology, which only leads to difficulty in interpreting comparisons between dressings
- a list of suggested methods is provided that should be used in dressing assessments

at the wound–skin interface, penetration into the tissues is small. This is more likely with the use of silver nitrate (53). Systemic toxicity, argyria, is unlikely as absorption from dressings is so small and probably depends on wound size (54). This systemic risk is probably overstated, just as the risk of thyroid disorder is after the use of povidone–iodine in chronic wounds (16). Nevertheless, argyria may theoretically result when there is a very large open wound and dressings that release large amounts of silver ions are used. There have been no consistent reports of silver allergy, unlike the use of topical antibiotics, such as neomycin, and some other antiseptics.

EVIDENCE FOR THE USE OF SILVER DRESSINGS

There are already a large number of silver-containing dressings, and the list is growing (55,56). Evidence of their efficacy in clinical trials, judged by the criteria of the Cochrane Collaboration, is lacking (57,58). More reviews of efficacy can be expected, which will beg the need for powered, randomised, controlled clinical trials. The lack of level 1 evidence is balanced, to some extent, by in vitro, experimental and small clinical cohort studies, some of which have been industrially sponsored and a few having been comparative (42). The choice of a silver dressing still mainly relies, for most products, on this in vitro evidence and small clinical series (15).

Some confusion about toxicity has resulted, which has involved cell culture systems and donor-site wounds (59,60), and even the possibility that silver may promote healing (61). Some attempts have been made to measure silver content and silver release, as well as cost-effectiveness (18,62); the silver dressings do come at a relative premium. If the silver dressings are toxic to healing tissues in clinical practice, or cannot be shown to promote aspects of healing in stalled healing of chronic wounds, then perhaps they should be reserved for treating open wounds, which have an increasing bioburden with critical colonisation. This in turn depends on whether this can be defined and certainly will need clear guidelines for the definition of colonisation, which may progress to infection. The current indication for most silver dressings is in acute and chronic open-wound management, burns, and for the preparation of a wound bed for skin grafting; some evidence exists that nanocrystalline technology can lead to the removal of or reduction in an increasing bioburden, critical colonisation and infection in an open wound and burns, and has the potential to reduce reservoirs of resistant organisms or act as a barrier to cross-contamination, for example in pressure sores colonised by MRSA.

MEASUREMENT OF ANTIBACTERIAL ACTIVITY

The promotion of antibacterial activity is a key feature of the marketing of all silver dressings (63), but the evidence of antibacterial efficacy in clinical wounds is still, to some extent, speculative (64). There is a need for quantitative microbial counting in clinical practice, although this has been used in experimental wounds (65) and extensively in infected burns (23). This has not become consistently used or reproducible in trials involving chronic wounds such as leg ulcers or pressure sores. This research can cause difficulties for Local Research Ethics Committees and does require exceptional patient compliance. There is little doubt of the antibacterial properties of silver but industry-led trials have used different organisms and methodology, which only leads to difficulty in interpreting comparisons between dressings. In addition, it has to be asked if these in vitro laboratory findings can be extrapolated to clinical use. The levels of silver ion released by dressings in vitro have been measured and presented in several ways (29), which can be confusing, and it has been suggested that several of these methods should be used in dressing assessments:

i) Expression of silver concentration as parts per million (ppm) has been used and 5–50 parts of silver per million is toxic to most bacteria (66). Acticoat, Aquacel Ag and Silvasorb deliver concentrations of 1–100 ppm (14).

ii) Minimum inhibitory concentrations (MIC) are more conventional units, and MIC levels of 30–40 mg/l of silver are microbicidal (67). Levels of up to 50–100 mg/l have been reported to be released from nanocrystal-impregnated silver dressings into water (68). Minimum

bactericidal concentration has been used in connection with concentrations required to prevent mutants (66).

iii) Zones of inhibition (ZOIs) have been used around dressings placed in agar plates. The nanocrystalline technology associated with Acticoat dressings was effective using this measurement against *S. aureus*, *Pseudomonas* and *Candida* (52,67), but good ZOIs have been reported in other publications, which tested Acticoat, Aquacel Ag, Arglaes, Contreet, Silvalon and Silvasorb dressings but with varying efficacy (55,56,67,69).

iv) Other studies have used a $\log^{10}$ reduction in bacteria to assess microbicidal activity. A 10^3 reduction is considered to confer microbicidal levels, but exposure times of dressing to bacteria need to be stated (55,56). Similar reductions in bacterial counts have been used by measuring colony forming units/ml (70).

Silver dressings are bactericidal and fungicidal, and importantly they are effective against resistant organisms or known pathogens such as MRSA and *Pseudomonas* (42,44, 52,66,71). Increased or maintained wound temperature, which is associated with fewer dressing changes, and alkaline pH enhance this antimicrobial activity. Nanocrystalline dressing technology is probably the most effective at achieving this (34). The silver ion is bactericidal through the several mechanisms described earlier, but silver nitrate is poor for antibacterial action as it needs repeated applications due to the inactivation of silver by the constituents of exudates and is painful (20). The action is enhanced by combination with a sulphonamide (SSD), although it is still probably the silver ions that are the most active bactericidal component. SSD is messy to use, and the need for pseudoeschar removal increases nursing time, which may also need extra facilities such as hydrotherapy (72).

Using silver dressings as a barrier to cross-contamination by resistant organisms such as MRSA and other multiple resistant isolates is also an attractive prospect (47). The rise of MRSA in the increasing incidence of health care–associated infections appears to be unstoppable as it is now independently found in primary and secondary health care, in addition to cross-contamination. Nanocrystalline silver dressings offer a barrier to MRSA in addition to prevention of cross-contamination (73). Infection control is expensive, so this use of silver dressings for barrier function has potential, for vulnerable patients in intensive care or the elderly in nursing homes (48).

SUMMARY OF RESULTS OF IN VITRO LABORATORY STUDIES OF BACTERICIDAL DRESSING PROPERTIES

The various silver dressings are claimed by their manufacturers to have specific properties, which are addressed in Appendix. High silver ion concentration and sustained release at the wound interface are claimed by nanocrystalline silver technology produced by the sputter technique, which has been well described (36) (Acticoat, Smith and Nephew). Other dressings are claimed to give microbicidal levels of silver once microorganisms are absorbed with wound exudate into a dressing, which also has additional properties such as odour or exudate control (Aquacel Ag, Convatec; Actisorb silver, Johnson and Johnson; Contreet Foam, Coloplast). Using the techniques of ZOI, microbial transmission and log 10^3 bacterial reduction, most of 14 silver dressings being tested were found to be effective antibacterial agents (55,56). The high antibacterial effectiveness of nanocrystal technology (74) has also been shown against MRSA and vancomycin-resistant enterococci, *Pseudomonas* spp. and fungi in other studies (36,45,47). Dressings such as Calgitrol (Biomedical Technologies) with silver concentrated on the surface of the dressing also seem to do well in these vitro studies, whereas dressings such as Silvalon (Argentum, Keomed) and Contreet Foam (Coloplast) with high silver content in the dressing are less effective. However, in vivo, it may be that the dressing-contained, not dressing-surface, silver dressings may be just as effective. It is the extra fluid handling (or use for wound 'wicking') of some dressings, such as Aquacel Ag and Contreet Foam, that is as important (67,75,76), or the ability to use silver dressings with other active

Key Points

- it is important that test methodologies, and the origin of test bacterial strains, are clear so that clinicians can compare like with like and understand that further evidence is required to allow extrapolation of laboratory findings to the perceived difficulties associated with delayed healing in chronic wounds

Key Points

- there is a fear that all antiseptics are toxic to human tissue and there should be no expectation that silver ions in high concentration would be non toxic
- once a chronic wound bed is clean and in a healing phase, on balance, other non antiseptic dressings should be considered that carry no risk of toxicity
- testing the antibacterial action of silver ions not only depends on testing in vitro but also in experimental wounds that are infected
- several studies have shown that some clinical advantages are associated with the use of silver dressings but these can be at best, only recommendations
- even the more acceptable published work is mostly case series and is usually non-comparative or retrospective and possibly flawed thereby

dressings such as fibroblast-derived dermal substitute (77).

Although nanocrystalline silver technology was found to have the highest and most sustained silver release, another comparative in vitro study has suggested that other silver dressings (Aquacel Ag and Acticoat) had the best antistaphylococcal and anti-*Pseudomonas* effects (67). This study compared seven dressings using a simulated wound fluid model, which tested the activity of silver dressings against *S. aureus* and *Pseudomonas aeruginosa*. This finding has been sustained in further studies (14,69,78), but not by others (68), or with mixed findings (70). In this latter study, a broth was used for the experiment in which Acticoat and Contreet Foam (which was the most rapid) gave the best results. It was alleged that, in addition to activity against MRSA and other pathogens, these silver dressings were also more effective against Gram-negative organisms. A further study has shown that SSD and chlorhexidine were more effective bactericidally than silver dressings (79). It is important that test methodologies, and the origin of test bacterial strains, are clear so that clinicians can compare like with like and understand that further evidence is required to allow extrapolation of laboratory findings to the perceived difficulties associated with delayed healing in chronic wounds.

TOXICITY OF SILVER

Most of the studies that have looked at toxicity have also been undertaken in vitro or in experimental wounds. There is a fear that all antiseptics are toxic to human tissue (27,33,80), and there should be no expectation that silver ions in high concentration would be non toxic. In very general terms the more silver that is available for microbicidal purposes, the more it is toxic to host tissues, but in most of these experimental studies, the microenvironment of a healing wound is not reproduced. For instance, the frequency of dressing change and the ability of the dressings to handle exudate cannot be taken into account. However, it seems irrational that silver dressings would be used in the management of wounds that were not infected, that had a low bioburden or in which there was no clinical suspicion of delayed healing related to the presence of microorganisms.

Although protective against *Pseudomonas*, nanocrystalline dressings appeared to be as safe as a control in cultured skin substitutes in athymic mice, whereas in vitro the same dressings had been found to be toxic (81). This in vitro toxicity has been confirmed in other studies using cultures of keratinocytes and fibroblasts, and also in a clinical study of donor sites:

- in monolayers or bilayers with a three-dimensional lattice, or in the collagen lattice contraction model incorporating equine fibroblasts (60,82)
- in human keratinocyte culture, with a caution for use on cultured skin grafts (83), although this was a non comparative, relatively poor study
- in a study of 17 clinical donor sites, nanocrystalline silver dressings were found to be toxic, but these wounds had a non existent bioburden and the dressings used were soaked, not moist, which could have caused problems with overhydration of the wound surface and maceration of the surrounding healthy skin (59).

To the contrary, there are studies that suggest silver is not toxic or even promotes healing. For instance, silver nitrate may cause staining but has been found to be proinflammatory (84). It has also been claimed that nanocrystalline silver dressings reduce metalloproteinases (MMPs) or total proteases in wounds through their direct antibacterial activity, and may even encourage optimal patterns of healing, through apoptosis and reduced inflammation (36). Similar results were obtained in another study confirming the antibacterial action of silver against *Pseudomonas* and staphylococci with promotion of granulation tissue but with reduction of MMPs and promotion of apoptosis (61). Although SSD and nanocrystalline silver dressings were found to be non toxic to keratinocytes, the addition of chlorhexidine was toxic (79,85).

It seems pointless using an antibacterial dressing, including the silver dressings, in the management of an open wound when there is no suggestion of infection or even when there is a minimal bioburden. Once a chronic wound bed is clean and in a healing phase, on balance,

other, non antiseptic dressings should be considered that carry no risk of toxicity.

EXPERIMENTAL AND CLINICAL EVIDENCE IN FAVOUR OF SILVER DRESSINGS

The antibacterial effect of silver that has been assessed in clinical studies is convincing (61,83,86–88). In addition, nanocrystalline silver dressings have been shown to improve survival in infected experimental models (65), including a rat-burn sepsis model (87), and to reduce the need for frequent dressing changes (86). Testing the antibacterial action of silver ions not only depends on testing in vitro, which has been described earlier, but also in experimental wounds that are infected, or in the presence of organic material such as proteinaceous exudate or inorganic ions such as chloride, sulphate and phosphate.

Most clinical studies included small numbers of patients and are non comparative studies. There are four main groups of dressings that contain silver and have been assessed in clinical studies (54):

- nanocrystalline silver dressings (Acticoat), which release a high sustained level of silver
- dressings that absorb fluid and exert the action of lower levels of silver contained within the dressing, for example Actisorb silver and Aquacel Ag
- dressings that do both, such as Contreet Foam, which is alleged to optimise a high concentration of silver at the wound surface, with sequestration of bacteria from the wound and further exposure to silver within the dressing
- dressings that release a silver compound rather than silver ions, such as Urgotul, which releases SSD at lower levels than from the cream base.

Several studies have shown that some clinical advantages are associated with the use of silver dressings, but these can be, at best, only recommendations. Many case reports have been presented and published but have not been included in this review because of their anecdotal and often skewed interpretations. Even the more acceptable published work is mostly of case series and is usually non comparative, or retrospective, and possibly flawed thereby. None of these studies has been adequately powered, and follow up is invariably short (rarely more than 4 weeks) and has used many surrogates of healing rather than complete wound closure.

Nanocrystalline silver technology dressings had favourable results in an audit involving burns in 70 patients, in whom less instances of cellulitis and antibiotic use were reported (89). Other non comparative studies have shown safety and clinical benefits, such as less pain in burns (90,91). Advantages were also reported, using this type of dressing, in a prospective series of 29 patients with chronic wounds, who were found to have less pain (92). A further study, in which nanocrystalline silver dressings were compared against topical antibiotics in 20 patients who had meshed skin grafts, showed that the dressing group had better epithelialisation of their grafts (93). There were similar results in 14 burns patients when nanocrystalline silver dressings were compared with SSD(94), and a retrospective study involving 20 patients that showed that nanocrystalline silver dressings were better than SSD in preventing MRSA colonisation of burn wounds (95). It was suggested that these novel dressings can act as a barrier in a study of 10 patients who had MRSA-colonised chronic wounds (73). Similar results have been reported by others involving 30 patients with chronic diabetic and ischaemic ulcers that were treated simultaneously with human fibroblast–derived dermal substitute (77). The clinical antimicrobial effect of nanocrystalline silver technology, compared with silver nitrate, has been explored in a randomised trial of 30 patients with burns. The dressings were judged to be easy to use with less pain, reduced infection measured by using biopsies and a reduced incidence of bacteraemia (68).

Aquacel Ag has also been found to be effective, in terms of wound management attributes, in a limited series of small clinical studies of burns. In a phase II non comparative study of 24 patients, 22 evaluable, with mid-thickness burns, Aquacel Ag was alleged to have conformed well, with ease of use (96). Similarly, in 30 patients with stalled healing of chronic, mixed venous, diabetic or pressure ulcers, the use of Aquacel Ag was found to decrease ulcer size and exudate, to be associated with less pain and to improve granulation tissue quality over a 4-week study period (76).

Key Points

- as silver dressings are currently gaining in widespread clinical use, it may be hard to justify the required, randomised, controlled clinical trials
- dressings containing the nanocrystalline form of silver appear to have the best evidence of consistency in relation to clinical outcomes
- nanocrystalline silver containing dressings significantly reduce the bacterial burden in chronic wounds, and this antibacterial barrier property may prove beneficial in the prevention of cross infection, of MRSA in particular in both the acute an community sectors
- there may be further benefit for the reduction of infection in the use of antibiotics in the management of burns

Another study found that the wound area of 18, 15 evaluable, chronic ulcers of mixed aetiology was reduced following the allegedly safe use of Aquacel Ag, but there was no significant reduction in bacterial levels in the wounds (97).

Several studies have testified to the successful use of Contreet Foam dressings. In 25 patients with leg ulcers, in a non comparative study, it reduced ulcer area and was found to be safe with good fluid handling capabilities over a 4-week period (98). In another 6-week comparative study against Biatain, it was found to be superior in treating diabetic foot ulcers (99). A randomised, but not powered, multicentre study showed that Contreet Foam was more effective than a non silver foam in critically colonised chronic venous ulcers. In the 4 weeks of study, the Contreet Foam-treated ulcers significantly decreased in size with better odour control, fewer leakages and maceration and longer wear times (100). This study has been analysed by another group of authors for efficacy, efficiency and effectiveness, and they concluded that Contreet Foam may provide benefit for the treatment of critically colonised wounds (18). From the same manufacturers has come a new dressing, a silver-containing, polyester–carboxymethyl, cellulose–petrolatum surface dressing. Similar findings of reduction in bacterial colonisation were found in a non comparative study of 30 patients (101).

Activated charcoal–silver-containing dressings have also been assessed in chronic wounds and to lead to bacterial reduction over 2 weeks (102). In a larger, but not powered, comparative study, Silvercel was compared against Algosteril in 99 patients from 13 centres (103). The recruited patients' chronic venous and pressure sores, in the silver dressing group, had less associated clinical infections that required antibiotics therapy over the relatively short 14-day period of observation.

CONCLUSIONS

The evidence base for the use of silver dressings in clinical practice is poor. Randomised controlled trials are available, but few in number. Multicentre studies, which could address this lack of evidence-based medicine, with adequate numbers, strict definitions and prolonged follow up by trained, unbiased (ideally blinded) observers would be prohibitively expensive with a considerable time to undertake. There seems little point undertaking more laboratory-based in vitro studies of the antibacterial qualities of silver dressings, or of their toxicity, unless a new dressing is introduced and needs to have its qualities measured against dressings already in clinical practice. These antibacterial and toxicity studies are well developed with reproducible data, but they are of level III importance, or less, but do represent a piece of the jigsaw. There appears to be some in vitro toxicity associated with the silver dressings, but it is important to reiterate that it is probably pointless to use silver dressings clinically once they have reduced or abolished infection, a heavy bioburden, or critical colonisation and good-quality granulation tissue has been formed. The evidence that they may promote healing does bear further laboratory, and clinical, investigation.

As the silver dressings are currently gaining in widespread clinical use, it may be hard to justify the required, randomised controlled clinical trials. It seems that nanocrystalline, silver dressing technology achieves the highest silver concentration of the modern silver dressings with sustained release in vitro. It must be borne in mind that the level of silver released, by all the new dressings, is less than that reached by application of SSD cream, which has been judged to be safe and effective by the regulatory authorities since 1968. A properly powered clinical trial is needed to justify the extra cost, clinical superiority or equivalence and safety of silver dressings against an established antiseptic such as povidone–iodine. As long as silver dressings have continued popular use such a trial is not likely to be initiated, unless undertaken independently without sponsorship.

The extrapolation of laboratory findings direct into clinical practice should be undertaken with caution. Clinical wounds are complex, in which many cascades involved in wound healing overlap, or may be out of synchronisation. The clear benefits of the antimicrobial effects of silver dressings must be weighed against their possible cytotoxic effects (81). This is precisely why current evidence suggests they should only be used for wound bed preparation, and once the bioburden is

reduced to a level to encourage healing, then the silver dressings should give way to less expensive maintenance dressings. In 'clean' wounds (59) or in the sterile environment of tissue culture (60), silver may be toxic.

The colonisation of open wounds by resistant organisms, the rise of community-acquired MRSA in particular, may offer another potent use for silver dressings. Nanocrystalline silver dressings could act as an antimicrobial barrier and help reduce the risk of cross-contamination, which has been suggested by many authors (47,48,52,68,70,73,87).

It has been alleged that silver dressings do need to be combined with a complementary secondary dressing for optimal performance, for fluid or exudate handling, for example. Some silver dressings do already have this function incorporated into them, such as Acticoat absorbent and Moisture Control, Aquacel Ag, Contreet Foam and the silver hydrocolloids and hydrogels. Others, such as Actisorb silver, have an in-built odour control. The dressings are listed in the appendix. It is apparent that few products have consistent bench-to-bedside evidence for use in either chronic ulcers or acute burns. Dressings containing the nanocrystalline form of silver appear to have the best evidence of consistency in relation to clinical outcomes. Nanocrystalline silver-containing dressings significantly reduce the bacterial burden in chronic wounds, and this antibacterial barrier property may prove beneficial in the prevention of cross-infection, of MRSA in particular, in both the acute and community sectors. There may be further benefit for the reduction of infection and the use of antibiotics in the management of burns.

This review is the unbiased opinion of the author and is based on a review of relevant evidence found on Medline and Embase and may therefore be considered to be peer-reviewed evidence. It has not included any published case reports or Symposium Proceedings.

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Key Points

- this review is the unbiased opinion of the author and is based on a review of relevant evidence found on Medline and Embase

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APPENDIX

Current list of silver dressings (in alphabetical order)

Acticoat	Smith and Nephew
Actisorb silver	Johnson and Johnson
Aquacel Ag	Convatec
Arglaes	Medline Maersk
Avance	SSL
Calgitrol	Biomedical Technologies
Contreet Foam	Coloplast
Physiotulle	Coloplast
Polymem	Ferris
Silvasorb	Acryl Med
Silvercel	Johnson and Johnson
Silverlon	Argentum, Keomed
Tegaderm Ag	MMM
Urgotul	Urgo Laboratoires