The silver debate:
a new consensus on what constitutes credible and attainable evidence

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Foreword

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The current controversy surrounding silver dressings is symptomatic of a greater issue in wound care. Following publication of systematic reviews and clinical trials that have raised doubts about the efficacy of silver dressings and other devices such as negative pressure systems, attention has focused on the high costs of these treatments. It is clear from feedback in the UK and elsewhere in Europe that all expenditure on wound treatments is coming under scrutiny from reimbursement agencies, purchasers and procurement managers. At the heart of the silver debate is concern about the quality of the evidence and, in turn, the cost effectiveness of silver dressings, based on their unit costs and healing times, with quality-of-life issues being overlooked. As a result, clinicians wishing to achieve the best possible clinical outcomes will find they need to base patient care on a realistic appraisal of the evidence and a great deal of pragmatism.

This supplement has been commissioned to clarify the issues relating to the silver debate and describe current thinking on them. The existing evidence is reviewed in order to demonstrate its breadth and highlight that the evidence needs to be commensurate with the regulatory class of the product. To this end, it is important that we reach an accord on what evidence is realistic and attainable for wound care. While the evidence on silver does not meet the criteria of the Cochrane-style systematic review, it cannot be ignored as wholly inadequate. Indeed, the picture is changing rapidly, with many new articles adding to the evidence base.

Alternative assessment methodologies, such as that used in the GRADE system, include all of the available evidence, not just a selected portion as is the case with meta-analyses. In order to address the issues relating to the clinical use of silver and other topical antimicrobial dressings, a group of experts has recently published a Best Practice Statement, compiled in accordance with the AGREE standards. The Best Practice Statement is the first step in an ongoing process of providing clinical guidance on the preferred use of wound products and merits the support of the industry and clinicians. It also goes a long way in promoting good dressing usage — that is, putting the right dressing on the right wound/patient at the right time and circumstances — which, in itself, will start to control the use of wound products and the associated spend. For this reason, this type of exercise should earn the support of Medicines Management as part of their efforts to control wound care expenditure. Indeed, this is the topic of the second article in this supplement, which sets the scene for the appropriate use of silver dressings.

This supplement clearly describes the issues relating to the silver debate. In doing so, the current situation is made clear: if patients are to receive safe, effective and cost-effective wound care, then these issues must be addressed and settled to the satisfaction of all concerned. The key messages are that silver dressings must be used appropriately, that quality of life is a key factor in wound care, and that all of the available evidence must be considered before issuing recommendations on clinical usage. We must endeavour to convince those responsible for purchasing that the unit cost of dressings and devices cannot be the only criterion that influences wound care practice, and that it should not be considered in isolation of the risk of increased morbidity and mortality.

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4 http://www.agreecollaboration.org/
Why use topical antiseptics?

Not all wounds heal in a timely fashion at an expected rate. In many cases, this delay in healing occurs because an infection is present. In some cases, the infection manifests as a wound biofilm, with the wound developing a subtle form of inflammation. In such instances, topical treatment with antiseptics is warranted. This article describes when they need to be used.

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The pathogens responsible for wound infection delay healing by destroying viable tissue cells. They also attract polymorphonucleocytes (PMNs) to the wound, which express enzymes that destroy invading microbes and, in turn, ‘digest’ viable tissue cells. While systemic antibiotic therapy is indicated for established skin infections, the increase in antibiotic resistance has led to a resurgence of interest in topical antiseptics in wound care. However, there is always a risk that topical antiseptics may be used inappropriately or misguidedly. Lipsky and Hoey neatly summed up the current position: ‘Various agents [topical antimicrobials] have been applied topically to treat infected wounds for millennia, but their proper role remains unclear’. This article seeks to clarify when topical antiseptics should be used in wound care.

The complexity of healing

Some wounds heal in a timely fashion; others require a longer, sometimes inestimable, period to heal; a smaller group still never achieve closure. There are many reasons why wound healing may be delayed: these may be patient related, practitioner related, resource related and wound/biological related. The biological factors are listed in Table 1.

The economic, social and quality-of-life consequences of delayed healing are high. The estimated cost of wound care to the NHS is between £2.3 billion and £3.1 billion per year, from a NHS budget of £110 billion per year. Wounds are costly in other terms. While quality of life is an abstract concept that is difficult to measure, the tangible effects include financial hardship and social and psychological challenges.

Diagnosis of wound infection

One of the stumbling blocks in the efficient management of infected/at-risk wounds is not being able to diagnose the infection accurately. To provide direction in the quest for an accurate diagnosis of wound infection, it is suggested that wounds are not viewed as a homogenous entity but from a heterogenous perspective. In essence, the practitioner must first classify whether the wound is acute or chronic. By definition, acute wounds have a short duration — that is, they are newly formed lesions in which healing should progress in a timely fashion (i.e. at an expected rate) provided that the wound remains in a healthy state. The health of a wound can be assessed on clinical grounds as ‘healthy’, ‘unhealthy’ (because of infection) and ‘unhealthy’ (for other reasons). Harding et al. described a healthy healing wound as ‘neither inflamed nor inert in appearance, not painful or tender

Table 1. Biological factors associated with delayed healing11

- Microbial numbers / pathogenicity / virulence / synergy
- Granulation tissue defects
- Inflammatory mediators / human and bacterial toxins
- Senescent neutrophils
- Tissue hypoxia
- Metabolic wastes
- Reduced fibroblasts / collagen production
A healthy wound that has closed by primary intention should remain closed and not dehisce. In an acute wound healing by secondary intention, the healing rate can be predicted, but only in some wound types, such as pilonidal sinus excisions, and abdominal and axillary wounds. The edges of epithelialising wounds should advance by approximately 5mm each week.

The term ‘chronic wound’ is widely defined as wounds that do not heal in a timely fashion, but this is of limited value clinically as it relies on retrospective judgement and does not give any insight into why healing was delayed. If healing is stalled and the wound is considered unhealthy for reasons not associated with infection, then the factors outlined in Table 1 need to be addressed. It is not within the scope of this paper to discuss these in detail.

As we have not yet arrived at a universally accepted definition of wound infection, how to

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**Figure 1. The states of colonisation and infection**

<table>
<thead>
<tr>
<th>Wound bioburden</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonised</td>
<td>Infected</td>
</tr>
<tr>
<td>Sub-clinical</td>
<td>Clinical</td>
</tr>
<tr>
<td>Biofilm</td>
<td>Local infection</td>
</tr>
<tr>
<td>Climax community, polymicrobial, suppressed immune response</td>
<td>Classical signs, rubor, tumor, calor, dolor</td>
</tr>
<tr>
<td>Local infection</td>
<td>Local infection</td>
</tr>
<tr>
<td>Subtle Signs</td>
<td>Spreading infection</td>
</tr>
<tr>
<td>e.g. acute cellulitus, bacteraemia, septicaemia</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2. Indications for wound specimen collection for microbiological analysis**

- Acute wounds with signs of infection
- Chronic wounds with signs of spreading or systemic infection
- Infected chronic wounds that have not responded to or are deteriorating despite appropriate antimicrobial treatment
- As required by local surveillance protocols for drug-resistant microorganisms

* in patients with signs of sepsis blood cultures are important, and cultures of other likely sites of infection should be considered.
† Also consider for high-risk chronic wounds with signs of localised infection, e.g. delayed (or stalled) healing, in patients who have diabetes mellitus or peripheral arterial disease, or who are taking immunosuppressants or corticosteroids
diagnose infection in all wound types is still the subject of debate. While the criteria for diagnosing surgical site infection are established, opinion still differs on what constitutes (accurate) clinical signs of infection in other wound types. Furthermore, (cost) effective treatment is reliant on accurate diagnoses. Here, simplicity is the key. To avoid the scepticism that surrounds the postulated prodromal phase of infection (critical colonisation), this article will use more clinically and microbiologically meaningful terms: colonised (healthy) and infected (unhealthy) wounds. The model is applicable to both acute and chronic wounds.

**Wound infection**

Prior to colonisation, a wound is considered to be contaminated when it harbours transient microorganisms. Contaminating bacteria are considered to be in a planktonic (non-attached) phenotype and so are highly susceptible to removal/eradication. In the subsequent phase of colonisation, the bacteria assess the local environment using chemical receptors on their cell wall and then express adhesins if the signals received promote attachment. At this stage the bacteria are still considered to be in a reversible state of attachment and can be easily sluiced from the wound surface. The wound, therefore, remains ‘healthy’.

However, if the wound microenvironment favours microbial growth, the bacteria enter an irreversible state of adhesion. Here, the bacteria firmly attach to the wound, express extracellular substances and become encased within an extracellular polymeric substance (EPS). The bacteria have now altered their phenotypical state from planktonic (free floating) to biofilm (sessile or attached). The biofilm bacteria now begin to proliferate and, over time, the wound microbiology becomes more complex, with the numbers of microbes in the developing community reaching a critical level. The wound has now become ‘unhealthy’. The point at which the community reaches its critical level is specific to each individual wound, the patient and the microbial species present, and so no one critical level can be considered universal for all wounds. As a state of colonisation is the ‘accepted’ norm, the reason for the delay in healing is more likely than not to be microbial in origin.

Figure 1 denotes the states of colonisation and infection and proposes that the state of infection may exist at both sub-clinical and clinical levels. This state of sub-clinical infection is considered to be synonymous with that of biofilm infection. An increasing wound bioburden will not necessarily induce a host response if the bacteria are in a sessile (attached) state. This supports the concept of sub-clinical infection. In some cases, it is necessary to take a specimen for microbiological analysis. It is not possible to cover this in full here, but a brief indication of when this is necessary is given in Table 2.

**Treatment options**

If non-infection-related causes of delayed healing have been ruled out, then active treatment is required, irrespective of whether or not there are any clinical signs of infection. Topical antiseptics are commonly used in wound care. However, their safety and efficacy are the source of some discord, with Cochrane reports and a randomised controlled trial offering little or no support for their use. The reasons for this are unclear but overzealous interpretation of research results, unrealistic expectations, misuse, peer pressure and locus of control have been suggested. Others have adopted a more pragmatic approach that takes into account various forms of evidence, including empirical evidence.

Nevertheless, it must be acknowledged that there is little robust evidence on the efficacy/cost effectiveness of topical antiseptics in wound care. However, the in vitro spectrum of activity of antiseptics exceeds that of antibiotics and antiseptics are therefore effective against a wide range of infectious agents. While antiseptics have been shown to be cytotoxic in vitro, close examination suggests that the in vivo relevance of this is limited. However, microbial resistance to antiseptics has been reported in vitro. Bacterial spores, mycobacteria and Gram-negatives demonstrate intrinsic resistance, and plasmid-mediated resistance to antiseptics has also been observed, but this appears to be more relevant to mercuric compounds and other metallic salts.

The shrewd use of topical antiseptics may lower our dependence on antibiotics, thereby limiting their use to demanding clinical events. The use of topical antiseptics in wounds with chronic inflammation (biofilms) that have not responded to ‘traditional’ antimicrobial intervention (antibiotics) is justified. Medicated dressings in which the active agent comprises a solution released at clinically relevant concentrations over time can help to control the wound bioburden. Furthermore, these dressings can also help to reduce the risk of cross contamination and therefore support infection control measures. Guidelines based on high-qual-
ity clinical evidence are urgently required.

Topical antiseptics have a valid role to play both in managing clinically infected wounds\(^2\) and wounds at risk of infection.\(^19\) Their role in prophylaxis is more controversial, although they have been shown to reduce morbidity and mortality in severe burns.\(^31\) While empirical observation suggests that the prophylactic application of topical antiseptics is widespread, it is accepted that their extended use is contrary to good clinical practice.\(^32\)

**The way forward**

This paper has discussed the process of microbial wound colonisation and has linked this to potential infection. If these colonised wounds are considered ‘at risk’, is it now time to reconsider who is the ‘at risk’ patient? Should we now consider a recognised prophylactic role for topical antiseptics on the basis that ‘prevention is better than cure’? In the past, prophylactic use was not encouraged because of the risk of increased dressing expenditure plus selection for resistance. The case for widespread antiseptic resistance is not proven.

In these circumstances, the reaction is sub-clinical in nature.\(^71\) Consequently, these wounds still require active intervention as biofilm infected wounds are nonetheless predisposed to develop a subtle form of inflammation. As we learn more about wound biofilm manifestations, it is likely that we will learn to visualise clues of their presence.

Based on the at-risk patient and the above sub-clinical infection proposal, active intervention with topical antimicrobials has the potential to contain patient care costs, reduce clinician time and improve quality of life by reducing patient morbidity.

**References**

While cleansing with uncontaminated saline, or even tap water, at dressing change is effective,¹,² it is also logical to consider using a topical antimicrobial, particularly if critical colonisation or local infection is present or it is necessary to reduce the bioburden as part of an antibiofilm strategy.³ A wide range of antimicrobials is available:

- Chlorhexidine, in the form of solutions and impregnated dressings
- Povidone-iodine, in the form of solutions, sprays and slow-release dressings (eg. cadexomer iodine)
- Silver, in the form of ionic silver contained in dressings (including nanocrystalline dressings)
- Polyhexamethylene biguanide (PHMB), in the form of solutions and impregnated dressings (polyhexanide)
- Hypochlorite, in the form of several eponymous solutions (EUSOL, Milton, Dakin’s)
- Triclosan, in the form of solutions and coated/impregnated sutures
- Honey and sugar, either as a direct application or incorporated into dressings
- Hydrogen peroxide, in the form of solutions and creams
- Acetic acid, which is thought to have an effect on *Pseudomonas* spp.
- Potassium permanganate, a solution that is claimed to reduce exudate levels.

Despite this wide choice, the routine use of antimicrobials in wound care is more likely to occur in a hospital environment.

This article describes the advantages and disadvantages of these antimicrobials, with a focus on silver dressings.⁴

Antimicrobials: advantages and disadvantages

Many will regard some of antimicrobials listed above as primarily of historical interest. To avoid any confusion over definitions, in this article the term ‘topical antimicrobial’ is synonymous with antiseptics. It is also assumed that antibiotics are reserved for systemic use (never topical) and disinfectants are used to sterilise instruments and cleaning surfaces, infants’ feeding bottles and toilets.

Eusol went out of fashion because of fairly convincing experimental data showing unacceptable toxicity to host tissues. It may be useful in short-term wound bed preparation prior to split-thickness skin grafting as it is a chemical debrider of superficial, non-viable tissue, adherent bacteria and slough. However, this would be at the expense of damage to underlying healthy granulation tissue.⁵

Povidone-iodine and chlorhexidine have been used for many years for hand cleansing, skin preparation and on open wounds. Their use has been reviewed many times,⁶-¹⁰ with generally supportive findings.

Honey, particularly Manuka, is claimed to have antimicrobial activity but no clinical trials that are scientifically acceptable in terms of power, randomisation or defined outcomes have found it has clear benefits over other topical antimicrobials.¹¹

An overview of the evidence on the efficacy of silver dressings

While there is a plethora of clinical and anecdotal evidence on the efficacy of silver dressings, there is no rigorous RCT data to support this. This has led procurement managers to defer the inclusion of silver dressings on wound formularies, despite its clinical popularity. This article gives an overview of the evidence on topical antimicrobials, in order to determine whether there is a case for such a stance.

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There has been a resurgence of interest in the phenolic antiseptic, triclosan, not just in terms of handwashing and skin preparation, but also as a coating or component of sutures.\textsuperscript{12} (Triclosan is the only antimicrobial that has been successfully used in a surgical suture.)

Polyhexamethylene biguanide (PHMB) has been popular for many years in North America and mainland Europe as an effective antimicrobial wound irrigant, gel and dressing, but has only recently gained acceptance in the UK.\textsuperscript{13,14} PHMB has a wide spectrum of antimicrobial activity with low toxicity.

The early, first-line use of antiseptics to control bacterial levels in the wound and thus prevent the risk of infection is a widely accepted aspect of wound management.\textsuperscript{15-18} However, the prevention and management of infection with the use of topical antimicrobials is only one part of wound care, which must also include adequate assessment, multidisciplinary holistic and nutritional support, and appropriate treatment of underlying pathologies with compression (venous leg ulcers), pressure redistribution (pressure and diabetic foot ulcers), attention to arterial inflow (all wounds, but particularly arterial and diabetic) and diabetes (glycaemic control).

Antimicrobial silver dressings

The use of silver in wound dressings was widely introduced over the past decade, although the value of silver as an antimicrobial in general has been known for centuries, and its combination as silver sulphadiazine has been a mainstay of prophylaxis and treatment of infection in burns. Interestingly, as yet no adequately powered, randomised clinical trial (RCT) has unequivocally established that any of the topical antimicrobials is only one part of wound care, which must also include adequate assessment, multidisciplinary holistic and nutritional support, and appropriate treatment of underlying pathologies with compression (venous leg ulcers), pressure redistribution (pressure and diabetic foot ulcers), attention to arterial inflow (all wounds, but particularly arterial and diabetic) and diabetes (glycaemic control).

Mechanisms of action

All antiseptics are strictly topical agents, which act by chemically inactivating many aspects of microorganisms’ cell function. This is in contrast to antibiotic action (which is much more specific in its selection of bacteria) and disinfectants (which damage both the host and microbial cells). This property makes antiseptics effective in the prevention of critical colonisation and local infection.

It is inappropriate to think of silver dressings in a generic sense because of their different modes of action within the wound. The majority of studies on the antimicrobial efficacy of silver dressings have involved nanocrystalline dressings, which are able to maintain a higher level of the active silver cation (Ag\textsuperscript{+}) (between 5mg/l and 40mg/l) than any other type of silver dressing because of the large area of the silver-coated/donating dressing that is present on the wound surface.\textsuperscript{28-31} Despite protein-binding, this mechanism of action enhances the spectrum and speed of kill of microorganisms.\textsuperscript{25-34}
The minimum inhibitory concentration (MIC), which is used to test the in vitro activity of antibiotics, is the most widely measure of antiseptic antimicrobial activity. A dressing is more likely to be effective if it can achieve a satisfactory MIC at the wound surface. If adequate MICs are not reached, then it is unlikely that the expense of an antimicrobial wound dressing would be justified.

Indications for use in chronic wounds
It has been suggested that silver dressings could be of value in the following areas:
- In wound bed preparation
- As a barrier function by reducing the number of surface microorganisms. This could be exploited to prevent the transmission of microorganisms, particularly resistant forms, from chronic wounds such as pressure ulcers and acute sutured wounds to other patients. This could be of further importance if patients are transferred from one hospital department to another, particularly if the transfer is from a low- to a high-risk area
- In the prophylaxis of bacterial colonisation and biofilm formation
- In the treatment of critical colonisation and local infection, with prudent antibiotic use.

Table 1. Indications for antibiotic therapy in wound care

<table>
<thead>
<tr>
<th>Indications</th>
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<tbody>
<tr>
<td>• Cellulitis, particularly with evidence of spreading redness and heat,</td>
</tr>
<tr>
<td>oedema and pain</td>
</tr>
<tr>
<td>• Lymphangitis</td>
</tr>
<tr>
<td>• Bacteraemia</td>
</tr>
<tr>
<td>• SIRS and MODS*</td>
</tr>
<tr>
<td>• Definite pathogens (beta-haemolytic Streptococcus and Pseudomonas spp.)</td>
</tr>
<tr>
<td>• Large numbers of pathogenic organisms (critical colonisation-infection)</td>
</tr>
<tr>
<td>• Poor host defences (as in immunosuppression or diabetes mellitus)</td>
</tr>
</tbody>
</table>

* SIRS = systemic inflammatory response syndrome; MODS = multiple organ dysfunction syndrome

Table 2. Hierarchy of clinical evidence

Promotion of healing by silver
The value of topical antimicrobials in the management of chronic wounds is mostly related to the control of critical colonisation and early local infection. However, in addition to the research on burns, there is some evidence that silver in the
higher concentrations furnished by nanocrystalline technology does promote healing, possibly through mechanisms other than infection control, but certainly more quickly than in low concentrations. Several experimental studies in animals have shown that, by reducing the bacterial load, silver reduces anti-inflammatory action, with reduced metalloproteinase activity, pro-inflammatory cytokines and cell apoptosis. The clinical evidence ranges from being anecdotal (case reports) to more convincing data from clinical trials, but, once again, there is a lack of adequately powered RCTs to support this.

A trial that had the potential to unequivocally prove the value of silver dressings was published in 2009. In this VULCAN study, 304 patients with a chronic venous leg ulcer were randomised to receive one of five antimicrobial ‘silver-donating dressings’, Aquacel Ag, Acticoat, Acticoat 7, Acticoat Absorbent, Contreet Foam or Urgotul SSD, or an unspecified, non-antimicrobial, control dressing. However, the study was flawed in that it did not state that the dressings were used on critically colonised or locally infected wounds, and there was no mention of microbiology testing. The authors concluded that the use of silver dressings did not enhance healing in these ulcers, although they did acknowledge that there was no delay in healing or toxicity.

None of the manufacturers of these dressings, which are designed for antimicrobial indications and differ in their mode of action and the amount of silver they release, claim that silver heals infected ulcers. To place dressings that release a high concentration of silver at an ulcer surface for 12 weeks seems illogical and potentially dangerous. The conclusion that no particular benefit accrues from the use of silver dressings is inappropriate and plays into the hands of those who hold the purse strings when it comes to dressing choice.

Advantages of silver
The use of antiseptics in wound care, and silver in particular, is still controversial. Much of the positive evidence is experimental and the clinical evidence anecdotal. As stated above, a RCT could answer these clinical questions but, alas, the VULCAN RCT failed to do so. Resources for further such clinical research are limited. If another RCT were to be conducted, an informed multidisciplinary team, probably including members from industry, would be needed to formulate the best research questions to answer the most relevant clinical questions. Valuable insights could also be gained from the use of other study designs.

Pragmatic guidelines on how to improve the quality of research in wound care at all levels of the research hierarchy have been drafted, but these have not received universal support as in the absence of level I evidence silver dressings may not be supported because of their high unit costs.

Laboratory based evidence
The in vitro and in vivo techniques used to assess the value of silver in wound care have been extensively reviewed. These have included in vitro experiments to determine the wide antibacterial spectrum of silver in laboratory animals with simulated colonised/infected wounds. The results show that silver has a wide antimicrobial spectrum, although differing and therefore confusing units have been used for measurement including parts/million, MIC, minimal bacterial concentration and zones of inhibition. In vitro models used to test the efficacy of silver have ranged from scald injuries to full-thickness defects with bacterial inoculation. In log reduction assays, antiseptics were found to be potent antibacterials, with nanotechnology silver dressings conferring the best results. A three log reduction of microorganisms on a wound surface is regarded as significant.

Clinical evidence in chronic wounds
There is substantial published clinical evidence that antimicrobial dressings have a role to play in wound care, both in reducing colonisation and improving healing rates. This is supplemented by even more short series and case reports, which are presented at every major wound healing symposium.

Dressings that incorporate nanocrystalline technology and deliver higher concentrations of silver should probably not be used indefinitely because of the theoretical risk of silver absorption. If critical colonisation/local infection is not under control within 2–3 weeks of continuous use, then the need for antibiotics should be considered. This would probably require admission and intravenous administration.

More evidence is needed to show whether silver dressings can be used safely to control surface microbial colonisation and whether any silver dressings are effective in providing barrier/prophylaxis functions, as part of an infection control strategy.
Cost effectiveness

Economic analyses should be undertaken separately from clinical trials as their endpoints, power and scientific design are different. The VULCAN study did attempt this with the use of the EuroQuol 5 dimensions quality of life and Short Form 6 dimensions questionnaires. The authors modelled their results to indicate that the antimicrobial dressings used were not effective in promoting healing. However, this conclusion cannot hold as their primary hypothesis and endpoints were wrong (i.e. that silver antimicrobial dressings could heal non-infected ulcers).

Others have undertaken retrospective analyses using Markov modelling and shown that silver foam dressings and nanocrystalline silver dressings could reduce the risk of infection in chronic and acute wounds, with ensuing cost savings. Length of hospital stay has been measured in studies where silver dressings were used in burn wounds, with favourable outcomes. However, it would be difficult to use this endpoint in studies involving patients with chronic wounds as treatment is mostly undertaken on an outpatient basis.

Disadvantages of silver

Antiseptic and antibiotic resistance

Theoretical concerns have been raised that, like antibiotics, topical antimicrobials might select resistant organisms and promote their transmission. This has been addressed in an EC document from the Directorate General for Health and Consumers, which collated the evidence against triclosan (the most studied topical antimicrobial/antiseptic). The document presents the existing data on triclosan’s selection of human pathogens from the environment, any development of antibiotic-resistant organisms, any transmission of resistance and the (unlikely) risk of selection- or antibiotic-related resistance or transmission following antiseptic usage. The document concluded that the medicinal use of triclosan is valuable and sustainable without these potential risks, but prudence is required in its general, non-medical use.

The same almost certainly applies to all other antiseptics, including povidone-iodine, the biguanides and silver. It is inconceivable that the use of topical antimicrobials/antiseptics could be lost from wound care because of these very theoretical risks, particularly given the need to avoid antibiotic misuse and overuse, which clearly does lead to resistance and the emergence of human pathogens.

Antiseptics exert their antimicrobial action through non-specific toxic actions on cells, including the denaturation of enzymes and membrane proteins, cell respiratory processes and efflux pumps, but they are relatively innocuous to healing tissue. They are, therefore, a safe option for antimicrobial use in wound care. Furthermore, they can be used to treat critical colonisation/local infection before even considering antibiotics. Because antiseptics have multiple mechanisms of action, the development of resistance is less likely than with antibiotics. To date, no evidence of resistance has been reported following the clinical use of modern silver dressings. The emergence of resistance can be minimised if the level of silver ions released from silver dressings is high and the bacterial activity is rapid.

Topical tissue toxicity and systemic toxicity

Local staining caused by silver dressings does not appear to be a major complication and is usually temporary. The staining is probably due to the sustained release and high bioavailability of some silver dressings. While the level of staining relates to the silver concentration at the wound-skin interface, penetration into the tissues is limited. Systemic toxicity (argyria) is unlikely as the level of absorption from dressings is very small and probably depends on the wound size. While the systemic risk is probably overstated, argyria could theoretically result when there is a very large open wound and dressings releasing large amounts of silver ions are used.

A report of raised levels of silver in plasma after prolonged use of silver dressings for the treatment of epidermolysis bullosa in children has led to their removal from a hospital formulary. This seems excessive as all of the wounds healed without evidence of argyria or silver toxicity, and this has not been confirmed by others. Indeed, there have been no consistent reports of silver allergy. Interestingly, although silver dressings were used for an inappropriate indication and length of time in the VULCAN study, there was no delay in healing compared with the control during the 12-week study period.

Need for best data

The Cochrane Collaboration has consistently followed a rigid line that only level I evidence from adequately powered and randomised RCTs can confirm what constitutes optimal wound care.
involved in Cochrane analyses. Of course, best ever, this was subsequently challenged by those poor. Unless the evidence base improves, further Cochrane reviews will be pointless.

Alternative approaches have sought to use the best evidence available and suggest methods of undertaking clinically meaningful research. However, this was subsequently challenged by those involved in Cochrane analyses. Of course, best evidence is needed but the questionable hypotheses and methodology used in some RCTs, such as VULCAN, has only served to give silver dressings a bad press. VULCAN presents a missed opportunity because of its flawed study design. It has inappropriately added fuel to the fire that silver is expensive and ineffective — as any topical antiseptic would be if tested in this fashion — and adds to the false arguments of non-clinical procurement managers. The arguments against silver dressings often do not consider the need for a suitable alternative.

Practitioners do need help in the form of more convincing data. However, only industry-led studies are likely to meet the huge cost of such trials, in which case there is always the risk of a conflict of interest. The need for scientific rigour is clear, but the latter may need to be modulated to produce the evidence required. There is a strong case to keep silver dressings in wound care formulares, particularly those offering a rapid and sustained bactericidal effect and no reported risk of resistance. This whole controversy is covered in depth in the final article in this supplement.

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Silver-containing antimicrobial dressings have come under close scrutiny after recent publications have cast doubt on their clinical value. It is now apparent that the availability of modern wound dressings, in particular those containing silver, is being restricted across the UK. Ostensibly, this is because there is insufficient clinical evidence, as judged by systematic reviews of randomised controlled trials (RCTs), to support their use, although this may be a smokescreen for cost cutting at trust level. Nevertheless, the popularity of silver dressings is still undiminished among tissue viability and wound care nurse specialists, many surgeons and podiatrists. This article aims to define and clarify the wider issues associated with this ‘arbitrary’ move.

Why are there so few RCTs in wound care?
The evidence available to support the ‘open’ marketing of silver-containing dressings is, importantly, sufficient for the relevant regulatory body, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, which acts in accordance with the European Medical Device directives. Many wound dressings have been granted the ‘CE’ mark, certifying that a product has met the appropriate consumer safety, health or environmental requirements. The CE logo has become a symbol for the free marketability of goods within the European Economic Area; by affixing the CE marking to a product, the manufacturer declares that it meets EU safety and health and environmental requirements. Thereafter, it is incumbent upon manufacturers to provide further clinical and scientific data to provide the evidence base necessary for the clinician. It is at this point that the issues for debate start.

What is not for debate is the essential requirement for ‘evidence-based’ wound management: this is a tenet of clinical practice. It is what constitutes evidence that is at issue. For some years, many have regarded the Cochrane systematic review of RCTs as the central precept in evidence-based medicine (EBM). More recently, the Cochrane Wounds Group has, with contributions from others, conducted and published such reviews on wound treatments. This group adheres to the hierarchy of evidence that puts RCTs and meta-analyses of RCTs at the pinnacle. This is, by definition, an exclusive (rather than inclusive) procedure that is conducted on data with internal (but not external) validity.

Herein lay the problem as I see it. Wound care has developed largely through empirical evidence, which is both experiential and pragmatic. The exact reasons for this are unclear, but given that much of the available evidence relates to the use of medical devices rather than drugs or surgical devices, it is by definition less robust. Furthermore, the trials that have been conducted were rarely state funded, instead being largely industry sponsored and dressing related, resulting in much of it being observational in essence. This is why there is no substantial evidence base in the form of RCTs.

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An approach to assessing evidence that can inform clinical decision-making

Following the Cochrane meta-analyses findings, doubts are being expressed about efficacy of silver dressings. However, the need for topical antimicrobials has not diminished, and the evidence for non-silver agents is no better than that for silver. This article describes an alternative system to Cochrane for analysing the evidence base, and suggests a practical approach to making a case for silver to procurement managers.
Using evidence to make informed decisions

What then is the preferred way forwards? First, it is necessary to consider the available evidence for silver, and then to critically evaluate the capacity of the Cochrane approach, alongside others, to accurately summarise evidence for the guidance of the clinician.

A brief review of all of the evidence, in vitro and in vivo, together with the current thinking and concerns about the evidence hierarchy, will help to provide a perspective. First, there can surely be no reasonable doubt that, in vitro, silver is a proven broad-spectrum antimicrobial, being active against a wide range of wound pathogens, including resistant organisms such as meticillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE), as well as numerous other known human pathogens.11-23 This is of particular significance in its reported effect against organisms in biofilms.24-26 This antimicrobial evidence, while being both consistent and considerable, is not included in the typical Cochrane systematic review — a fact that some might regard as an anomaly.

Next, it is necessary to summarise the clinical evidence. While Cochrane systematic reviews claim that there is ‘insufficient evidence’ to support the clinical use of silver dressings, the most recent review2 acknowledged the existence of 26 relevant RCTs, incorporating 2066 patients, at the time of analysis. Many of these studies were excluded from analysis on the basis of deficiencies in conduct and/or reporting. While the Cochrane approach of excluding seriously flawed RCTs from meta-analyses is understandable, it would be another matter if it were being over fastidious in its selection criteria, as has been suggested elsewhere.24

Another problem is that there is no clear unanimity in the findings of systematic reviews. Another meta-analysis (this time not by Cochrane), which evaluated RCT evidence on the effect of silver treatments/dressings on complete wound healing, wound size reduction and healing rate, found ‘strong evidence’ for an association between silver and wound healing based on wound size reduction, but no evidence based on complete wound healing or healing rates. All included RCTs were quality assessed, with the overall study quality being classified as ‘fair’, but with most studies having some bias.27

This apparent contradiction between meta-analyses, and concerns about the quality of many RCTs, raises questions about the philosophy of regarding the RCT so highly in the hierarchy of evidence, something that has already been articulated by many luminaries of modern medicine,28-33 and is still the subject of debate.24

A cynic might say, with some justification, that the crux of the problem is that most evidence in wound care is poor. It could be argued, therefore, that the focus of attention should be as much on the quality of wound care research in general as on the need for better designed RCTs that ask the right research questions. Nevertheless, clinicians have to make a choice, regardless of whether the evidence is adequate or not, on what treatment to use on any given wound. This esoteric debate is of little value if, collectively, we cannot offer clinicians ‘informed’ advice on therapy.

The VULCAN RCT2 has been cited as a scientific rationale for removing silver dressings from wound formularies, based on a demonstrated lack of healing efficacy. However, the study has serious methodological flaws,35,36 the central one being that the silver dressings were used for prolonged periods of time (up to 12 weeks) without clinical justification, contrary to current best practice. Unfortunately, these shortcomings were not recognised by subsequent authors who have seized on the opportunity to extol the VULCAN trial findings, apparently without any insight into what constitutes good wound care practice.4,36 Like all antimicrobials, silver dressings must be used, with justification, in an appropriate and structured manner for limited periods, with clear clinical objectives in mind. In this respect, the VULCAN study lacks ‘external validity’.37 Michaels et al.2 were not alone in making the fundamental mistake of judging silver dressings as wound ‘healing’ treatments. Systematic reviews, and by association RCTs, also have this failing.38

In an attempt to establish an international baseline for clinical usage, a Best Practice Statement on the use of topical antimicrobials/antiseptics39 has been drafted by a panel of multidisciplinary, international experts in the field, and is currently (March 2011) out for wider consultation. It clearly states that products such as silver wound dressings should be used ‘in a timely and appropriate manner which is tied to accurate assessment and regular re-assessment’.

This is a responsible attempt by those active in the field of wound healing to address concerns raised about the use of silver dressings, mindful of the potential catastrophe that could lie in wait for
those vulnerable patients with infected wounds denied access to effective antimicrobial dressings.

In order to avoid confusion, this latter point requires clarification. The purpose of systematic reviews is ‘to facilitate the choices that practitioners, consumers, policy makers and others face in health care’. However, there is a common perception that this is not the case, particularly when a review concludes that the evidence for any given product is insufficient. In such instances, no ‘default’ therapeutic advice or recommendations are given. This leaves us with the option of either considering the use of alternative topical agents to silver, or to fund well-designed trials. Unfortunately, the latter is highly unlikely to be a viable economic option. Furthermore, while there is substantial evidence on other topical antimicrobials (iodine, honey and polyhexanide), none of it is more robust than that on silver.

Repercussions
To withdraw silver without adequate justification, or clinical advice on effective alternatives, will compromise care, and increase morbidity and mortality. The latter has been established through audit and shows that the arbitrary withdrawal of silver has led to increased incidence of septicaemia and death.6 Those responsible for wound formularies and purchasing should be mindful of the potential human costs associated with the decisions they take, and that, in the event of a documented increase in septicaemia, they should be held professionally accountable.

Responsible clinicians will continue to seek to use silver dressings in the fight against wound infection. The risks associated with arbitrary restrictions or removal of products should be borne in mind by all those responsible for the prevention and management of wound infection.
An alternative approach
So where do we, collectively, stand? The proponents of Cochrane EBM maintain that, according to their preferred system, there is insufficient evidence to recommend silver dressings. However, this is not the only methodology for objectively assessing and appraising evidence. Since 2004, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system has been available and has subsequently been widely adopted.\(^{4,5}\) This system has the distinct advantage of considering all available evidence, and offering recommendations based on analytical review.\(^{4,6}\) There are no ‘GRADE’ type studies currently available on wound treatments from which clinicians and purchasers can draw conclusions.

Many clinicians and scientists insist that there is now good \textit{in vitro} evidence\(^{4,5,6}\) and, relatively speaking, substantial clinical evidence for topical use of silver.\(^{5-7}\) This is the practical, pragmatic approach outlined in Box 1 when making a case for silver dressings to procurement managers.

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