Silver based wound dressings and topical agents for treating diabetic foot ulcers (Review)

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[Intervention Review]

Silver based wound dressings and topical agents for treating diabetic foot ulcers

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ABSTRACT

Background

Foot ulceration affects 15-20% of people with diabetes. It is a major precursor to amputation in this patient group, and early and appropriate treatment provides the greatest opportunity for healing. The use of silver for its antimicrobial properties has re-emerged, and modern wound dressings that release a sustained amount of free silver ions, are now widely used in wound management.

Objectives

To evaluate the effects of silver-containing dressings and topical agents on infection rates and healing of diabetes related foot ulcers.

Search strategy

Searches were made of the Cochrane Wounds Group Specialised Register (August 2005), the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* Issue 3 2005) MEDLINE (1966 to October week 2 2004), EMBASE (1980 to October week 2 2004) and CINAHL (1982 to October week 2 2004). *The Journal of Wound Care* (Volume 12/13 Issues 1-10) was hand-searched. Manufacturers, researchers and local and international wound groups were contacted in order to identify unpublished trials. Web sites for wound groups and World Wide Wounds (www.worldwidewounds.com) were searched.

Selection criteria

Randomised controlled trials and non-randomised controlled clinical trials were considered for inclusion. Studies were included if they involved participants with Type 1 or Type 2 diabetes and related foot ulcers, met the requirements for randomisation, allocation and concealment where appropriate, and compared the intervention with a placebo or a sham dressing, an alternative non silver based dressing or no dressing, and reported outcomes that represent healing rate or infection.

Data collection and analysis

Two authors independently evaluated the papers identified by the search strategy against the inclusion criteria but identified no trials eligible for inclusion in the review. It was not possible to perform planned subgroup and sensitivity analysis in the absence of data. In future, if eligible trials become available, a random effects model will be applied for meta-analysis in the presence of statistical heterogeneity (estimated using the I^2 statistic). Dichotomous outcomes will be reported as risk ratios with 95% confidence intervals

(CI), and continuous outcomes as weighted mean differences (WMD) with 95% CI. Statistical significance will be set at P value < 0.05 for all outcomes and the magnitude of the effect will be estimated by calculating the number needed to treat (NNT) with 95% CI.

Main results

No studies were identified that met with the inclusion criteria

Authors' conclusions

Despite the widespread use of dressings and topical agents containing silver for the treatment of diabetic foot ulcers, no randomised trials or controlled clinical trials exist that evaluate their clinical effectiveness. Trials are needed to determine clinical and cost-effectiveness and long term outcomes including adverse events.

PLAIN LANGUAGE SUMMARY

Silver based wound dressings and topical agents containing silver for treating diabetic foot ulcers

People with diabetes can develop foot ulcers. These are often due to reduced blood supply, reduced sensation, a change in the amount of movement in the lower leg, a foot deformity or the presence of some trauma. Therapies for foot ulcers include pressure reducing or relieving footwear and wound care through frequent dressing changes. Healing the wound can be delayed by poor control of blood sugar levels, compliance with therapies and the amount of bacteria on the wound surface. Foot ulcers in people with diabetes frequently become infected. Silver is an antimicrobial and dressings which contain silver have been developed. The authors of this Cochrane review wanted to find evidence on whether silver based dressings reduced infection and encouraged wound healing. They searched the medical literature for randomised and controlled clinical trials but found no studies which were eligible for inclusion in the review. We therefore do not know if silver containing dressings and topical agents containing silver are beneficial to diabetic foot ulcer healing.

BACKGROUND

Foot ulceration affects 15 to 20% of all individuals with diabetes and precedes up to 85% of amputations in this patient group (Armstrong 1998; Boulton 2000; Oyibo 2001; Valk 2001;Van Acker 2002). The five-year re-ulceration rate is approximately 70%, and, for those undergoing lower-limb amputations, there is a 50% chance of losing the remaining limb within three years (Valk 2001; Van Gils 1999). The five-year mortality rate for bilateral amputees is high (Van Gils 1999), usually as a result of more widespread organ damage of which amputation is a strong marker.

A study in the United States reported that costs for medical care for peripheral neuropathy and associated complications, such as ulceration, to be in the vicinity of US$10 billion per annum for the year 2001 (Gordois 2003). In the United Kingdom, direct health care costs associated with diabetes related amputation are approximately £8000 per patient per year, based on acute care costs for 1996/97 (Clark 2003). More difficult to quantify, but equally important, is the impact of diabetic foot ulceration on indirect costs, including the cost of carers, loss of employment, and increased reliance on social welfare (DiabCost 2002). Quality of life is reduced by both the presence of an ulcer, and often as a consequence of treatment (Kinmond 2003; Meijer 2001; Tennvall 2000). Treatment methods for diabetic foot ulceration often entail burdensome regimes including pressure relief - often in the form of a below knee cast or custom footwear - daily dressing changes and frequent trips to various health professionals. Although these treatment regimes are essential for healing and prevention of further complications, they can last for many months and have a profound effect on activities of daily living and quality of life.

Ulceration usually occurs when one or more of the following are present: peripheral neuropathy (particularly loss of feeling/protective sensation), foot deformity, and minor trauma (Currie 1998; Reiber 1999). Less frequently diabetic foot ulceration may present as a symptom of deeper infection such as cellulitis, an abscess, or osteomyelitis. Another less frequent precursor to ulceration is peripheral vascular disease, as impaired circulation contributes significantly to non-healing of ulcers and subsequent risk for amputation (Boulton 2000). This multifactorial nature of diabetic foot ulceration has prompted the development of a range of grading systems that allow classification of characteristics such as aetiology, depth, presence/absence of infection and the involvement of deeper structures such as bone. Grading systems such as Wagner or the Texas Foot Classification System are used widely for descriptive purposes, deciding treatment plans, and to assign a level of risk for amputation (Armstrong 1998; Boulton 2000).

Timely resolution of diabetic foot ulceration is essential if further tissue loss and infection are to be avoided. Current guidelines recommend the use of pressure relieving devices, appropriate dressings to promote healing and prevent infection, and where appropriate, debridement, drainage and revascularization (ACFAS 2000; Apelqvist 2000). In addition, optimisation of glycaemic control and patient education are important factors in achieving successful ulcer healing (Boulton 2000; Eaglestein 2001). Amputation should not be overlooked as a means of successful management, and in fact, early and appropriate amputation can prevent the need for more extensive surgery and greater complications at a later date.

Despite the need for speedy resolution in order to avoid greater complications, it is not uncommon for diabetic foot ulcers to reach a point where progress slows or even stops altogether. Commonly referred to as 'delayed' or 'non-healing' this phenomenon contributes significantly to the chronicity associated with diabetic foot ulcers, and can occur despite appropriate treatment and management of all contributing factors. There are several factors that have the potential to contribute to a delay in wound healing, including poor patient compliance with treatment regimes, poorly controlled glycaemic (blood sugar) levels and poor tissue oxygenation (ADA 1999). Also implicated in the delayed or non-healing of diabetic foot ulcers, is the impaired immune response to injury commonly seen in people with diabetes that frequently results in poor, or no progress, after initiation of the inflammatory phase of healing (the initial healing phase involving the arrival of blood cell types and removal of bacteria from the site). This ultimately affects formation of granulation tissue (new tissue containing all the cellular components for skin formation), which is a pre-requisite to epithelialisation or complete skin healing (Moore 2003). Modern dressings such as Dermagraft (Smith and Nephew) and Apligraf (Novartis) have been developed in an attempt to overcome these cellular deficiencies and promote wound closure (Curren 2002; Marsten 2003).

Also implicated in the delayed or non-healing of diabetic foot ulcers, is the amount of bacteria on both the wound surface, and less often, in deeper wound tissue (Edwards 2004; Schultz 2003). Terms used to describe the 'bacterial bio burden', or different levels of bacteria on the surface of an ulcer, include 'contaminated', 'colonised' or 'infected', and obtaining a degree of bacterial balance have been cited as a key objective in successful wound care (Ballard 2002; Sibbald 2003). 'Contaminated' refers to a level of bacteria that is not harmful to the host (in this case the diabetic patient) and where micro-organisms are not replicating (re-producing) and pose no threat to healing (Sibbald 2003). 'Colonised' ulcers will display a greater concentration of micro-organisms that impede wound healing but do not result in overt signs of clinical infection such as erythema, pus and pain (Sibbald 2003). The exact bacterial concentration at which colonisation or 'critical colonisation' occurs, has yet to be determined (Sibbald 2003). 'Infected' refers to a wound state characterised by the defeat of the hosts immune system by replicating micro-organisms or bacteria. Again, the exact level at which 'colonisation' becomes 'infection' is not known, however a long established rule is a level of bacteria equal to or greater than 10^5 colony forming units per gram of tissue (cfu/g), or 100,000 or more bacterial cells per gram of wound tissue, is sufficient to confirm infection (Bowler 2003; Edwards 2004; Sibbald 2003). It has been argued however, that the 10^5 rule may not apply to ulcers such as those affecting the diabetic foot, due to the complex nature of the bacteria that typically affects them (Bowler 2003). Studies have demonstrated common isolates affecting diabetic foot ulcers include both aerobic (needing oxygen to survive) and anaerobic (thrive in low to no oxygen) organisms including, *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus* and *Enterococcus* species, *Pseudomonas aeruginosa, Peptostreptococcus* and coliform bacteria (Armstrong 1995). Sibbald 2003 suggest this unusual mix of bacterial species may impact on such things as virulence and bacterial characteristics, causing these micro-organisms to behave outside the normal spectrum.

Although the debate continues over the definition of 'colonised' versus 'infected' and the implications of this for wound healing remain unclear, a variety of modern wound dressings have been developed that claim to restore the bacterial burden to an acceptable level and that this will promote healing. Silver containing dressings are one such new group of dressings and are available in a variety of forms including foams, hydrofibres and hydrocolloids, all containing free silver ions as the active ingredient. Silver has long been recognised as a powerful antimicrobial and was used as early as 1895 for dressing surgical wounds and minimising post-operative infection (Lansdown 2004). In the same era, Crede began using silver nitrate to prevent neonatal eye infections (Burrell 2003). Silver is an effective antimicrobial due to its ability to bind to the DNA of bacteria and bacterial spores, reducing their ability to replicate (Ballard 2002; Cooper 2004) and is reported to be effective against almost all known bacteria including fungi and some viruses (Ovington 2001). The silver binds to the cell membranes causing significant damage and preventing replication (Ballard 2002). Antibiotic research in the 1940s saw investigations into the further use of silver in medicine decline and not re-emerge until the 1960s, after which time silver was incorporated into a variety of preparations for use in wound healing (Burrell 2003). Silver salts such as silver nitrate and silver sulphadiazine were commonly applied to burns (Burrell 2003). Silver can be delivered to a wound in a number of chemical formulations including metallic, nanocrystalline or ionic silver. A preparation may have a high concentration of silver but the availability of the silver to the wound may vary. For this reason studies may use the term 'free' silver to describe the amount of bioavailable silver from the product. The amount and rate of free silver released onto the wound surface will impact on its antimicrobial activity and Lansdown has reported that levels in excess of 20 mg/l demonstrate the best results (Lansdown 2002). Manufacturers of silver dressings (Appendix 1)

claim to combine the antimicrobial properties of sustained silver release with the ability to manage exudate and maintain a moist wound surface.

Greater clarification is required about the possibility of toxicity through prolonged exposure to, or use of, wound dressings that contain silver. Whilst many claim the use of dressings containing silver is safe and does not expose patients to the possibility of toxicity, Lansdown expressed the need for more investigation before a consensus can be reached (Lansdown 2004). As Lansdown rightly points out absorption of silver depends on such things as depth and extent of the wound, mode and frequency of application, silver content and specifically the amount of exudate secreted from the wound, which usually governs the amount of silver released.

There is little available data on the cost effectiveness of dressings containing silver, particularly when used to treat diabetes related foot ulcers. Work presented by Scanlon 2004 indicated a 48% increase in cost effectiveness of silver-containing hydro-activated foam when compared with 3 alternative dressings when used to treat venous leg ulcers. However community prescription cost data for England (Dept Health 2005) shows that over million pounds (UK £) was spent on just one type of silver dressing (Actisorb silver, 10.5cm by 10.5cm) in 2004.

An earlier systematic review (O'Meara 2001) failed to identify any randomised controlled trials evaluating the affect of silver containing dressings and topical applications on diabetes related foot ulcers, and as such, this review was undertaken in order to determine whether more recent studies could be reported.

OBJECTIVES

To evaluate the effects of silver containing dressings and topical agents on infection rates and /or healing of diabetes related foot ulcers.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective randomised controlled trials (RCTs) and non-randomised controlled clinical trials (CCTs) both published and unpublished were eligible if they compared the effectiveness of dressings and topical agents containing silver (used alone or in combination with other dressings/agents), in resolving infection and/or promoting healing of infected and uninfected diabetes related foot ulcers.

For the purposes of the review clinical infection of soft tissue was defined as the presence of purulent secretion (pus) or two or more of: erythema, warmth, tenderness/pain or induration (hardening of tissue). Indicators of more invasive infection included systemic signs such as fever, chills, elevated erythrocyte sedimentation rate and C-reactive protein, abscess, cellulitis or osteomyelitis.

Types of participants

Trials recruiting people with Type 1 or Type 2 diabetes and related foot ulcers including neuropathic, ischaemic and neuroischaemic ulcers were considered for inclusion. Presence of infection at baseline did not exclude studies from the review. Studies that recruited people both with and without diabetes were considered if the results for the study group with diabetes could be reported separately or were provided by the researchers for the purposes of the review. Similarly, studies that recruited people with ulcers related to venous disease, vasculitis or any chronic condition other than diabetes were considered, if the results relating to people with a diabetic foot ulcer were reported separately or were made available for the purposes of this review. Information about these and other variables, including concurrent therapy such as antibiotics, was to have been recorded.

Types of interventions

Any wound dressing or topical agent containing silver, used singly and in combination to treat diabetes related foot ulcers. Eligible comparison interventions included no dressing, sham dressing (identical but without silver) and dressings or topical agents not containing silver. Studies that used these in combination with other therapies such as antibiotics, pressure relieving devices or secondary dressings were eligible.

Types of outcome measures

Primary outcomes

Trials reporting any of the following primary outcomes were eligible;

1. Proportion of ulcers completely healed;
2. Change in total ulcer area (either absolute or percentage change);
3. Time to complete healing or reduced size;
4. Signs and symptoms of clinical infection.

Secondary outcomes

1. Ulcer re-occurrence rates;
2. Adverse effects of treatment;
3. Quality of life;
4. Costs;
5. Hospital admissions;
6. Amputation;

7. Death.

Studies reporting secondary outcomes only were not included.

Search methods for identification of studies

Electronic searches

The Cochrane Wounds Group Specialised Register (August 2005) and the The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 3 2005) were searched using the search strategy below. An additional search of MEDLINE (1966 to October Week 2 2004), CINAHL (1982 to October Week 2 2004) and EMBASE (1980 to October Week 2 2004) was conducted in October 2004 using a modified search strategy (Appendix 2).

Search Strategy for CENTRAL:

1. FOOT ULCER explode all trees (MeSH)
2. DIABETIC FOOT explode all trees (MeSH)
3. (foot and ulcer*)
4. (diabetic near foot)
5. (diabet* near ulcer*)
6. (diabet* near wound*)
7. (#1 or #2 or #3 or #4 or #5 or #6)
8. SILVER explode all trees (MeSH)
9. silver
10. contreet or avance or calgitrol
11. acticoat or actisorb or arglaes or silvasorb
12. aquacel*
13. (calcium next alginate)
14. (#8 or #9 or #10 or #11 or #12 or #13)
15. (#7 and #14)

The web site for World Wide Wounds (www.worldwidewounds.com) was searched for relevant studies.

Searching other resources

Researchers, manufacturers and local and international wound groups (Appendix 3) were contacted to determine whether other published or unpublished trials were available. The Journal of Wound Care (Volume 12 Issue 1-10 and Volume 13 Issues 1-10) was hand searched. Conference proceedings for major wound group meetings (The World Union of Wound Healing Societies and The European Wound Management Association) were also hand searched for years 2003 and 2004. Bibliographies of potentially included studies were reviewed.

Data collection and analysis

Selection of studies

Search results were independently assessed by two authors (SB and PW) and studies potentially meeting the selection criteria were independently assessed by two authors (SB, PW) and studies potentially meeting the eligibility criteria were obtained in full and assessed independently against the inclusion criteria by the same two independent authors. Any disagreement between the two authors regarding quality, inclusion or exclusion of a study, was resolved through discussion and consensus between the authors.

Data extraction and management

The Cochrane Wounds Group data extraction form was to be used for included studies

Assessment of risk of bias in included studies

Studies were to be assessed according to the following quality criteria:

1. Extent of allocation concealment at point of randomisation;
2. Method of generation of the randomisation sequence;
3. Evidence of masked outcome assessment;
4. Evidence of masking of subjects;
5. Detailed inclusion and exclusion criteria;
6. Length of follow up and extent of loss to follow up;
7. Whether participants were analysed in the groups to which they were originally randomised (intention to treat);
8. Withdrawals reported by treatment group with reasons.

Data synthesis

It had been planned that dichotomous outcomes would be reported as risk ratios with 95% confidence intervals (CI), and for continuous outcomes the weighted mean difference (WMD) with 95% CI was to have been used. Statistical significance was set at P value < 0.05 for all outcomes and the magnitude of the effect was to be estimated by calculating the number needed to treat (NNT) with 95% CI. Statistical pooling was only to be considered in studies that presented as sufficiently similar in terms of participant characteristics, interventions and outcomes. Heterogeneity was to have been estimated using the I^2 statistic.

Subgroup analysis and investigation of heterogeneity

It was intended that subgroup analysis would be used to assess the effect of type of intervention used (single agent or combination, moist wound healing or other); concomitant therapy (debridement, antibiotics, pressure off-loading); types of controls used (placebo, other intervention); presence of infection; baseline ulcer grade; ulcer aetiology; diabetes type, and duration. Sensitivity analysis would determine study quality in terms of allocation concealment and attrition

RESULTS

Description of studies

See: Characteristics of excluded studies; Characteristics of studies awaiting classification.

No studies meeting the inclusion criteria for this review were identified from the search and were eligible for inclusion in the review. Five studies (Gottrup 2003; Jude 2004; Rayman 2003; Russell 2004; Scalise 2003) potentially meeting the inclusion criteria are listed in the 'References to Studies' section of this review under 'Studies Awaiting Assessment'. Among these five studies is an evaluation of the clinical results of earlier studies using silver dressings, and comparisons of the effect of silver dressings on diabetes related foot ulcers when compared with the effect of either standard wound care or an alternative non-silver dressing. All these studies are abstracts which have been presented at conferences and as such have limited information available, researchers for these studies were contacted where possible and invited to provide additional information however, to date no information has been received. A list of excluded studies can be reviewed in the 'Tables' section of this review under 'Characteristics of excluded studies'. Sixteen of these studies were excluded as their study design did not meet the eligibility criteria, 18 were excluded as they did not include participants with diabetes related foot ulcers and 11 were excluded as they were in-vitro studies or studies not involving humans.

Risk of bias in included studies

No eligible studies were identified.

Effects of interventions

No eligible studies were identified.

DISCUSSION

No eligible studies were identified. Whilst we believe the search strategy was exhaustive, it may be that studies that could potentially meet the criteria for inclusion were missed because their findings have not yet been published. Although we made every effort to contact researchers and manufacturers, and searched recent conference proceedings for relevant abstracts, we acknowledge the difficulties in identifying unpublished data and accept that some unpublished work may have been missed. Several abstracts identified from conference proceedings from 2003 and 2004 revealed information pertaining to studies recently completed or still underway, and it is possible that such work will be identified in future updates of this review.

The results of this review demonstrate a lack of appropriately randomised and controlled trials evaluating the effect of silver based products on infection and healing of diabetic foot ulcers. It is important that such studies are conducted using a sufficiently large sample size. Results from studies involving different patient groups cannot necessarily be generalised to this patient population. People with diabetes experience disease specific co-morbidities, for example the development of an altered immune response, that may or may not resemble immune changes resulting from other pathologies and specific aetiologies that contribute to the development of an ulcer. Concomitant therapies will also differ between groups experiencing venous leg ulcers, burns and diabetic foot ulcers, and these other therapies will no doubt impact on study outcomes. Appropriate study design and analysis is especially important in this patient group as it is rare for diabetic foot ulcers to be treated or managed with a wound dressing alone. Pressure off-loading, debridement and the use of systemic antibiotic therapy are used routinely in the management of diabetic foot ulcers and all will impact on healing and infection rates. It is essential that the degree to which each impact on outcomes is investigated. Diabetes duration and age will also likely impact on outcomes and should not be disregarded.

Some difficulties do exist with studying this population and date back to such age old arguments as 'What features define a chronic wound?' Whilst many organisations and institutions have a definition they routinely use, no such definition is universally accepted and contributes to difficulties in determining inclusion and exclusion criteria and defining the study population. Earlier in this review we discussed the lack of definite cut off points for determining when an ulcer is 'colonised' as opposed to 'infected', and at what point is wound healing compromised. It is perhaps just as important that studies are conducted that define these terms more conclusively and investigate the relationship, if any, between bacterial load and healing.

Currently, study outcomes vary greatly and range from qualitative findings such as 'pain' and ease of use', to more quantitative data including the number of bacteria identified via wound swab before and after treatment. We would recommend that where possible, studies consider reporting 'time to complete healing' as this should be the main aim of all wound management. Change in total ulcer area should always be reported as both absolute and percentage change.

Whilst no studies were identified that met the inclusion criteria for this review future updates will identify any studies evaluating the effect of silver dressings and topical agents on diabetic foot ulcers.

AUTHORS' CONCLUSIONS

Implications for practice

No RCTs or CCTs were identified therefore we cannot conclude whether silver based dressings and topical agents result in benefits or harms for people with diabetes related foot ulcers. RCTs are required in order to determine the clinical and cost effectiveness of silver based treatments for diabetes related foot ulcers.

Implications for research

RCTs that evaluate the effect of silver containing dressings and topical agents and their effect on healing of diabetes related foot ulcers are required.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Ballard 2002	A narrative on use of silver in wounds and discussion of Avance hydropolymer dressing including two case studies.
Bishop 1992	Participants did not include those with diabetic foot ulcers. Prospective randomised evaluator blinded trial assessing the effect of silver sulfadiazine 1% versus a biologically active tripeptide copper complex 0.4% and an inert placebo on wound healing.
Bowler 2003	An in-vitro study using a simulated wound fluid model comparing the activity of an antimicrobial absorbant Hydrofibre with Silver sulphadiazine Cream on 3 pathogens; Staphylococcus Aureus, Pseudomonas Aeruginosa and Candida Albicans.
Caruso 2004	Did not involve patients with diabetic foot ulcers. Phase 2 non-comparative trial with burns patients.
D'Alicandro 2003	Comparison of a multilayer dressing releasing silver crystals and use of hyperbaric oxygen treatment in 12 patients with venous and arterial wounds.
Demling 2001	Did not involve patients with diabetic foot ulcers.
Griffiths 2000	Case study only.
Holder 2003	An in vitro study investigating the effectiveness of Acticoat.
Karlsmark 2003	Did not include participants with diabetic foot ulcers. Followed the effect of Contreet Foam on 25 patients with venous leg ulcers over 4 weeks.
Lansdown 2003	Review paper discussing use of Contreet Foam and Contreet Hydrocolloid.
Larsen 2003	In vitro study demonstrating antimicrobial activity of a silver-containing foam against 17 microorganisms commonly found in chronic wounds.
Margraf 1977	Did not include patients with diabetic foot ulcers.
McCarry 2004	Open label study examining affect of Acticoat 7 in 7 patients with chronic diabetic foot ulcers.
Muller 2003	An in vitro study on effectiveness of Actisorb Silver 220 on bacteria and endotoxins.
Nadal 2003	Evaluation of combined treatment of surgery and nanocrystalline silver dressing in 24 patients.
O'Neill 2003	Observation of the interaction of two silver dressings with wound pathogens.

(*Continued*)

Olsen 2000	An open trial evaluating healing of donor sites in pigs treated with silver-coated dressings.
Pittarello 2003	Observational study examining effect of Contreet-H on 10 chronic wounds including 3 diabetic foot ulcers.
Raineri 2004	Uncontrolled prospective study evaluating effect of an ionised nanocrystalline silver dressing in 40 patients.
Romanelli 2003a	Did not include patients with diabetic foot ulcers. Evaluation of performance parameters of a silver-containing foam dressing and quality of life in 3 patients with venous leg ulcers.
Romanelli 2003b	An evaluation of Acticoat 7 in treatment of 12 patients with either leg ulcers or pressure ulcers.
Romeo 2003	Evaluation of effect of combined treatment of a nanocrystalline silver dressing and hydrogel in 11 patients including 6 with diabetes.
Scanlon 2003	Did not include patients with diabetes related foot ulcers. A cost effectiveness study examining the effect of four different wound dressings including a silver containing foam and a silver/charcoal cloth on healing of venous leg ulcers.
Sibbald 2001	Uncontrolled prospective study of a case series of 29 patients with chronic non-healing wounds treated with ionised nanocrystalline silver dressing (Acticoat).
Sibbald 2004a	Did not include patients with diabetic foot ulcers. A 4 week block randomised multi-centre parallel trial comparing a standard foam with a silver impregnated foam dressing in 109 patients with non-healing venous and mixed arterial/venous leg ulcers.
Sibbald 2004b	Not a randomised trial or a controlled clinical trial. A single centre four-armed study examining effect of a silver containing Hydrofibre on a variety of chronic wounds including 10 diabetic foot wounds.
Smith 2003	No participants with diabetic foot ulcers.
Thomas 2003	Descriptive paper on antimicrobial effect of 10 silver dressings in vitro.
Tipton 1965	Did not include patients with diabetic foot ulcers.
Tredget 1998	Did not include patients with diabetic foot ulcers. Randomised, prospective, clinical study evaluating effect of Acticoat wound dressing on 30 burns patients.
van Hesselt 2004	An in vitro study testing the effect of three samples of colloidal silver on test organisms.
Vanscheidt 2003	Did not include patients with diabetic foot ulcers. Open-label, multicentre, non comparative study evaluating the affect of Aquacel Ag on 18 patients with chronic leg ulcers of mixed etiology.

(*Continued*)

Vogensen 2003	Not a randomised trial. Did not include people with diabetic foot ulcers. Evaluation of effect of an antibacterial foam dressing containing silver in 3 patients with venous leg ulcers.
Voigt 2001	Descriptive paper on use of Acticoat in a burns unit.
Voyatzoglou 2004	An open, prospective study evaluating the affect of Contreet Foam Non-adhesive and Contreet Foam Adhesive in 15 patients with diabetic foot ulceration. Insufficient information regarding randomisation.
Wright 1998a	An in vitro study examining the effect of a silver film dressing and a silver absorbant dressing on commonly found bacterial and yeast wound pathogens.
Wright 1998b	In vitro study evaluating effectiveness of silver-based products on antibiotic resistant organisms.
Wright 1999	No patients with diabetic foot ulcers.
Wright 2002	Does not involve patients with diabetic foot ulcers.
Wunderlich 1991	Did not include patients with diabetic foot ulcers. Controlled, randomised study on 40 patients with venous leg ulcers comparing treatment with silver-impregnated activated charcoal xerodressing and conventional therapy.
Yin 1999	In vitro evaluation of the antimicrobial effectiveness of Acticoat silver dressing, silver nitrate, silver sulfadiazine and mafenide acetate.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Gottrup 2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	further information sought

Jude 2004

Methods	
Participants	
Interventions	
Outcomes	
Notes	further information sought

Rayman 2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	further information sought

Russell 2004

Methods	
Participants	
Interventions	
Outcomes	
Notes	further information sought

Scalise 2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	further information sought

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Modern Silver Based Dressings

Dressing	Manufacturer
Acitcoat and Acticoat 7	Smith and Nephew
Actisorb Silver 220	Johnson and Johnson
Avance	SSL International
The Contreet range	Coloplast
Arglaes and Silvasorb	Medline Industries
Aquacel Ag	ConvaTec
Calgitrol	Magnus Bio-Medical Technologies
Silverlon	Argentum Medical

Appendix 2. Ovid Search Strategy

1. exp leg ulcer
2. exp foot ulcer
3. exp diabetic foot
4. (leg and ulcer$)
5. (foot and ulcer$)
6. (diabetic near foot).mp
7. (diabet$ near ulcer$).mp
8. diabet$ near infection$).mp
9. (diabet$ near wound$).mp
10. 1 orn2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp silver
12. silver
13. contreet
14. acticoat
15. aquacel$
16. (calcium next alginate).mp
17. avance

18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 10 and 18

Appendix 3. Manufacturers and Wound Groups

Manufacturers	Wound Groups
Smith and Nephew	Australian Wound Management Association
Coloplast	European Wound Management Association
ConvaTec	
Johnson and Johnson	
SSL International	
Better Health Care	
Medline Industries	
Magnus Bio-Medical Technologies	

WHAT'S NEW

Last assessed as up-to-date: 15 November 2005.

30 July 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 1, 2006

16 November 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Shan Bergin - Author of manuscript, one of the independent reviewers of papers selected or identified for possible inclusion in review, reviewed all papers / studies included in review.

Paul Wraight - Independently reviewed all studies identified as potentially meeting criteria for review, editorial role in production of manuscript, assisted in selection of studies for inclusion in review.

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

*Occlusive Dressings; Administration, Topical; Diabetic Foot [*drug therapy]; Silver [*administration & dosage]; Wound Healing [*drug effects]

MeSH check words

Humans