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# Topical silver for treating infected wounds

Review

Intervention

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## Abstract

English

### Background

Topical silver treatments and silver dressings are increasingly used for the local treatment of contaminated or infected wounds, however, there is a lack of clarity regarding the evidence for their effectiveness.

### Objectives

To evaluate the effects on wound healing of topical silver and silver dressings in the treatment of contaminated and infected acute or chronic wounds.

### Search methods

We sought relevant trials from the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Wounds Group Specialised Register in March 2006 and in MEDLINE, EMBASE, CINAHL, and digital dissertations databases up to September 2006. In

addition, we contacted companies, manufacturers and distributors for information to identify relevant trials.

## Selection criteria

Randomised controlled trials (RCTs) assessing the effectiveness of topical silver in the treatment of contaminated and infected acute or chronic wounds.

## Data collection and analysis

Eligibility of trials, assessment of trial quality and data extraction were undertaken by two authors independently. Disagreements were referred to a third author.

## Main results

Three RCTs were identified, comprising a total of 847 participants. One trial compared silver-containing foam (Contreet®) with hydrocellular foam (Allevyn®) in patients with leg ulcers. The second trial compared a silver-containing alginate (Silvercel®) with an alginate alone (Algosteril®). The third trial compared a silver-containing foam dressing (Contreet®)) with best local practice in patients with chronic wounds.

The data from these trials show that silver-containing foam dressings did not significantly increase complete ulcer healing as compared with standard foam dressings or best local practice after up to four weeks of follow-up, although a greater reduction of ulcer size was observed with the silver-containing foam. The use of antibiotics was assessed in two trials, but no significant differences were found. Data on pain, patient satisfaction, length of hospital stay, and costs were limited and showed no differences. Leakage occurred significantly less frequently in patients with leg ulcers and chronic wounds treated with a silver dressing than with a standard foam dressing or best local practice in one trial.

## Authors' conclusions

Only three trials with a short follow-up duration were found. There is insufficient evidence to recommend the use of silver-containing dressings or topical agents for treatment of infected or contaminated chronic wounds.

# Plain language summary

English

**Topical silver for treating infected wounds.**

People with chronic wounds such as foot ulcers and leg ulcers and acute wounds such as surgical wounds often find their wound becomes infected. Healing the wound can be delayed by the amount of bacteria on the wound surface. Wound care involves frequent dressing changes. 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.

Three studies looking at people with chronic wounds were included in the review and found that silver-containing foam dressings did not result in faster wound healing after up

to four weeks of follow-up. One study did find that the overall size of the ulcer reduced more quickly when dressed with a silver-containing foam.

There is no enough evidence to recommend the use of silver-containing dressings or topical agents for treating infected or contaminated chronic wounds.

# Background

## Wounds and wound infection

Wounds are either acute or chronic and can result from venous or arterial insufficiency, diabetes, burns, trauma, chronic pressure or surgery (O'Meara 2001; O'Meara 2008). Wounds can become contaminated with bacteria, but frequently do not show signs or symptoms of infection, and healing is not impaired (Dow 1999). However, when colonisation becomes clinical infection, wound healing is likely to be impaired (Ovington 2003). The classic clinical signs of infection in acute wounds include: localised pain and swelling; spreading erythema (redness of the skin); the appearance of a purulent exudate (pus); odour; and a density of more than a million colony-forming bacterial units per $mm^3$ tissue (Cutting 2005; NNIS 2004). For infected chronic wounds, more specific indicators of critical colonisation are: increasing pain; increased exudate levels; discolouration of the granulation tissue; foul odour; and wound breakdown (Cutting 2005; Gardner 2001).

Wound infection is one of the most common surgical complications (Wilson 2004), and leads to significant mortality and morbidity. Surgical site infections (SSI) are the commonest form of hospital-acquired infections for surgical patients in both the UK (HPA 2004) and in the USA (NNIS 2004), occurring in approximately 10% (Coello 2005) and 38% (NNIS 2004), respectively, of patients each year in those countries. SSIs delay wound healing, prolong hospital stay, cause unnecessary pain and, in extreme cases, can cause the death of the patient (Emmerson 1996; Plowman 2000). SSI are estimated to occur in up to 15% of elective surgical patients and approximately 30% of surgical patients whose procedure was classed as contaminated or dirty (Bruce 2001).

## Treatment of contaminated and infected wounds

A range of interventions may be deployed for patients with infected, acute or chronic wounds from various aetiologies (causes). Interventions may be systemic (e.g. antibiotics, antidiabetics or vascular surgery, i.e. treatments that affect the patients entire body), or consist of local management of the wound. Options for the latter include various types of dressings (e.g. gauze, bandages); topical applications (locally applied drugs such as antiseptics, enzymes) (Nelson 2007; O'Meara 2001; O'Meara 2008; Vermeulen 2004); debriding agents (Bradley 1999); and wound cleansing (Dow 1999; Edwards 2008; Moore 2005). Furthermore, local wound care may aim at preventing infection when the wound is still in a contaminated state.

## Dressings and topical agents for contaminated and infected wounds

It is thought that dressings act as barriers against exogenous bacteria (Sharp 2001) and, therefore, prevent wound contamination or infection. Topical agents used with dressings to

treat wound infections include antibiotics, antiseptics or disinfectants, as these agents destroy micro-organisms or limit their growth. The choice of dressings and topical agents for contaminated and infected wounds is not always based on a firm rationale (Lewis 2001).

Some topical agents are used in conjunction with antimicrobial solutions that irrigate or cleanse wounds. These solutions usually have only a brief contact time with the wound surface, unless used as a pack or soak. These include the hypochlorites (e.g. Eusol), hexachlorophane (constituent of some soaps and other skin cleansers), and substances such as potassium permanganate and gentian violet (both used in solution for skin cleansing). Another group of topical preparations has been designed to stay in contact with the wound surface for a longer period of time ideally until the next dressing change. This group includes creams, ointments and impregnated dressings. Most topical antibiotics belong to this category, for example mupirocin, which is active against Gram-positive organisms, and fusidic acid for staphylococcal infections. Neomycin sulphate is used to treat bacterial skin infections. When large areas of skin are treated, ototoxicity (a deleterious effect on hearing) may occur as a possible adverse effect. SSD has a broad-spectrum action and is commonly used for treating infected burns (BNF 2001). Some products, such as povidone iodine, chlorhexidine, benzoyl peroxide, and hydrogen peroxide, fall into both categories (BNF 2001).

## Historical use of silver for contaminated and infected wounds

Silver is currently one of the more popular topical antiseptic agents added to dressings (Dowsett 2004). The use of silver as a prophylactic and treatment for infection and other diseases dates back to about 1000 BC, when the ancient Greeks and the Romans used it as a disinfectant (Russell 1994); placing silver coins in jars of water and other liquids to sterilise the liquids (Demling). One of the earliest publications to mention silver was a textbook, The Surgeons Mate, published in 1617 by John Woodall, Surgeon-General to the East India Company, in which a solution of one part silver and three parts nitric acid was heralded as a treatment for wounds including leg ulcers (Klasen 2000).

In the early 19 th century Grawitz reported the antimicrobial properties of silver, noting that a highly diluted solution of silver nitrate could effectively inhibit the growth of *Staphylococcus aureus* (Klasen 2000). In Germany, around 1880, the obstetrician KSF Credé placed a 2% silver nitrate solution in the eyes of newborn babies to prevent ophthalmia neonatorum, a serious problem of this era caused by a gonococcal infection of the conjunctiva (White 2001). His son continued in his footsteps and explored the effect of metallic silver on *Staphylococci* and *Streptococci* through in vitro testing. He discovered that when slivers of silver were removed from an inoculated dish after 24 hours, no micro-organisms flourished in those places where the pieces of silver had been placed (Klasen 2000). Credé is also credited with the development of two silver salts, silver citrate and silver lactate, as delivery mechanisms (Klasen 2000). In 1895, the surgeon Halstead used silver-wire sutures and silver-foil dressings in an effort to help prevent postoperative sepsis. As the science of bacteriology and technological advancements progressed towards the end of the 19 th century, further investigations confirmed the antimicrobial properties of silver. By the early 20 th century, silver and its compounds were readily used by medical professionals to counter bacterial infections in acute and chronic wounds, including burns (White 2001).

However, after the Second World War interest in silver solutions appeared to wane, particularly with the discovery of antibiotics such as penicillin and sulphonamide. Despite this, infection continued to be a problem in wound healing. As a result, in the 1960s, silver was revived as a topical antimicrobial prophylactic for burns (Moyer 1965). Moyer 1965 demonstrated that silver nitrate solutions applied to thick cotton dressings were effective against *S. aureus* , *Pseudomonas aeruginosa* and haemolytic *Streptococci* . Another benefit of silver was that it did not appear to promote the development of bacterial resistance (White 2001). Over the last 40 years, the growing threat of antibiotic resistance, coupled with heightened concerns about the safety and toxicity of topical antiseptics (Hollinger 1996), appears to have incited another surge of interest in silver (Lansdown 2002), particularly in the area of wound care products. The antimicrobial activity of silver ions in very low concentrations ($10^{-6}$ to $10^{-9}$ M) has stimulated research to determine its mode of action (Russell 1994; Thurman 1989; White 2001). Silvers alleged antimicrobial effect and low toxicity mean that it could be a potential asset to the topical treatment of infected wounds.

## The mechanism of action of silver for contaminated and infected wounds

When silver is used for antimicrobial purposes, it is silver ions, and not atoms, that exert the effect (Thompson 1973). Silver dressings contain silver atoms that are slowly released as positively-charged silver cations (Ag+). These Ag+ ions appear to have a strong antimicrobial effect: they bind to bacterial walls, causing disruption of the wall and the death of the bacteria (Lansdown 2002). Ag+ ions also bind to bacterial enzymes thereby preventing them from performing their function as well as to bacterial cell DNA, thus interfering with cell division and replication (Thompson 1973).

Silver-containing dressings all have a silver reservoir, but differ in the way the Ag+ ions are released. Mostly, Ag+ ions are released from the dressing through oxidation when the silver atoms come in contact with fluid. Silver-coated dressings incorporate small silver particles (nanocrystals) to increase the exposure area and to facilitate the release of Ag+ ions. Alternatively, the silver can be incorporated as complex silver molecules in creams, ointments, hydrocolloids, hydrogels or foam dressings, which regulate the speed of delivery.

Various writers have raised important questions regarding the use of silver in contaminated and infected wounds. Firstly although the multifaceted effect of silver carries a low risk of resistance, studies in burn wounds have shown that bacteria (in particular *Pseudomonas* species) may become resistant to SSD and silver nitrate (Modak 1981). Secondly the amount of silver incorporated in the various dressings and the rate of release of Ag+ ions appear to influence the resulting antimicrobial effect (Ovington 2004). So far, this effect has been studied mainly in animal or laboratory experiments, which makes extrapolation to the human situation difficult (Poon 2004). The question of whether a greater, or faster, release of Ag+ ions has an effect on wound healing remains unanswered. Thirdly the in vivo presence of a biofilm (an extracellular polysaccharide matrix) around the bacteria reduces the antimicrobial effect of silver, because the silver binds to the proteins of this matrix instead of to the bacterial cell walls (Mertz 2003). Another potential concern is that silver does not act specifically against bacteria, but acts on any alien and host proteins. Hence, when relatively few bacteria are present in the wound the effect on host tissue is greater,

and that could slow down healing (Innes 2001). Thus, a possible toxic effect should be considered. Argyria, in which silver accumulates in the skin and other tissues, has an undesirable cosmetic effect, but its toxic effect is still unknown ( Lansdown 2006 ).

# Objectives

To evaluate the effects of topical silver and silver-containing dressings on the healing of contaminated and infected, acute and chronic wounds.

# Methods

## Criteria for considering studies for this review

### Types of studies

We considered all randomised controlled trials (RCTs) evaluating the effects of dressings containing silver (or topical silver added to a wound dressing) in the treatment of contaminated and infected open wounds of any aetiology (that is ischaemia, diabetes, burns, trauma, chronic pressure or after an operation). Ostomies (e.g. colostomies) were not considered as open wounds in this review. Infection was defined as: localised pain and swelling, spreading erythema (redness), appearance of a purulent exudate, odour, and the presence of a positive bacterial culture with more than $10^6$ colony-forming units per $mm^3$ tissue (Mangram 1999). Trial authors' definitions of infection (e.g. critical colonisation) were also accepted.

### Types of participants

Men and women aged 18 years and over, with contaminated and infected open wounds of any aetiology, and in any care setting.

### Types of interventions

Wound dressings containing silver or with added silver.
Likely comparisons included:

- dressings with silver (added) compared with any dressings without silver;
- dressings with silver (added) compared with dressings with any other antiseptic;
- different silver dressings;
- dressings or topical agents containing different dosages of silver;
- topical preparations of silver, for example SSD cream, or solutions containing silver.

### Types of outcome measures

#### Primary outcomes

Our primary outcome measure of interest was:

- an objective measure of healing rate, such as time to complete healing, rate of change in wound area and volume, proportion of infected wounds healed within a trial period.

Trials were to be included only if the primary outcome was reported.

#### Secondary outcomes

Secondary outcomes included:

- days of wound infection (Mangram 1999; McLaws 2000).
- adverse effects;
- use of systemic antibiotics;
- pain;
- patient satisfaction;
- quality of life;
- length of hospital stay;
- costs.

## Search methods for identification of studies

### Electronic searches

We searched the following databases:

- The Cochrane Wounds Group Specialised Register - March 2006 - (this register contains references from comprehensive searches of nineteen electronic databases, hand searches of journals and conference proceedings, and contacts with manufacturers and experts in the field of wound care);
- The Cochrane Central Register of Controlled Trials (CENTRAL) ( *The Cochrane Library* 2006, Issue 1);
- MEDLINE (2002 to September 2006);
- EMBASE (2002 to September 2006);
- CINAHL (2002 to September 2006);
- and digital dissertations at http://www.umi.com (until September 2006).

The search strategy for Ovid MEDLINE is shown in Appendix 1 and was modified where appropriate for EMBASE and CINAHL. We limited the Ovid search for MEDLINE and EMBASE to humans (which was not possible for CINAHL), and applied a filter to identify randomised controlled trials in all three databases. We searched all Ovid databases from January 2002 until September 2006, as the preceding years were covered by the central search by the Cochrane Wounds Group for inclusion in CENTRAL.

Search strategy for CENTRAL:
#1. WOUND INFECTION explode all trees (MeSH)
#2. SURGICAL WOUND INFECTION explode all trees (MeSH)
#3. (wound near infect*)
#4. (skin near infect*)
#5. (surgical near infect*)
#6. (#1 or #2 or #3 or #4 or #5)
#7. SKIN ULCER explode all trees (MeSH)
#8. FOOT ULCER explode all trees (MeSH)
#9. LEG ULCER explode all trees (MeSH)
#10. VARICOSE ULCER explode all trees (MeSH)
#11. VENOUS ULCER explode all trees (MeSH)
#12. DIABETIC FOOT explode all trees (MeSH)
#13. WOUND HEALING explode all trees (MeSH)
#14. DECUBITUS ULCER explode all trees (MeSH)
#15. WOUNDS PENETRATING explode tree 1 (MeSH)
#16. WOUNDS GUNSHOT single term (MeSH)
#17. WOUNDS STAB explode tree 1 (MeSH)
#18. BURNS explode tree 1 (MeSH)
#19. BITES AND STINGS explode all trees (MeSH)
#20. (leg near ulcer*)
#21. (foot near ulcer*)
#22. (feet near ulcer*)
#23. (skin near ulcer*)
#24. (varicose near ulcer*)
#25. (venous near ulcer*)
#26. (diabetic near ulcer*)
#27. (diabetic next foot)
#28. (varicose near wound*)
#29. (bed near sore*)
#30. (pressure near sore*)
#31. (decubitus near ulcer*)
#32. (pressure near ulcer*)
#33. (bed near ulcer*)
#34. (surgical near wound*)
#35. (gun or guns or gunshot)
#36. (stab or stabs or stabbing)
#37. (burn or burns or scald*)
#38. (bite or bites or biting)
#39. laceration*

#40. (#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or
#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39)
#41. infect*
#42. swell*
#43. erythema*
#44. pain*
#45. (purulent or exudate*)
#46. odour
#47. (positive near culture*)
#48. hypertherm*
#49. swollen
#50. coloni*
#51. contamin*
#52. inflamm*
#53. (dirty near wound*)
#54. devital*
#55. necro*
#56. rubor
#57. calor
#58. dolor
#59. (#41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55
or #56 or #57 or #58)
#60. (#40 and #59)
#61. (#6 or #60)
#62. SILVER explode all trees (MeSH)
#63. silver*
#64. contreet
#65. acticoat
#66. aquacel
#67. avance
#68. urgotul
#69. actisorb
#70. arglaes
#71. sulphadiazine
#72. nanocrystalline
#73. sulfadiazine
#74. hydron
#75. katomed
#76. simanite
#77. silverlon
#78. sildimac
#79. dimac
#80. silvadene

#81. agsd
#82. ssd
#83. flammazine
#84. flamazine
#85. flammacerium
#86. sulplata
#87. sulfaplata
#88. silvazine
#89. siax
#90. (#62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76
or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89)
#91. (#61 and #90)

There was no restriction on the inclusion of reports based on publication language or publication status.

### Searching other resources

We also contacted companies, manufacturers and distributors of silver dressings for details of unpublished and ongoing trials and scrutinised citations within all obtained trials and major review articles to identify any additional trials.

## Data collection and analysis

### Selection of studies

Two authors (HV and DU) independently assessed the titles and abstracts of studies identified in terms of their relevance and design. Full versions of articles were obtained if the initial assessment of these met the inclusion criteria. Another author (JvH) evaluated the discrepant judgments.

### Data extraction and management

Details of trials were extracted and summarised using a data extraction sheet. If data were missing from reports, or clarification was needed, the authors were contacted to obtain missing information. Data from trials published in duplicate were to be included only once. Data extraction was undertaken by one author (HV or JvH) and checked for accuracy by a second (MS). Any discrepancy was resolved by discussion.

We extracted the following data:

- Characteristics of the trial (method of randomisation, setting, location of care, country, source of funding);
- Participants (number, age, sex, type of wound, definition used for infection, wound size, duration of wound, length of follow up, concurrent illnesses);
- Intervention (kind of silver dressing, dosage of silver used, frequency of dressing changes, concurrent interventions);

- Comparative intervention (other dressing with or without silver, dosage of silver used, number of dressing changes, concurrent interventions);
- Outcome measures;
- Primary outcome: time to complete healing, rate of change in wound area and volume, number and proportion of infected wounds healed within trial period;
- Secondary outcomes: days of wound infection (signs and symptoms of clinical infection and changes in bacterial flora); number and proportion of adverse effects on silver, number of patients reporting pain, patient satisfaction, quality of life (QoL), length of hospital stay (LOS), cost of treatment.

### Assessment of risk of bias in included studies

Authors (HV, JvH, and MS) independently and systematically assessed the methodological quality of the trials, using the criteria of the Dutch Institute for Health Care Improvement (www.cbo.nl) and Dutch Cochrane Centre regarding internal validity (www.cochrane.nl). Any disagreement was referred to a third author (DU) for adjudication.

The criteria mentioned above include the following items:

(1) ***Minimisation of selection bias***

- Was allocation of the intervention randomised?
- Was allocation concealed for the researcher who recruited the patients?
- What was the unit of allocation?
- Were both groups comparable at baseline, or was there adjustment for imbalance in the analysis?

(2) ***Minimisation of attrition bias***

- Were withdrawals properly described?
- Was an intention-to-treat analysis used?
- Was there evidence of differential loss to follow up?

(3) ***Minimisation of detection bias***

- Were all patients blinded to the intervention?
- Were all healthcare workers blinded to the intervention?
- Were all outcome assessors blinded to the intervention?

(4) ***Minimisation of follow-up bias***

- Was the proportion of completed follow up greater than 80%?
- Were both groups under investigation treated the same apart from the intervention?

- Was there evidence of reliability and validity of outcome measures?

Additionally, we assessed whether a medical ethics committee approved the trial and whether the patients gave informed consent to their participation.

### Data synthesis

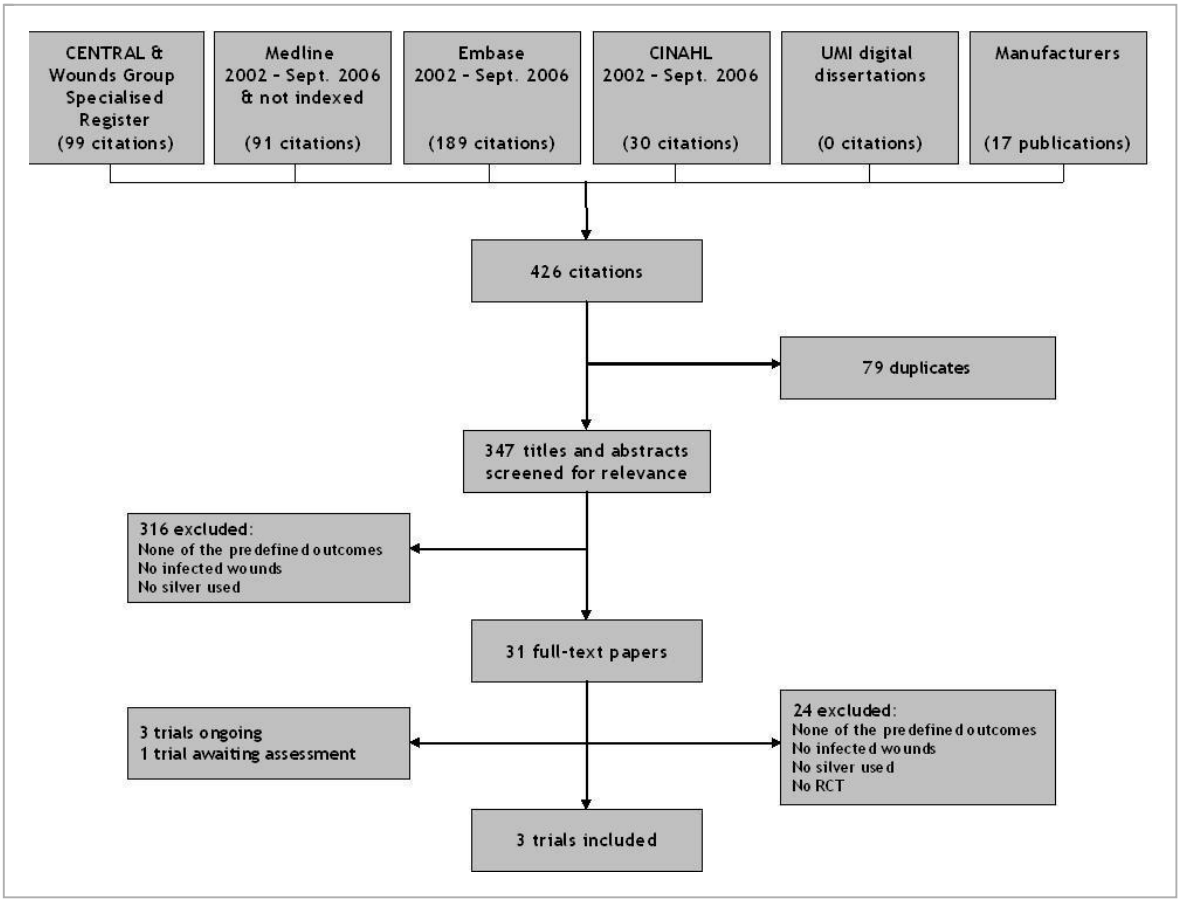
Quantitative data were entered into RevMan 4.2 by two authors (HV and JvH) and analysed using the Cochrane Collaboration software (RevMan 4.2) and were checked by MS and DU. For each outcome, summary estimates of treatment effect (with 95% confidence intervals (CI)) were calculated for every comparison. For continuous outcomes, the weighted mean differences (WMD) were presented, when appropriate. For dichotomous outcomes, the absolute risk reduction, i.e. risk difference (RD), was presented, which is an absolute effect measure that expresses the difference between the experimental and control event rates and allows calculation of NNTs. We refrained from a sensitivity analysis because of the small number of included trials.

# Results

## Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

The search identified 347 possibly relevant titles, of which 31 were still considered potentially relevant after the first screening of the titles. Their abstracts or full-text articles were obtained and screened by two independent authors for the inclusion and exclusion criteria (Table: *Characteristics of excluded studies* and Figure 1). Three ongoing RCTs were identified (Table: *Characteristics of ongoing studies* ). Two authors were approached for further information and data, but in vain. Contact details for one author were irretrievable. One trial in Japanese is awaiting assessment (**Yura 1984**).




## Figure 1.

Open in figure viewer

Flow chart.

The table *Characteristics of excluded studies* summarises the trials that did not meet the inclusion criteria and the reasons for their exclusion from this review.

Three RCTs met the inclusion criteria (Table: *Characteristics of included studies* ).

One trial was performed as a multi-centre trial in France and was published in 2005 (Meaume 2005); the other two were multinational trials published in 2005 (Jørgensen 2005) and 2006 (The CONTOP trial)(Münter 2006). Both Meaume 2005 and Münter 2006 reported an a priori sample size calculation. Trial sizes ranged from 99 to 619 patients with a total of 847 participants included in three trials. The wounds mainly comprised pressure, diabetic, and venous leg ulcers. The presence of infection in the Meaume 2005 trial was defined by having two or more of the following criteria; continuous pain, erythema, oedema, heat, or moderate to high levels of exudate; in the other two trials presence of an infection was based on various other clinical signs of 'critical colonisation' (Cutting 2005; Gardner 2001), i.e. delayed healing due to bacteria, increased pain, increased exudate levels, discolouration and malodour.

In the Jørgensen 2005 trial a silver-containing foam (Contreet®) dressing was compared with a standard foam dressing (Allevyn®) for four weeks in patients with infected chronic venous, or mixed leg ulcers.

In the Meaume 2005 trial a silver-containing alginate (Silvercel®) was compared with an alginate (Algosteril®) for four weeks in patients with infected venous leg ulcers and pressure ulcers.

In the Münter 2006 trial, a silver-containing foam dressing (Contreet®) was compared with best local practice, i.e. a range of dressings depending on the common practice in each contributing centre, for four weeks in patients with chronic wounds (mainly venous leg ulcers), donor sites, and postoperative wounds, with clinical signs of bacterial infection or contamination.

## Risk of bias in included studies

### Potential for selection bias

In all three trials the authors stated that patients were allocated randomly to treatment. Randomisation for two trials was computerised; Jørgensen 2005 used block-randomisation, Meaume 2005 used two a priori randomisation lists, and Münter 2006 used a 'computer-generated' block- randomisation in sealed envelopes. In all three trials the extent of allocation concealment was not clear. In all studies individual patients (i.e. not wounds) were allocated to the treatment groups. Treatment groups were comparable at baseline for wound size, aetiology and duration in the Jørgensen 2005 and Münter 2006 trials, but not in the Meaume 2005 trial, where the Silvercel group included more people with diabetes, participants were younger, and had a larger baseline wound area than in the Algosteril®) group.

### Potential for attrition bias

All three trials conducted intention-to-treat analysis, while Jørgensen 2005 and Meaume 2005 also performed per-protocol analysis for some performance endpoints(e.g. odour, exudate, quality of life).

In the Jørgensen 2005 trial, 13 of the 65 patients withdrew from the group treated with silver-containing foam dressings. Seven of these were due to violation of the inclusion criteria discovered in the monitoring process, including an unknown number of ulcers that did not meet the defined size limits. Another five exclusions were due to the use of antibiotics: three for use unrelated to the trial ulcer, two for trial ulcer infections. One patient was excluded because of other, unknown, protocol violations. Seven of the 64 patients were excluded from the group treated with standard foam dressings; five due to violation of the inclusion criteria, one due to unrelated use of antibiotics, and one due to unknown protocol violations. The authors used a per protocol analysis for some outcomes (e.g. odour, exudate, quality of life) and this is highly susceptible to attrition bias.

In the Meaume 2005 trial in total 19 patients discontinued the study but were included in the ITT analysis; 10 in the silver-containing alginate group and 9 in the control group. The reasons for these dropouts were; alginate dressing no longer indicated (2), consent withdrawal (1), wound grafting (2), wound infection (3), wound aggravation (6), cardiac arrest (1), car accident (1), patient transferred to another hospital (2), and patient went on holidays (1).

In the Münter 2006 trial some patients left the study prematurely, but the actual number was not stated. A 'last observation carried forward' principle was used to compensate for this loss to follow-up.

### Potential for detection bias

In none of the three trials, were the patients, health care professionals and outcome assessors blinded to the treatment given.

### Potential for follow-up bias

Follow up was greater than 80% in all three included studies.

In the Meaume 2005 trial patients were treated the same apart from the intervention. This was not clear in the Jørgensen 2005 and Münter 2006 trials.

In the Jørgensen 2005 and Münter 2006 trials, the relative wound area reduction was used as indicator for healing. Jørgensen 2005 measured wound size using transparent wound tracing sheets and computer software. The study personnel subjectively evaluated other outcomes, such as odour, maceration and dressing characteristics. General well-being was measured using the generic EQ-5D (EuroQol) questionnaire. Investigators in the Münter 2006 trial measured wound size using greatest length and greatest width. The available evidence for reliability and validity of the outcome measures used was stated only in a study by Russell et al. (Russell 2005), who reported that 20% to 40% reduction in wound area between two to seven weeks would be a reliable predictor of healing.

In the Meaume 2005 trial complete healing, absolute wound area reduction, and relative wound area reduction were used as indicators for healing. Each week the wound areas were measured by planimetry and all wounds were photographed. The mASEPSIS score (ranging from 0 to 350) was used to assess wound severity. This was described as a modified version of the validated ASEPSIS score.

### Consent, approval and financial support

All three trials gained approval from an ethical committee, and patients gave their written informed consent to participate. Each trial was financially supported; Jørgensen 2005 and Münter 2006 by Coloplast A/S, Humlebaek, Denmark, and Meaume 2005 by Johnson & Johnson Wound Management.

Overall the methodological quality of the three included trials was acceptable. See Table 1 for a summary of information concerning the quality of included studies.

**Table 1.** Quality of included studies

| | Jørgenson, 2005 | Meaume, 2005 | Münter, 2006 |
|---|---|---|---|
| **(1) Potential selection bias:** | | | |
| Was allocation of the intervention randomised? | Yes | Yes | Yes |

| | | | |
|---|---|---|---|
| Was allocation concealed for the researcher who recruited the patients? | ? | ? | ? |
| What was the unit of allocation? | individual patients | individual patients | individual patients |
| Were both groups comparable at baseline, or was there adjustment for imbalance in the analysis? | Yes | No | Yes |
| **(2) Potential attrition bias:** | | | |
| Were withdrawals properly described? | Yes | Yes | No |
| Was an intention-to-treat analysis used? | No | Yes | Yes |
| Was there evidence of differential loss to follow up? | No | No | ? |
| **(3) Potential detection bias:** | | | |
| Were all patients blinded to the intervention? | No | No | No |
| Were all healthcare workers blinded to the intervention? | No | No | No |
| Were all outcome assessors blinded to the intervention? | No | No | No |
| **(4) potential follow-up bias:** | | | |
| Was the proportion of completed follow up greater than 80%? | Yes | Yes | Yes |
| Were both groups under investigation treated the same apart from the intervention? | ? | Yes | ? |
| Was there evidence of reliability and validity of outcome measures? (as chosen in this review) | Yes | Yes | Yes |
| | | | |
| | Yes | Yes | Yes |

| | | | |
|---|---|---|---|
| Did an ethical committee approve the study? | | | |
| Did patients give informed consent to their participation? | Yes | Yes | Yes |
| Source of funding | Financially Supported by Coloplast A/S, Humlebaek, Denmark | Financially Supported by Johnson & Johnson Wound Management | Financially Supported by Coloplast A/S, Humlebaek, Denmark |

## Effects of interventions

Each of the three included trials described a unique comparison, so there was no opportunity to perform a meta-analysis.

### COMPARISON 1: Silver-containing foam dressings compared with hydrocellular foam

One trial (**Jørgensen 2005**) compared silver-containing foam (Contreet®) with hydrocellular foam (Allevyn®). Wound duration at the start of the trial was similar in both groups (medians 1.1 and 1.0 years, respectively), but ranged substantially (from 0.1 to 32 years). Baseline median wound sizes were also similar: 5.9 (range: 1.9-37.4) and 6.8 (range: 2.1-33.8) $cm^2$, respectively.

*Primary outcome* :

### Wound healing

Four different measures of wound healing were used:

1. the number of ulcers healed completely (within the four-week trial period);
2. the mean and median ulcer area in $cm^2$;
3. the mean and median relative reduction in ulcer area in %, calculated as the median of each patients' wound size reduction; and
4. the number of ulcers not responding to the treatment and increasing in size.

1. Assessments of healing were made after one, two, three and four weeks of treatment. There was no significant difference in rates of complete healing; five ulcers out of 65 patients (8%) treated with Contreet® and five out of 64 (8%) treated with Allevyn® healed completely during the trial period (RD: 0.00; 95% CI: -0.09 to 0.09) (Analysis 1.4).
2. The median ulcer area after four weeks of treatment was not significantly smaller in the Contreet® group (3.0 $cm^2$; range: 0.0-35.9) than the Allevyn® group (4.5 $cm^2$; range: 0.0-33.6). The WMD was -0.30 cm2 (95% CI: -2.92 to 2.35) (Analysis 1.5).
3. The median relative reduction in ulcer area after four weeks of treatment, was significantly (P=0.034) greater in the Contreet® group (54.8% of the original size,

i.e. 45.2% reduction) than the Allevyn® group (74.6% of original size, i.e. 25.4% reduction). The WMD was -15.70 $cm^2$ (95%CI: -29.5 to -1.90). (Analysis 1.6).

4. Nine of 65 (14%) of the ulcers in the Contreet® group, and 16 of the 64 (25%) in the Allevyn® group did not respond to the treatment and increased in size (RD: -0.11; 95% CI: -0.25 to 0.02) (Analysis 1.7).

In summary, although relative wound size reduction was significantly quicker in the Contreet group, there was no significant difference in rates of complete wound healing after four weeks.

*Secondary outcomes*

### Days of wound infection

Days of wound infection were not reported for this comparison.

### Adverse effects

Four instances (8%) of device-related adverse effects were recorded in the Contreet® group (satellite ulcers and deterioration of periulcer skin), and three (5%) in the Allevyn® group (maceration, eczema and satellite ulcers)(no significant difference). These were all skin reactions (RD: 0.02; 95% -0.07 to 0.12) (Analysis 1.8).

### Use of systemic antibiotics

Five of the 65 (8%) patients in the Contreet® group, and one of the 64 (2%) patients in the Allevyn® group (RD: 0.06; 95% CI: -0.01 to 0.13)(Analysis 1.9) used antibiotics at some time during the trial period, all of which were excluded from per protocol analyses.

### Pain

Average intensity of pain was rated between 0 and 10. Patients in both groups indicated a decrease of pain during the treatment. No data were reported in the study report.

### Patient satisfaction and QoL

Patient satisfaction was measured using odour, leakage and the EQ-5D tool for the health-related QoL. EQ-5D questionnaire (1=perfect health, 0=death) demonstrated no significant difference in quality of life at the end of the trial period for both treatment groups, (Contreet foam group at baseline scored a mean of 0.69 and moved to a score of 0.79 at week 4; people in the Allevyn group had baseline scores of 0.71 moving to 0.79 at week 4).

Wound odour, evaluated weekly on a four-point scale by the study personnel (who were aware of the treatment group, so were not blinded), was lower in patients in the Contreet® group (for every week) compared with the Allevyn® group. At the end of the trial, 10 out of 52 (19%) patients in the Contreet® group and 22 out of 57 (39%) treated with Allevyn® still presented some odour (P value 0.030; RD: -0.19; 95% CI: -0.36 to -0.03)(Analysis 1.13). Leakage was assessed (unblinded) at one and four weeks: at week four, significantly fewer

patients in the Contreet® group (10 out of 52 (19%) patients) experienced leakage compared with those treated with Allevyn® (28 out of 57 (49%) patients) (P value 0.002; RD: -0.30; 95% CI: -0.47 to -0.13) (Analysis 1.15); this was not the case at one week.

### Length of hospital stay and costs

Length of hospital stay and costs were not reported for this comparison.

## COMPARISON 2: Silver containing alginate compared with alginate

One trial (**Meaume 2005**) compared silver containing alginate (Silvercel®) with alginate alone (Algosteril®). At baseline the silver group differed from the comparison group. Significantly fewer patients in the silver group were aged 80 years or over (21% compared with 52% in the alginate group), significantly more patients had diabetes (33% versus 12%) and their wounds tended to be larger in size at baseline (39.1 $cm^2$ versus 23.9 $cm^2$ ) and of longer duration (32.6 versus 18.3 months). In the analysis the difference in wound size was compensated for by subtracting the baseline values. The remaining characteristics did not differ between the groups.

*Primary outcome:*

### Wound healing

Four different measures of wound healing were used:

1. the number of ulcers healed completely (within the four-week trial period);
2. the absolute wound area decrease (within the four-week trial period);
3. relative wound area decrease (within the four-week trial period); and
4. healing rate measured as $cm^2$ per day at 1, 2, 3, and 4 weeks, and for the total four-week trial period.

For the first three measurements no statistically significant differences were found.

1. At the end of the four-week trial period 1 ulcer healed in both groups; 1/51 versus 1/48 (risk difference 0.00; 95% confidence interval -0.06 to 0.05)(Analysis 2.1).
2. The mean absolute reduction in wound area in the silver containing alginate group was 8.9 (16.0)$cm^2$ versus 4.4 (11.3) $cm^2$ in the alginate group (weighted mean difference 4.50 $cm^2$; 95% confidence interval -0.93 to 9.93)(Analysis 2.2) .
3. Within the four-week trial period the relative wound area decreased in the silver containing group by 23.7% and in the alginate group by 24.0% (weighted mean difference -0.30 $cm^2$; 95% confidence interval -17.08 to 16.48)(Analysis 2.3).
4. The wound healing rate in $cm^2$ per day at week 1; was -0.79 for the silver containing alginate group versus -0.37 in the alginate group, at week two -0.55 versus -0.23, at week three -0.14 versus -0.14, at week four -0.52 versus -0.16, and for the complete four-week trial period -0.32 versus -0.16 (Analysis 02:4-08). For the fourth measurement **Meaume 2005** reported a statistically significant difference of P=0.024. We calculated the weighted mean difference of 0.16 $cm^2$;

95% with a confidence interval of -0.03 to 0.35 (Analysis 2.8) which indicates only a small treatment effect.

*Secondary outcomes*

### Days of wound infection

Meaume 2005 used the mASEPSIS score as a combined infection parameter from which we could not extract the duration of wound infection.

### Adverse effects

In both groups 5 patients experienced an adverse event; 5/51 in the silver alginate group versus 5/48 in the alginate group (risk difference -0.01; 95% confidence interval -0.12 to 0.11) (Analysis 2.9). In the silver-containing alginate group the adverse effects were; peri-wound eczema, peri-wound irritation due to maceration, extension of slough plus a dry wound, pruritus plus pain and pain during dressing change plus peri-wound erythema plus pruritis. In the alginate group were observed; pain during dressing change, peri-wound eczema, intermittent burning sensation immediately after dressing application, increase wound size plus pain, and erythema plus pain.

### Use of systemic antibiotics

In the silver containing dressing group to 4/51(7.8%) patients received systemic antibiotics compared with 5/48 (10.4%) patients in the alginate group, risk difference -0.03; 95% confidence interval -0.14 to 0.09) (Analysis 2.10).

### Pain

Pain was not measured for this comparison, but mentioned as an adverse effect.

### Patient satisfaction and QoL

Patients satisfaction and QoL were not measured for this comparison.

### Length of hospital stay and costs

Not reported for this comparison.

## COMPARISON 3: Silver-containing foam compared with best local practice

One trial (Münter 2006) compared Contreet® with best local practice, i.e. a range of dressings: foams & alginates (53%), hydrocolloids (12%), gauze (3%), silver dressings (17%), other antimicrobial dressings (9%) or other active dressings (6%).

Wound aetiologies were similarly distributed in both groups. Baseline wound sizes in the Contreet and local best practice groups were reported (medians: 20.0 $cm^2$ and 12.0 $cm^2$, and means: 52.9 $cm^2$ and 36.6 $cm^2$, respectively), although variation was high (from 0.1 to 700 $cm^2$ and from 0.1 to 400 $cm^2$, respectively). Exudate levels at baseline in the Contreet® and best practice groups were 'moderate' (three-level rating scale) and the condition of the peri-

ulcer skin was normal in 24.3% and 24.0%, respectively. Quality of life scores were similar at baseline.

*Primary outcome* :

### Wound healing

This was expressed as the median relative reduction in ulcer area in %.

The median relative reduction in ulcer area after four weeks of treatment was 50% in the Contreet® group, and 34% in the best local practice group, it should be noted that this result is against the direction of baseline bias. Analysis of the results at the final visit whilst carrying forward the last observation, showed a difference of 47% compared with 32% in favour of Contreet®, which was statistically significant (P=0.0019). In subgroups of venous leg ulcers and pressure ulcers the results as to ulcer area reduction were similar. Trialists did not report how many patients had final endpoint data and how many required that data from the last observation was carried forward.

In summary, relative wound size reduction was significantly quicker in the Contreet group. However, this outcome parameter was used as an unblinded, surrogate endpoint for wound healing.

*Secondary outcomes*

### Days of wound infection

Not reported for this comparison.

### Adverse effects

None reported.

### Use of systemic antibiotics

Not reported.

### Pain

The pain score was derived from a numerical box scale ranging from 0 to 10. Median pain scores both during and between dressing changes were low: 1 in the Contreet® and 2 in the best practice group, i.e. significantly in favour of the Contreet® group (P<0.0001 and P=0.0011, respectively). Apparently, the dressing change did not lead to an increased pain sensation.

### Patient satisfaction and QoL

QoL was assessed using the five dimensional EuroQol questionnaire (EQ-5D). Median baseline EQ-5D scores were 0.62 in both groups. At study conclusion these were 0.71 in the Contreet® and 0.69 in the best practice groups. No statistical comparison was performed.

Malodour, scored on a four-point rating scale, had disappeared after one week in the Contreet® group and after two weeks in the best practice group (P<0.0001). No exact numbers were given. Leakage was considered the main reason for dressing changes in

14.8% of patients in the Contreet group and 25.8% in the best practice group (RD: -0.11, 95% CI: -0.18 to -0.05). (Analysis 3.1).

### Length of hospital stay and costs

Length of hospital stay and costs were not measured for this comparison, although the authors justified the cost-effectiveness of Contreet® by calculating the mean dressing wear times in the Contreet® and best practice groups (3.1 and 2.1 days, respectively; P<0.0001) and the time spent on a typical dressing (0-10 minutes and 10-20 minutes, respectively; P=0.003). Because these parameters, as well as wound healing rates, were in favour of Contreet®, the authors state this saves the costs of nurses' and patients' time and dressing materials.

## Discussion

Whilst silver-containing dressings are increasingly used, we found only three randomised controlled trials evaluating the effectiveness of silver to treat contaminated or infected wounds. None of the trials demonstrated clear evidence of the effectiveness of topical silver in terms of increased healing rates. Hence, there is a lack of appropriate randomised clinical trials evaluating the effect of silver-based products, as was noted earlier by Bergin 2006 when studying silver for diabetic foot ulcers.

All three trials had a short follow-up of only four weeks (although they concerned chronic wounds) and used multiple time points and parameters to measure wound healing. These multiple measurements increase the chance of false positive results, therefore any statistically significant results on wound healing should be considered with caution. Secondly, the various ways of measuring wound healing used in these trials can been regarded as surrogate endpoints, because only complete wound healing is most relevant to the patient.

To accelerate wound healing, infection of the wound needs to be dealt with. Surprisingly we found that the duration of wound infection was not measured in any of the included trials, although this seems the very reason why silver-containing dressings should be used in contaminated or infected wounds. Furthermore, none of the silver-containing dressings appeared to significantly reduce the need for systemic antibiotic treatment.

Skin reactions were the most frequently described adverse effect in the trials by Jørgensen 2005 and Meaume 2005, but occurred in both in the silver-containing group and in the control groups.

A possible stinging sensation is mentioned in the product information of various silver-containing dressings. Pain was reported in the Münter 2006 trial, showing low pain scores, which were even lower in the silver-containing dressing group. In the Meaume 2005 trial only one patient treated with the silver-containing dressing complained about pain. This is in contrast with the notion that (dressing changes in) chronic wounds, particularly (infected) venous leg ulcers, are painful (Moffat 2002). Possibly the exudate level of the studied wounds, which were contaminated or infected, was such that dressings did not adhere or caused considerable pain.

In two of the included trials (Jørgensen 2005; Münter 2006) quality of life was investigated, but showed no significant differences. Patient satisfaction was not investigated at all. Two trials measured odour and leakage. In the trial of Jørgensen 2005 it was shown that silver-containing foam dressings were significantly better at reducing odour and leakage than standard foam dressings. In the trial of Münter 2006, patients treated with silver-containing foam experienced less pain, showed a quicker reduction of odour, and required less frequent dressing changes due to leakage. These secondary advantages of silver can be used in balancing the pros and cons for the use of silver.

Length of hospital stay and costs were not investigated in the trials included. Hence, we cannot draw any conclusions on this point from the randomised data we have presented here.

The following limitations of this review should be noted:
The trials we found comprised different wounds, dressings, and endpoints, which prohibited any meta-analysis. All 3 studies were small and of low power. Hence, although the methodology of the included trials was acceptable, we should be cautious about drawing firm conclusions on the use of silver in contaminated or infected wounds. We can conclude that high-level clinical evidence is missing regarding the effectiveness of silver in treating infected wounds.

Secondly, the absence of a measurable effect of silver-containing dressings on wound healing is influenced by the short treatment and follow-up durations in the included trials, as chronic wounds usually require a much longer healing period. If one would choose to settle for a shorter follow-up, the duration of wound infection should have been used as an outcome parameter. This gives information about an important factor in delayed wound healing.

Thirdly, whilst rates of systemic antibiotic use was reported, duration of wound infection was not.

Fourthly, the trials included a large number of (not always clinically relevant) endpoints, as well as repeated measurements (e.g. at three, seven, 14 and 21 days for one endpoint), which may illustrate the eagerness of the investigators (or the sponsors) to identify any differences between treatments, at the cost of an increased chance of falsely positive results.

Finally, it is hard to persuade readers of the objectivity of a trial when financed by a single manufacturer, as was the case in all three trials.

In general, the results of this systematic review are in accordance with other systematic reviews on local wound care, which all indicate a paucity of high-level evidence (Bergin 2006; Nelson 2007; Temple 2004; Ubbink 2008; Vermeulen 2004). To illustrate this paucity, Bergin 2006 found no eligible studies at all for inclusion in their review of "Silver-based wound dressings and topical agents for treating diabetic foot ulcers". At present, three trials evaluating the effectiveness of topical silver in the treatment of infected wounds are stated as ongoing. Therefore, hopefully more relevant publications may be expected in the near future.

In conclusion, at present there is little high-level evidence existing to support the use of silver-containing dressings or applications in the treatment of colonised or infected wounds. Although trials are ongoing, more rigorous evaluation is essential before the use of silver becomes routine for local wound care. Until reliable data on relative effectiveness become

available, considerations such as cost-minimisation may be used to guide decisions on the use of silver-containing dressings.

# Authors' conclusions

## Implications for practice

There is insufficient randomised controlled trial evidence available to allow conclusions to be drawn about the use of silver-containing dressings or topical agents to enhance wound healing of infected chronic wounds.

## Implications for research

Stringent trial methodology and reporting is advocated for future research. The use of common, clinically relevant endpoints (time to complete wound healing, change in wound size, days of wound infection, pain, adverse effects, costs, and, preferably, a validated scale for patient satisfaction) should always be used. Whilst it is very difficult to blind patients and medical professionals with regard to the intervention, it is possible to blind outcome assessors, or to use computer programmes to measure wound size, although time to complete healing is the most important primary outcome. Finally a sufficiently long follow-up duration (at least six months) is essential for any wound healing effect to be detectable in chronic wounds.

This systematic review addressed topical silver for treating infected wounds. Topical silver has also been studied for the prevention of wound infections. These studies deserve systematic review as well. Financial support is needed to perform additional RCTs and SRs on research in wound healing and care. Therefore, decision makers should strive for this as long as we cannot provide them with strong recommendations. Collaboration of stakeholders (doctors, nurses and decision makers in local wound care) should provide convincing, high-quality research protocols to persuade sponsors to generate and support research that has the potential to answer the questions of decision makers and improve patient care.

# Acknowledgements

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# Data and analyses

Download statistical data

**Comparison 1.** Contreet Foam vs Allevyn Hydrocellular

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Wounds healed after 1 week of treatment | 1 | 129 | Risk Difference (M-H, Fixed, 95% CI) | Not estimable |
| 2 Wounds healed after 2 weeks of treatment | 1 | 129 | Risk Difference (M-H, Fixed, 95% CI) | 0.05 [-0.01, 0.10] |
| 3 Wounds healed after 3 weeks of treatment | 1 | 129 | Risk Difference (M-H, Fixed, 95% CI) | 0.05 [-0.03, 0.12] |
| 4 Wounds healed after 4 weeks of treatment | 1 | 129 | Risk Difference (M-H, Fixed, 95% CI) | -0.00 [-0.09, 0.09] |
| 5 Mean ulcer area after 4 weeks | 1 | 109 | Mean Difference (IV, Fixed, 95% CI) | -0.30 [-2.95, 2.35] |
| 6 Mean relative ulcer area after 4 weeks | 1 | 109 | Mean Difference (IV, Fixed, 95% CI) | -15.70 [-29.50, -1.90] |
| 7 Ulcers increased in size (non-responsives) | 1 | 129 | Risk Difference (M-H, Fixed, 95% CI) | -0.11 [-0.25, 0.02] |
| 8 Adverse effects (skin reactions) | 1 | 109 | Risk Difference (M-H, Fixed, 95% CI) | 0.02 [-0.07, 0.12] |
| 9 Systemic antimicrobials during the study | 1 | 129 | Risk Difference (M-H, Fixed, 95% CI) | 0.06 [-0.01, 0.13] |
| 10 Odour after 1 week | 1 | 109 | Risk Difference (M-H, Fixed, 95% CI) | -0.30 [-0.47, -0.14] |
| 11 Odour after 2 weeks | 1 | 109 | Risk Difference (M-H, Fixed, 95% CI) | -0.31 [-0.49, -0.14] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 12 Odour after 3 weeks | 1 | 109 | Risk Difference (M-H, Fixed, 95% CI) | -0.36 [-0.52, -0.20] |
| 13 Odour after 4 weeks | 1 | 109 | Risk Difference (M-H, Fixed, 95% CI) | -0.19 [-0.36, -0.03] |
| 14 Leakage after 1 week | 1 | 109 | Risk Difference (M-H, Fixed, 95% CI) | -0.17 [-0.35, 0.01] |
| 15 Leakage after 4 weeks | 1 | 109 | Risk Difference (M-H, Fixed, 95% CI) | -0.30 [-0.47, -0.13] |

**Comparison 2.** Silvercel Alginate vs Algosteril

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Wounds healed after 4 weeks | 1 | 99 | Risk Difference (M-H, Fixed, 95% CI) | -0.00 [-0.06, 0.05] |
| 2 Absolute wound reduction within 4 weeks | 1 | 99 | Mean Difference (IV, Fixed, 95% CI) | 4.5 [-0.93, 9.93] |
| 3 Relative wound reduction within 4 weeks in cm2 | 1 | 99 | Mean Difference (IV, Fixed, 95% CI) | -0.30 [-17.08, 16.48] |
| 4 Healing rate in cm2 per day in week 1 | 1 | 99 | Mean Difference (IV, Fixed, 95% CI) | 0.42 [-0.10, 0.94] |
| 5 Healing rate in cm2 per day in week 2 | 1 | 99 | Mean Difference (IV, Fixed, 95% CI) | 0.32 [-0.12, 0.76] |
| 6 Healing rate in cm2 per day in week 3 | 1 | 99 | Mean Difference (IV, Fixed, 95% CI) | -0.28 [-0.83, 0.27] |
| 7 Healing rate in cm2 per day in week 4 | 1 | 99 | Mean Difference (IV, Fixed, 95% CI) | 0.36 [-0.06, 0.78] |
| 8 Healing rate in cm2 per day in week 1 to 4 | 1 | 99 | Mean Difference (IV, Fixed, 95% CI) | 0.16 [-0.03, 0.35] |
| 9 Adverse effects | 1 | 99 | Risk Difference (M-H, Fixed, 95% CI) | -0.01 [-0.12, 0.11] |
| 10 Systemic antimicrobials during the study | 1 | 99 | Risk Difference (M-H, Fixed, 95% CI) | -0.03 [-0.14, 0.09] |

**Comparison 3.** Contreet Foam vs local best practice

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Leakage as main reason for dressing change | 1 | 619 | Risk Difference (M-H, Fixed, 95% CI) | -0.11 [-0.18, -0.05] |

# Appendices

## Appendix 1. MEDLINE Search Strategy

Search strategy for MEDLINE which will be adapted as necessary for EMBASE and Cinahl.
1. Exp WOUND INFECTION/
2. Exp SURGICAL WOUND INFECTION/
3. (wound adj6 infect$)
4. (skin adj6 infect$)
5. (surgical adj6 infect$)
6. (1 or 2 or 3 or 4 or 5)
7. Exp SKIN ULCER/
8. Exp FOOT ULCER/
9. Exp LEG ULCER/
10. Exp VARICOSE ULCER/
11. Exp VENOUS ULCER/
12. Exp DIABETIC FOOT/
13. Exp WOUND HEALING/
14. Exp DECUBITUS ULCER/
15. Exp WOUNDS PENETRATING/
16. Exp WOUNDS GUNSHOT/
17. Exp WOUNDS STAB/
18. Exp BURNS/
19. Exp "BITES AND STINGS"/
20. (leg adj6 ulcer$)
21. (foot adj6 ulcer$)
22. (feet adj6 ulcer$)
23. (skin adj6 ulcer$)
24. (varicose adj6 ulcer$)
25. (venous adj6 ulcer$)
26. (diabetic adj6 ulcer$)
27. (diabetic adj foot)
28. (varicose adj6 wound$)
29. (bed adj6 sore$)
30. (pressure adj6 sore$)
31. (decubitus adj6 ulcer$)

32. (pressure adj6 ulcer$)
33. (bed adj6 ulcer$)
34. (surgical adj6 wound$)
35. (gun or guns or gunshot)
36. (stab or stabs or stabbing)
37. (burn or burns or scald$)
38. (bite or bites or biting)
39. laceration$
40. (7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39)
41. infect$
42. swell$
43. erythema$
44. pain$
45. (purulent or exudate$)
46. odour
47. (positive adj6 culture$)
48. hypertherm$
49. swollen
50. coloni$
51. contamin$
52. inflamm$
53. (dirty adj6 wound$)
54. devital$
55. necro$
56. rubor
57. calor
58. dolor
59. (41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58)
60. (40 and 59)
61. (6 or 60)
62. exp SILVER/
63. $silver$
64. contreet
65. acticoat
66. aquacel
67. avance
68. urgotul
69. actisorb
70. arglaes
71. sulphadiazine
72. nanocrystalline
73. sulfadiazine
74. hydron

75. katomed
76. simanite
77. silverlon
78. sildimac
79. dimac
80. silvadene
81. agsd
82. ssd
83. flammazine
84. flamazine
85. flammacerium
86. sulplata
87. sulfaplata
88. silvazine
89. siax
90. (62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89)
91. (61 and 90)

# What's new

| Date | Event | Description |
|---|---|---|
| 7 September 2010 | Amended | Contact details updated. |

# History

Protocol first published: Issue 4, 2005
Review first published: Issue 1, 2007

| Date | Event | Description |
|---|---|---|
| 15 June 2010 | Amended | Contact details updated. |
| 11 August 2009 | Amended | Contact details updated. |
| 11 November 2008 | Amended | Contact details updated |
| 7 August 2008 | Amended | Converted to new review format. |
| 13 October 2006 | New citation required and conclusions have changed | Substantive amendment |

## Contributions of authors

HV contributed substantially to the protocol and:
a) developed the search strategy;
b) identified studies from the search;
c) undertook quality assessment;
d) extracted data from these studies;
e) entered data in RevMan;
f) performed data analysis;
g) interpreted the results;
h) drafted the review;
i) gave final approval of the review to be published.

JvH
a) developed the search strategy;
b) evaluated discrepant judgments of excluded studies;
c) undertook quality assessment;
d) extracted data from these studies;
e) entered data in RevMan;
f) performed data analysis;
g) interpreted the results;
h) drafted the review;
i) gave final approval of the review to be published

MSV contributed substantially to the protocol and:
a) verified the search strategy;
b) undertook quality assessment;
c) checked extracted data from these studies;
d) checked the data into RevMan;
e) interpreted the results;
f) gave final approval of the review to be published.

DU contributed substantially to drafting the protocol, supervised the draft process of the protocol and:
a) checked the rejected articles;
b) identified studies from the search;
c) resolved any disagreement in quality assessment;
d) checked the data into RevMan;
e) checked data analysis;
f) interpreted the results;
g) supervised the draft process of the review;
h) gave final approval of the version to be published.

## Declarations of interest

None declared

# Characteristics of studies

## Characteristics of included studies [ordered by study ID]

### Jørgensen 2005

| | |
|---|---|
| Methods | RCT<br>Computer-generated randomisation, block-randomised |
| Participants | People with moderately or highly exudating chronic venous, or mixed leg ulcers with clinical signs of critical colonisation |
| Interventions | Contreet (silver-containing foam)<br>compared with<br>Allevyn (foam) |
| Outcomes | Wound healing, wound area reduction, odour, maceration, ease of removal, ease of application, absorption capacity, leakage, QoL Patient: odour, influence on well being, comfort of dressing, adverse events |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

### Meaume 2005

| | |
|---|---|
| Methods | RCT<br>A priori randomisation lists, balanced by blocks of six. one list for venous leg ulcers and one list for pressure ulcers (stratification) |
| Participants | People with leg ulcers and pressure ulcers with at least two of the following criteria present; continuos pain, erythema, oedema, heat, moderate to high levels of serous exudate |
| Interventions | Silvercel (silver-containing alginate) compared with Algosterile (alginate) |
| Outcomes | Wound healing, wound area reduction, mASEPSIS score, wound severity scores, adverse events |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|

| | | |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

### Münter 2006

| | |
|---|---|
| Methods | RCT<br>Computer generated list in sealed envelopes, block-randomised |
| Participants | Patients with delayed healing ulcers, burns, donor sites and postoperative wounds (n = 619). |
| Interventions | Contreet (silver-containing dressing) compared with best local practice. |
| Outcomes | Reduction in ulcer area, exudate level, QoL: odour leakage, pain and EQ-5D, cost-effectiveness |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

[a] Abbreviations
QoL = quality of life
RCT = randomised controlled trial

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

| Study | Reason for exclusion |
|---|---|
| Boer, de 1981 | CCT |
| Carneiro 2002 | Wounds not infected, and mainly children |
| Cassino 2002 | Wound healing, no outcome measurement |
| Cochran 2002 | No silver |
| Colonna 2004 | CCT |

[a] Abbreviations
CCT = clinical controlled trial

| Study | Reason for exclusion |
|---|---|
| D'Alicandro 2003 | CCT |
| Fang 1987 | Wounds not infected |
| Foster 2000 | No silver |
| Gotschall 1998 | Children |
| Gregory 2002 | Wounds not infected |
| Healy 1989 | No silver, and wounds not infected |
| Kafali 2004 | No open wounds (Bartholin's cyst or abscess) |
| Karlsmark 2003 | Wounds not infected |
| Kucan 1981 | Primary outcome not reported |
| Lloyd 1989 | CCT on children |
| Rayman 2005 | No control group |
| Rogers 2000 | CCT |
| Serra 2005 | CCT |
| Sinha 1997 | Wounds not infected |
| Snelling 1978 | Wounds not infected, and a CCT |
| Unknown Author | Not a clinical trial (in vitro) |
| Wright 1999 | Not clinical trial (in vitro) |
| Wuite 1974 | Wounds not infected, and children |

[a] Abbreviations
CCT = clinical controlled trial

## Characteristics of ongoing studies [ordered by study ID]

### Allen 1996

| | |
|---|---|
| Trial name or title | Prospective study of clinical infections in wounds dressed with occlusive versus conventional dressings |

| | |
|---|---|
| Methods | |
| Participants | Patients with venous ulcers, burns, and donor sites |
| Interventions | Occlusive hydrocolloid dressing with or without silver sulphadiazine cream compared with conventional impregnated gauze dressing |
| Outcomes | |
| Starting date | Not known |
| Contact information | Irretrievable |
| Notes | Conference proceedings |

## Contretas-Ruiz 2004

| | |
|---|---|
| Trial name or title | Larval debridement therapy to control infection in venous leg ulcers: a comparative study |
| Methods | |
| Participants | Patients with chronic venous ulcers (n=19) |
| Interventions | Topical silver and curettage<br>compared with larval debridement therapy |
| Outcomes | Wound healing, quantitative cultures, odour, secretion |
| Starting date | Not known |
| Contact information | e-mail: rrm@servidor.unam.mx |
| Notes | Conference proceedings |

## Jude 2004

| | |
|---|---|
| Trial name or title | Non-ischemic diabetic foot ulcers: Effects of Aquacel Ag with Hydrofibre versus Alginate dressing |
| Methods | |
| | |
| [a] Abbreviations<br>n = number in sample group<br>QoL = quality of life | |

| | |
|---|---|
| Participants | Patiens with Wagner grade 1 or 2 diabetic foot ulcers (n=120) |
| Interventions | Hydrofibre dressing containing silver (Aquacel Ag)<br>compared with<br>alginate dressing |
| Outcomes | Healing rate, ulcer infection, time to resolution and recurrence of ulcer-related antibiotic use, dressing size and change frequency, resource utilization, adverse effects |
| Starting date | Not known |
| Contact information | e-mail:<br>Edward.Jude@tgh.nhs.uk |
| Notes | Conference proceedings |

[a] Abbreviations
n = number in sample group
QoL = quality of life

## References

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