Evidence based decisions in nursing and their effect on quality of care
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Chapter 6

Topical silver for preventing wound infection: a systematic review

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ABSTRACT

**Background:** Silver-containing treatments are popular and used in wound treatments to combat a broad spectrum of pathogens, but evidence of their effectiveness in preventing wound infection or promoting healing is lacking.

**Objectives:** To establish the effects of silver-containing wound dressings and topical agents in preventing wound infection and healing of wounds.

**Search strategy:** We searched the Cochrane Wounds Group Specialised Register (6 May 2009); The Cochrane Central Register of Controlled Trials (CENTRAL) (2009 Issue 2); Ovid MEDLINE (1950 to April Week 4 2009); Ovid EMBASE (1980 to 2009 Week 18); EBSCO CINAHL (1982 to April Week 4 2009) and Digital Dissertations (to May 2009) for relevant trials. We contacted manufacturers and distributors.

**Selection criteria:** Randomised controlled trials (RCTs) comparing silver-containing wound dressings and topical agents with silver-containing and non-silver-containing comparators on uninfected wounds.

**Data collection and analysis:** Two authors independently selected trials, assessed risk of bias, and extracted data.

**Main results:** We identified 26 RCTs (2066 patients). Heterogeneity of treatments and outcomes precluded meta-analysis. We grouped results according to wound type, and silver preparation.

**Burns:** Thirteen trials compared topical silver (in a variety of formulations - including silver sulfadiazine (SSD) cream) with non-silver dressings. One trial showed fewer infections with silver nitrate when compared with a non-silver dressing, but three trials showed significantly more infection with SSD than with the non-silver dressing. Six trials compared SSD cream with silver-containing dressings. One showed significantly fewer infections with the silver-containing dressing (Hydron AgSD) compared with SSD, the remaining five found no evidence of a difference. One trial compared two silver-containing dressings, and showed a significantly lower infection rate with silver-coated gauze (Acticoat®) than with silver nitrate gauze.

**Other wounds:** Six trials compared SSD/silver-containing dressings with non-silver dressings (nine dressings in total). Most comparisons (seven) found no significant differences in infection rates; one trial in a variety of wounds exhibited significantly fewer infections with SSD/hydrocolloid, but another, in acute wounds, found significantly more infections with SSD. Only one comparison showed a significant reduction in healing time associated with a silver-containing hydrofibre dressing in diabetic foot ulcers.

**Authors’ conclusions:** There is insufficient evidence to establish whether silver-containing dressings or topical agents promote wound healing or prevent wound infection; some poor quality evidence suggests SSD is harmful rather than beneficial.
BACKGROUND

Description of the condition
Wounds are a prevalent clinical problem and a burden to many patients, resulting in pain, discomfort, longer hospital stay, and considerable economic costs for the healthcare system. Wounds are either acute or chronic, and can result from venous or arterial insufficiency, diabetes, burns, trauma, chronic pressure or surgery.\(^1,2\) If wounds become contaminated with bacteria or clinically infected, wound healing is likely to be impaired.\(^3\) This holds true for both acute and chronic wounds. In addition, wound infection is one of the most common surgical complications,\(^4\) and leads to significant mortality and morbidity. The focus in wound care, therefore, is to prevent wound infection and to promote wound healing.

Prevention of wound infection has always been a challenge. It was not until the late eighteenth century that micro-organisms were recognised as the cause of infectious diseases, and the principles of asepsis and hygiene began to be more fully understood (germ theory, as developed by Pasteur during the period 1860 to 1863, and Lister’s development of antiseptic surgery).\(^5\) Good hygiene and use of antiseptics were initially considered effective strategies for the prevention of infection, including wound infection. Nurses developed stringent hygiene rules for dressing changes,\(^6-9\) and physicians experimented with various antiseptics. Some of these preventative actions have been investigated for their effectiveness in various types of wounds, including aseptic dressing techniques,\(^10,11\) hand-rubbing,\(^12-16\) sterile gloving,\(^17,18\) shaving,\(^19-21\) and skin disinfection.\(^22\)

Description of the intervention
Several antiseptic dressings or agents are available, each claiming advantages regarding wound healing or prevention of wound infection. The effectiveness of antiseptics such as povidone iodine, chlorhexidine, alcohol, and silver-based compounds against microorganisms has been studied in vitro as well as in vivo.\(^23-28\) In particular, silver-based compounds (e.g. silver sulfadiazine cream (SSD)) have been widely used on burns since the 1960s in an attempt to overcome the problem of wound infection,\(^29\) and increasingly, silver-containing dressings and topical applications are being used to prevent infection in non-burn wounds such as leg ulcers,\(^30\) diabetic foot ulcers,\(^31\) fingertips,\(^32\) and pressure ulcers.\(^33\) There is a growing number of silver-containing dressings and topical agents available for the treatment of skin wounds, including creams such as SSD, silver salts such as silver nitrate, alginates (e.g. Silvercel®), foams (e.g. Avance, Contreet Ag), hydrofibres (e.g. Aquacel® Ag), hydrocolloids (e.g. SSD/hydrocolloid, Contreet Ag) and polymeric films and meshes (e.g. Arglaes), including metallic, nanocrystalline (e.g. Acticoat®) or ionic silver (Aquacel® Ag).

How the intervention might work
Silver ions bind to the DNA of bacteria and bacterial spores, thus reducing their ability to replicate.\(^34,35\) Furthermore, silver is reported to be effective against all known bacteria,
fungi and some viruses. Few bacteria have been shown to develop resistance to silver (resistance is a major problem associated with use of antibiotics). Silver has also been described as effective against malodour. The various silver-containing dressings differ in the way the Ag+ ions are released. Mostly, Ag+ ions are released from the dressing through oxidation when the silver atoms come into contact with fluid. The silver can be incorporated as complex silver molecules in creams, ointments, hydrocolloids, hydrogels or foam dressings, which regulate the speed of delivery. Recent products have been produced in an attempt to ensure a more controlled and prolonged release of small (nanocrystalline) silver particles into the wound area. This nanocrystalline form releases silver ions faster than the normal silver materials, and, therefore, is claimed to have increased antimicrobial activity.

Why it is important to do this review
Silver-containing dressings have become popular despite the absence of a robust summary of the evidence for their role in preventing wound infection, and encouraging wound healing. The effect of silver-containing wound dressings and topical applications as treatments for infected wounds is the subject of a related review, which identified little evidence of effectiveness. It is timely, therefore, to conduct a systematic review of the effects of silver-containing dressings and topical agents for the prevention of wound infection and the promotion of wound healing in uninfected wounds.

OBJECTIVES
To summarise the evidence for the effects of silver-containing dressings and topical agents compared with non-silver dressings and topical agents in terms of preventing of wound infections and/ or promoting wound healing.

METHODS
Criteria for considering studies for this review
Types of studies
We considered all randomised controlled trials (RCTs), both published and unpublished, that evaluated the effects of silver-containing dressings and topical agents (used alone or in combination with other dressings/agents), in preventing infection or promoting the healing, or both, of uninfected wounds of any aetiology (cause) and in any care setting.

Types of participants
Men and women aged 18 years and over with any type of wound (not diagnosed as infected at baseline) in any care setting.
Types of interventions
Wound dressings and topical applications containing silver.
Eligible comparisons were:
1. Topical silver-containing agents compared with topical agents without silver;
2. Dressings containing silver compared with any dressings without silver (including dressings containing other antiseptics);
3. Comparisons between alternative topical preparations of silver (e.g. SSD cream);
4. Comparisons between alternative silver-containing dressings, including dose comparisons.

Types of outcome measures
Primary outcomes
1. Wound infection rate: 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 $10^5$ colony-forming units per mm$^3$ tissue. \(^{42}\) Trial authors’ definitions of infection (e.g. critical colonisation) were also accepted.
2. Wound healing: this was measured as time to complete healing, rate of change in wound area or volume, or both, or time to skin grafting.

Secondary outcomes
Adverse events; rate of use of systemic antibiotics; pain; patient satisfaction; health related quality of life (HRQoL); length of hospital stay (LOS); costs.

Search methods for identification of studies
Electronic searches
The following electronic databases were searched: Cochrane Wounds Group Specialised Register (Searched 6 May 2009); The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2009); Ovid MEDLINE (1950 to April Week 4 2009); Ovid EMBASE (1980 to 2009 Week 18); EBSCO CINAHL (1982 to April Week 4 2009); Digital dissertations at http://www.umi.com (to October 2008).

The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying reports of randomised controlled trials in MEDLINE (the sensitivity- and precision-maximising version (2008 revision)) Ovid format.\(^{44}\) The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network.\(^{45}\) No date or language restrictions were applied.

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 review authors (HV and DU) independently assessed the titles and abstracts of studies identified from the search in terms of their relevance and design. Full text versions of articles were obtained if, from the initial assessment, it was suggested they might meet the inclusion criteria. Another review author (either CV or MS) assessed those studies where there was disagreement.

Data extraction and management

Details of selected trials were extracted and summarised using a data extraction sheet. Data from trials published in duplicate were included only once. Data extraction was undertaken by one review author (CV), 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, type of wound(s), definition used to determine infection, wound size, duration of wound, length of follow-up, co-morbidities).
- Intervention (type of silver dressing or topical silver, dose of silver, frequency of dressing changes, co-interventions).
- Comparative intervention (type of dressing or topical application, dose of silver (where applicable), number of dressing changes, co-interventions).
- Primary outcomes: rate of wound infection; wound healing.
- Secondary outcomes: number and proportion of adverse events; rate of use of systemic antibiotics; pain; patient satisfaction; quality of life (QoL); length of hospital stay (LOS), and cost of treatment.

Assessment of risk of bias in included studies

Two review authors (CV and MS) independently assessed the risk of bias of each trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Any disagreement was referred to a third review author (DU) for adjudication.

The following criteria were applied: Sequence generation; Allocation concealment; Blinding of participant, care provider and outcome assessor; Incomplete outcome data; Drop-out rate (i.e. < 20%); Intention-to-treat analysis; Groups similar at baseline for the most important prognostic indicators; Sponsoring by a manufacturer who had a potential interest in the results; Co-interventions avoided or given to all groups?

We completed the risk of bias table for each eligible study and present an assessment of risk of bias using a ‘risk of bias summary figure’. This display of internal validity indicates the weight readers may give the results of each study.
**Data synthesis**
Quantitative data were entered into RevMan 5 by one review author (CV) and were checked by a second (MS). Summary estimates of treatment effect (with 95% confidence intervals (CI)) were calculated for each outcome and every comparison. For continuous outcomes, the mean difference (MD) is presented. For dichotomous outcomes, the risk difference (RD) is presented; this is an absolute effect measure that expresses the difference between the experimental and control event rates, and allows calculation of the number needed to treat (NNT). We refrained from a sensitivity analysis because of the lack of replication of comparisons.

**Subgroup analysis and investigation of heterogeneity**
We conducted predefined subgroup analyses for different wound types: burns, acute (e.g. surgical), chronic (e.g. ulcers) and mixed wound types.

Where studies evaluated similar interventions in a similar population we assessed statistical heterogeneity using the Chi² test and estimated the amount of heterogeneity using I². Where pooling seemed appropriate in view of clinical and methodological similarities between studies, we planned to use a fixed-effect model where I² was below 25%. We did not intend to pool studies where inter-study heterogeneity was high (I² greater than 75%), and we intended to use a random-effects model when I² was between 25% and 75%. We constructed a funnel plot to test for publication bias.

**RESULTS**

**Description of studies**
See Characteristics of included studies (Table 1).

**Results of the search**
The search identified 313 titles of potential relevance. Discrepancy in judgement regarding suitability occurred in approximately 10% of all abstracts, but was resolved after adjudication by a third review author. After the first screening, 59 citations were considered potentially relevant. Full text articles were obtained and screened by two review authors independently against the inclusion criteria (Figure 1). One ongoing trial was identified, and four trials are awaiting assessment.

Trials were excluded if no infection or healing parameters were reported; or if silver-containing agents were not used in one of the treatment arms; if the trials were not RCTs; or if trials were published in abstract form only and no additional information could be retrieved from the trial authors to allow a decision regarding eligibility for inclusion to be made.
**Included studies**

Twenty-six trials\(^49-74\) met the inclusion criteria (Table 1). All 26 were published between 1980 and 2008. Study sizes ranged from 14 to 465 participants, and a total of 2066 participants were enrolled. The majority of trials (i.e. 21 of the 26 (81%)) included fewer than 80 participants. Burns were the most frequently studied wound type (20 out of 26 (77%)), and there was substantial variation between trials in the percentage of total body surface area (TBSA) and depth of burn studied (14 trials studied partial-thickness or superficial burns, six studied full-thickness burns). One trial included a range of types of wound (i.e. venous leg ulcers, partial-thickness burns and donor sites).\(^59\) The remaining trials included minor soft tissue injuries,\(^53\) open surgical or traumatic wounds,\(^64\) venous leg ulcers,\(^73\) and diabetic foot ulcers.\(^62,63\) Around half of the trials (14 out of 26 (54%)) compared 1% SSD cream with another topical agent or dressing without silver.\(^49,50,53,55-59,62,66,69-71,74\) Six trials (23%) compared 1% SSD with other silver-containing topical agents or dressings such as Acticoat®, Aquacel® Ag, Hydron® AgSD, Sildimac®, SSD-cerium nitrate, and SSD with chlorhexidine digluconate cream.\(^51,52,54,60,67,68\) One trial compared a silver-coated gauze dressing (Acticoat®) with another topical agent or dressing without silver,\(^61\) and one trial compared a silver-coated gauze dressing (Acticoat®) with 0.5% silver nitrate solution.\(^72\) One trial compared an activated charcoal dressing containing silver (Actisorb Plus®) with other topical agents.\(^73\) Two trials compared a hydrofibre dressing, containing ionic silver (Aquacel®), with other topical agents.\(^63,64\) One trial compared a 0.5% silver nitrate solution with two other agents.\(^65\)
While most of the trials had two treatment arms, two trials had three treatment arms,\textsuperscript{59,65} and one trial had four treatment arms.\textsuperscript{53}

All but two trials reported infection rates,\textsuperscript{66,70} but the definitions of infection varied. Four trials (15\%) defined infection as the presence of more than $10^5$ organisms per gram of tissue;\textsuperscript{60,65,67,72} 15 trials (58\%) accepted positive wound swabs or clinical signs of infection as evidence of infection. Seven trials (27\%) provided no definition of infection.\textsuperscript{49,51,56,57,69,70,74} Twenty-one trials (81\%) reported healing rates predominantly in terms of days to complete healing, or time to complete re-epithelialisation. Pain was the secondary outcome measure most frequently reported. Three trials reported a sample size calculation.\textsuperscript{51,63,64} It was not clear whether informed consent was obtained in 11 trials, and in 13 trials the ethics review board approval was not reported.

**Excluded studies**

Eighteen trials did not meet the inclusion criteria. Six trials were not RCTs, five trials were only published in abstract form with no further information forthcoming from the study authors, and in four trials wounds were already infected. The three remaining trials were excluded because they did not compare dressings; no data was reported on the effect of silver; and the silver compound was not the comparator under investigation rather it was the type of bag covering the hand.

**Risk of bias in included studies**

A summary of the assessment of risk of bias based on the criteria outlined in Higgins\textsuperscript{46} is given in Figure 2 and Figure 3. In general, the overall methodological quality of the included trials was relatively poor, although a few trials were at low risk of bias.

**Analysis of time to healing as a continuous variable**

It is not appropriate to analyse time-to-event data - such as time to healing – using methods for continuous outcomes (e.g. using mean times-to-event) as the relevant times are only known for the subset of participants who have experienced the event (e.g. healing). The most appropriate way of summarising time-to-event data is to use methods of survival analysis and express the intervention effect as a hazard ratio. A hazard ratio is interpreted in a similar way to a risk ratio, as it describes how many times more (or less) likely a participant is to experience the event at a particular point in time if they receive the experimental rather than the control intervention. Inappropriate analysis of outcome data can introduce bias in the interpretation of the results.

**Effects of interventions**

Diverse interventions were evaluated in the 26 included trials, and, as a result, pooling was possible for only two trials. We have presented the results according to wound type, i.e. acute wounds (first burns and then other wounds), chronic wounds, and mixed wounds. Within each wound type we investigated the following comparisons:
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Setting</th>
<th>N (n) patient (wound)</th>
<th>Definition of infection</th>
<th>Unit of allocation</th>
<th>Wound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afilalo</td>
<td>Canada</td>
<td>ED</td>
<td>48 nr</td>
<td>patient burns &lt; 15% TBSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carneiro</td>
<td>Tanzania</td>
<td>Surgical ward</td>
<td>64 cultures</td>
<td>patient 2nd degree burns &lt; 30% TBSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caruso</td>
<td>USA</td>
<td>Burn centre</td>
<td>84 nr</td>
<td>patient superficial, mid-dermal, mixed partial-thickness burns 5-40% TBSA</td>
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<tr>
<td>De Gracia</td>
<td>Philippines</td>
<td>Burn service</td>
<td>60 cultures clinical criteria</td>
<td>patient moderate and severe burns &gt; 15% TBSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dire</td>
<td>Texas</td>
<td>ED</td>
<td>465 clinical criteria</td>
<td>patient minor, uncomplicated soft-tissue necessitating suturing</td>
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<tr>
<td>Fang</td>
<td>China</td>
<td>Nr</td>
<td>27 (54) cultures</td>
<td>wounds 2nd degree burns</td>
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<tr>
<td>Gerding</td>
<td>USA</td>
<td>Burn centre</td>
<td>47 (50) cultures</td>
<td>wounds partial-thickness burns</td>
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<tr>
<td>Gerding</td>
<td>USA</td>
<td>ED: Burn centre</td>
<td>64 (56) clinical criteria</td>
<td>wounds partial-thickness thermal burns &lt; 10% TBSA</td>
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<tr>
<td>Hansbrough</td>
<td>USA</td>
<td>nr</td>
<td>79 (158) nr</td>
<td>wounds partial-thickness burns 1-25% TBSA</td>
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<td>Homann</td>
<td>Germany</td>
<td>Burn centre</td>
<td>47 clinical criteria</td>
<td>wounds partial-thickness burns &lt; 50% TBSA</td>
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<td>Hutchinson</td>
<td>USA, UK,</td>
<td>nr</td>
<td>292 clinical criteria</td>
<td>patient partial-thickness burns partial-thickness donor sites venous leg ulcer</td>
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<td>Inman</td>
<td>Canada</td>
<td>Burn unit</td>
<td>121 clinical criteria accompanied with cultures &gt;10^5 organisms gram/tissue</td>
<td>patient full-thickness burns</td>
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<td>Innes</td>
<td>Canada</td>
<td>admitted</td>
<td>17 (32) cultures</td>
<td>wounds Burns requiring split skin graft</td>
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<td>Jacobs</td>
<td>Canada</td>
<td>private office</td>
<td>40 cultures clinical criteria</td>
<td>patient diabetic patients with Wagner grade 1 or 2 ulcers</td>
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<td>Jude</td>
<td>UK, Germany, nr Sweden, France</td>
<td>134 clinical criteria</td>
<td>patient diabetic patients with Wagner grade 1 or 2 foot ulcers ≥ 1cm²</td>
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<tr>
<td>Intervention (n)</td>
<td>Comparison (n)</td>
<td>Outcomes</td>
<td>Follow-up</td>
<td>Drop-outs</td>
<td></td>
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<tr>
<td>SSD (1%)/Bactigras (15)</td>
<td>DuoDerm (15)</td>
<td>Infection rate; wound healing rate; pain; patient satisfaction</td>
<td>nr</td>
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<tr>
<td>SSD (1%)/ chlorhexidine (32)</td>
<td>Phenytoin (32)</td>
<td>Infection rate; wound healing rate; pain; length of hospital stay</td>
<td>till discharge</td>
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<td>SSD (40)</td>
<td>Hydrofibre dressing containing ionic silver (42)</td>
<td>Infection rate; wound healing rate; adverse effects; use of systemic antibiotics; pain; costs</td>
<td>3 weeks</td>
<td>2</td>
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<tr>
<td>SSD (1%) (30)</td>
<td>SSD/ceurium-nitrate (30)</td>
<td>Infection rate; wound healing rate; adverse effects; use of systemic antibiotics; length of hospital stay</td>
<td>nr</td>
<td>11</td>
<td></td>
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<tr>
<td>SSD (99)</td>
<td>Bacitracin (109) Neomycin sulfate (110) Petrolatum (108)</td>
<td>Infection rate</td>
<td>nr</td>
<td>39</td>
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<tr>
<td>SSD (1%) (27)</td>
<td>Hydron-SSD (27)</td>
<td>Infection rate; wound healing rate</td>
<td>nr</td>
<td>nr</td>
<td></td>
<td></td>
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<tr>
<td>SSD (1%) (23)</td>
<td>Biosynthetic dressing (27) Paired Controls (7)</td>
<td>Infection rate; wound healing rate; pain; costs</td>
<td>nr</td>
<td>4</td>
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<td></td>
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<tr>
<td>SSD (1%) (26)</td>
<td>Biosynthetic dressing (30)</td>
<td>Infection rate; wound healing rate; pain; costs</td>
<td>nr</td>
<td>12</td>
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<td>SSD (1%) (79)</td>
<td>Collagenase ointment with polymyxin B sulfate/bacitracin (79)</td>
<td>Infection rate; wound healing rate; pain</td>
<td>nr</td>
<td>34</td>
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<tr>
<td>SSD (43)</td>
<td>Liposome hydrogel with PVP-I (43)</td>
<td>Infection rate; wound healing rate; adverse effects; pain</td>
<td>till healing</td>
<td>4</td>
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<td>SSD (1%)/ Hydrocolloid (58)</td>
<td>Hydrocolloid (108) Non-occlusive paraffin gauze (126)</td>
<td>Infection rate</td>
<td>3 weeks</td>
<td>70</td>
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<tr>
<td>SSD (1%) (54)</td>
<td>SSD/chlorhexidine digluconate 0.2% (67)</td>
<td>Infection rate; use of systemic antibiotics; pain</td>
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<tr>
<td>Nanocrystalline silver-coated (16)</td>
<td>Hydrophilic polyurethane (16)</td>
<td>Infection rate; wound healing rate; costs</td>
<td>&gt;3 months</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>SSD (20)</td>
<td>Benzoic acid-6%, salicylic acid-3%, Quercus rubra extract-3% (20)</td>
<td>Infection rate; wound healing rate</td>
<td>6 weeks</td>
<td>none</td>
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<td>Hydrofibre dressing containing ionic silver (67)</td>
<td>Calcium alginate dressing (67)</td>
<td>Infection rate; wound healing rate; adverse effects</td>
<td>8 weeks</td>
<td>21 but included in analysis</td>
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## Table 1: Cont.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Setting</th>
<th>N (n) patient (wound)</th>
<th>Definition infection</th>
<th>Unit of allocation wound</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Jurczak 2007</td>
<td>Great-Britain, Germany, France</td>
<td>nr</td>
<td>67</td>
<td>clinical criteria</td>
<td>patient</td>
<td>open surgical or traumatic wounds left to heal by secondary intent</td>
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<tr>
<td>Livingston 1990</td>
<td>USA</td>
<td>Burn unit</td>
<td>52</td>
<td>&gt;10⁵ organisms gram/tissue</td>
<td>patient</td>
<td>thermal injury requiring skin grafting</td>
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<tr>
<td>Mashhood 2006</td>
<td>Pakistan</td>
<td>outpatient</td>
<td>50</td>
<td>cultures clinical criteria</td>
<td>patient</td>
<td>superficial and partial-thickness burns &lt;15% TBSA</td>
</tr>
<tr>
<td>Miller 1990</td>
<td>USA</td>
<td>Burn centre</td>
<td>59</td>
<td>&gt;10⁵ organisms gram/tissue</td>
<td>wounds</td>
<td>full-thickness burns &lt; 40% TBSA</td>
</tr>
<tr>
<td>Muangman 2006</td>
<td>Thailand</td>
<td>Burn unit</td>
<td>50</td>
<td>swabs clinical criteria</td>
<td>patient</td>
<td>partial-thickness burns &lt;25% TBSA</td>
</tr>
<tr>
<td>Noordenbos 1999</td>
<td>USA</td>
<td>admitted</td>
<td>14</td>
<td>nr</td>
<td>wounds</td>
<td>partial-thickness burns 2-30% TBSA</td>
</tr>
<tr>
<td>Soroff 1994</td>
<td>USA</td>
<td></td>
<td>15</td>
<td>nr</td>
<td>wounds</td>
<td>partial-thickness burns &lt;25% TBSA</td>
</tr>
<tr>
<td>Subrahmanyan 1998</td>
<td>India</td>
<td>Inpatient</td>
<td>50</td>
<td>clinical criteria</td>
<td>patient</td>
<td>superficial thermal burns &lt; 40% TBSA</td>
</tr>
<tr>
<td>Tredget 1998</td>
<td>Canada</td>
<td>Burn unit</td>
<td>30 (60)</td>
<td>&gt;10⁵ organisms gram/tissue</td>
<td>wounds</td>
<td>deep partial and full-thickness burns</td>
</tr>
<tr>
<td>Wunderlich 1991</td>
<td>Germany</td>
<td>nr</td>
<td>40</td>
<td>swabs</td>
<td>patient</td>
<td>venous leg ulcers</td>
</tr>
<tr>
<td>Wyatt 1990</td>
<td>USA</td>
<td>ED</td>
<td>50</td>
<td>clinical criteria</td>
<td>patient</td>
<td>minor 2nd degree burns</td>
</tr>
</tbody>
</table>

N = Number of patients included; n = Number of patients or number of wounds in each treatment group; ED: Emergency Department; nr: Not reported; SSD = Silver sulfadiazine cream
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Setting</th>
<th>N (n)</th>
<th>intervention (n)</th>
<th>comparison (n)</th>
<th>outcomes</th>
<th>follow-up</th>
<th>drop-outs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jurczak</td>
<td>Great-Britain, Germany, France</td>
<td>nr 67</td>
<td>clinical criteria</td>
<td>patient open surgical or traumatic wounds left to heal by secondary intent</td>
<td>Hydrofibre dressing containing ionic silver (35) Povidone iodine dressing (32)</td>
<td>Infection rate; wound healing rate; adverse effects; pain</td>
<td>2 weeks</td>
<td>5</td>
</tr>
<tr>
<td>Livingston</td>
<td>USA</td>
<td>Burn unit 52</td>
<td>&gt;10 organisms gram/tissue patient thermal injury requiring skin grafting</td>
<td>Silver nitrate 0.5% (19) Ringer’s lactate (15) Neomycin with bacitracin (18)</td>
<td>SSD (25) Honey (25)</td>
<td>Infection rate; length of hospital stay</td>
<td>nr</td>
<td>none</td>
</tr>
<tr>
<td>Mashhood</td>
<td>Pakistan</td>
<td>outpatient 50</td>
<td>cultures clinical criteria patient superficial and partial-thickness burns &lt;15% TBSA</td>
<td>SSD (25)</td>
<td>Silver nitrate 0.5% (19) Ringer’s lactate (15) Neomycin with bacitracin (18)</td>
<td>Infection rate; wound healing rate; adverse effects; pain</td>
<td>&gt;3 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Miller</td>
<td>USA</td>
<td>Burn centre 59</td>
<td>&gt;10 organisms gram/tissue wounds full-thickness burns &lt; 40% TBSA</td>
<td>SSD (51) Polyethylene glycol 400, poly-2-hydroxyethyl methacrylate, and dimethylsulfoxide: Dimac-containing SSD (51)</td>
<td>SSD (51) Polyethylene glycol 400, poly-2-hydroxyethyl methacrylate, and dimethylsulfoxide: Dimac-containing SSD (51)</td>
<td>Infection rate; adverse effects; pain</td>
<td>2 weeks</td>
<td>8</td>
</tr>
<tr>
<td>Muangman</td>
<td>Thailand</td>
<td>Burn unit 50</td>
<td>cultures clinical criteria patient partial-thickness burns &lt;25% TBSA</td>
<td>SSD (25)</td>
<td>Nanocrystalline silver-coated dressing (25)</td>
<td>Infection rate; wound healing rate; adverse effects; pain</td>
<td>&gt;3 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Noordenbos</td>
<td>USA</td>
<td>admitted 14</td>
<td>wounds partial-thickness burns 2-30% TBSA</td>
<td>SSD (14)</td>
<td>Biosynthetic dressing with skin substitute (14)</td>
<td>Infection rate; wound healing rate; adverse effects; pain</td>
<td>&gt;3 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Soroff</td>
<td>USA</td>
<td>15</td>
<td>wounds partial-thickness burns &lt;25% TBSA</td>
<td>SSD (15)</td>
<td>Collagenase ointment with polymyxin B sulfate/bacitracin (15)</td>
<td>Infection rate; wound healing rate; adverse effects; pain</td>
<td>&gt;3 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Subrahmanyan</td>
<td>India</td>
<td>Inpatient 50</td>
<td>wounds superficial thermal burns &lt; 40% TBSA</td>
<td>SSD (25)</td>
<td>Honey (25)</td>
<td>Infection rate; wound healing rate; adverse effects; pain</td>
<td>&gt;3 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Tredget</td>
<td>Canada</td>
<td>Burn unit 30 (60)</td>
<td>&gt;10 organisms gram/tissue wounds deep partial and full-thickness burns</td>
<td>SSD (14)</td>
<td>Biosynthetic dressing with skin substitute (14)</td>
<td>Infection rate; wound healing rate; pain</td>
<td>&gt;3 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Wunderlich</td>
<td>Germany</td>
<td>nr 40</td>
<td>wounds venous leg ulcers</td>
<td>SSD (25)</td>
<td>Nanocrystalline silver-coated dressing (25)</td>
<td>Infection rate; wound healing rate; adverse effects; pain</td>
<td>&gt;3 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Wyatt</td>
<td>USA</td>
<td>ED 50</td>
<td>wounds minor 2nd degree burns</td>
<td>SSD (20)</td>
<td>Hydrocolloid (22)</td>
<td>Infection rate; wound healing rate; adverse effects; pain</td>
<td>&gt;3 weeks</td>
<td>1</td>
</tr>
<tr>
<td>------------------</td>
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</tr>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
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<tr>
<td>Blinding (performance bias and detection bias)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias): ITT analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias): Drop out rate described and acceptable (&gt; 80%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Financial support for trial or trialists?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Groups similar at baseline?</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co interventions avoided or similar?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
For each outcome and comparison the results are presented below. Trial details are summarised in Table 1. We were only able to assess the possibility of publication bias for one comparison, SSD/silver versus no silver, where we performed a funnel plot for the outcome of infection rate. The funnel plot included 10 trials with 11 comparisons demonstrating symmetry, indicating no publication bias.

1. Acute wounds: burns

1.1 Topical silver-containing agents compared with topical agents without silver (SSD versus no silver)

Eleven trials compared a topical application containing silver (1% SSD) with another topical agent or dressing not containing silver. Only two trials compared similar interventions and were pooled,\textsuperscript{55,56} while the remainder were considered separately.

1.1.1 SSD cream compared with biosynthetic dressing (Biobrane\textsuperscript{®}) (two trials)

Gerding\textsuperscript{55} enrolled 43 patients with 50 acute partial-thickness burns, and Gerding\textsuperscript{56} enrolled 52 patients with 56 acute partial-thickness thermal wounds in two trials comparing 1% SSD cream with a biosynthetic dressing.
Primary outcome: infection rate

Gerding\(^{55}\) defined wound infection on clinical grounds in conjunction with semi-quantitative surface swab cultures. In this trial a mixture of paired and unpaired data were presented; seven patients were used as matched controls by randomising the paired wounds to treatment with opposite modalities. Gerding\(^{56}\) defined wound infection on clinical grounds, but did not give a detailed description. In Gerding\(^{55}\) 4/23 wounds in the SSD group, and 4/27 in the biosynthetic dressing group were judged to be infected. While in Gerding,\(^{56}\) 2/26 wounds in the SSD group and 3/30 in the biosynthetic dressing group were infected.

Analysis 1.1: Number of patients that developed wound infection

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSD/Silver</th>
<th>NO Silver</th>
<th>Risk Difference M-H, Random, 95% CI</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Burns</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afifalo 1992</td>
<td>1</td>
<td>24</td>
<td>2</td>
<td>-0.04 [-0.18, 0.09]</td>
</tr>
<tr>
<td>Carneiro 2002</td>
<td>15</td>
<td>32</td>
<td>3</td>
<td>0.38 [0.17, 0.58]</td>
</tr>
<tr>
<td>Gerding 1988</td>
<td>4</td>
<td>23</td>
<td>4</td>
<td>0.03 [-0.18, 0.23]</td>
</tr>
<tr>
<td>Gerding 1990</td>
<td>2</td>
<td>26</td>
<td>3</td>
<td>-0.02 [-0.17, 0.13]</td>
</tr>
<tr>
<td>Hansbrough 1995</td>
<td>11</td>
<td>79</td>
<td>12</td>
<td>-0.01 [-0.12, 0.10]</td>
</tr>
<tr>
<td>Homann 2007</td>
<td>0</td>
<td>43</td>
<td>0</td>
<td>0.00 [0.04, 0.04]</td>
</tr>
<tr>
<td>Innes 2001</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>0.00 [-0.11, 0.11]</td>
</tr>
<tr>
<td>Livingston 1990</td>
<td>2</td>
<td>19</td>
<td>6</td>
<td>-0.23 [-0.49, 0.03]</td>
</tr>
<tr>
<td>Livingston 1990</td>
<td>2</td>
<td>19</td>
<td>8</td>
<td>-0.43 [-0.72, -0.14]</td>
</tr>
<tr>
<td>Noordenbos 1999</td>
<td>6</td>
<td>14</td>
<td>0</td>
<td>0.43 [0.16, 0.70]</td>
</tr>
<tr>
<td>Subrahmaniam 1998</td>
<td>5</td>
<td>25</td>
<td>0</td>
<td>0.20 [0.03, 0.37]</td>
</tr>
<tr>
<td>Wyatt 1990</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>0.00 [-0.09, 0.09]</td>
</tr>
<tr>
<td>1.1.2 Acute wounds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dire 1995</td>
<td>12</td>
<td>99</td>
<td>6</td>
<td>0.07 [-0.01, 0.14]</td>
</tr>
<tr>
<td>Dire 1995</td>
<td>12</td>
<td>99</td>
<td>5</td>
<td>0.08 [0.00, 0.15]</td>
</tr>
<tr>
<td>Dire 1995</td>
<td>12</td>
<td>99</td>
<td>19</td>
<td>-0.05 [-0.15, 0.04]</td>
</tr>
<tr>
<td>Jurczak 2007</td>
<td>4</td>
<td>35</td>
<td>4</td>
<td>-0.01 [-0.17, 0.14]</td>
</tr>
<tr>
<td>1.1.3 Chronic wounds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jacobs 2008</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>0.00 [-0.09, 0.09]</td>
</tr>
<tr>
<td>Jude 2007</td>
<td>11</td>
<td>67</td>
<td>8</td>
<td>0.04 [-0.07, 0.16]</td>
</tr>
<tr>
<td>1.1.4 Mixed wounds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hutchinson 1993</td>
<td>0</td>
<td>58</td>
<td>7</td>
<td>-0.06 [-0.10, -0.01]</td>
</tr>
<tr>
<td>Hutchinson 1993</td>
<td>0</td>
<td>58</td>
<td>2</td>
<td>-0.02 [-0.06, 0.02]</td>
</tr>
</tbody>
</table>

SSD: Silver sulfadiazine

Pooling these two trials \((1^2 = 0\%)\) using a fixed effect model showed no statistically significant difference between groups (RD 0.00; 95% CI -0.12 to 0.12) (Analysis 1.1).
Primary outcome: wound healing rate

Both trials reported the standard error of the mean; the standard deviation (SD) was calculated for our analysis. In both trials, healing was defined as complete re-epithelialisation. Gerding reported the mean time to complete healing as 21.3 days (SD 11.03) in the SSD group, and 13.7 days (SD 6.75) in the biosynthetic dressing group, while Gerding reported the mean time to complete healing as 15.0 days (SD 6.12) in the SSD group and 10.6 days (SD 4.38) in the biosynthetic dressing group (Analysis 1.2). Both trials reported a statistically significant difference in favour of the biosynthetic dressing, however, these original trials analysed time to healing (a time-to-event outcome) as a continuous variable, which is inappropriate and potentially misleading (since it cannot take account of people who did not heal). We did not have access to the original data and therefore could not re-analyse it.

Secondary outcome: pain

Both trials measured pain on a scale from one (none) to five (severe). The pain score was statistically significantly lower in the biosynthetic dressing groups (pooled, fixed-effect, MD 1.41; 95% CI 0.99 to 1.83). Both trials reported standard error of the mean, we calculated the SD for the purposes of analysis.

Secondary outcome: costs

Gerding reported no statistically significant differences in the mean material costs, based on the total cost of topical cream, dressing materials and medications used in each case.
Nursing costs were $238 in the SSD group and $71 in the biosynthetic dressing group (P value < 0.001). No SDs were reported; therefore no mean difference could be calculated. Gerding\textsuperscript{56} reported that mean costs, based on hospital charges, were significantly lower in the biosynthetic dressing group (MD 70; 95% CI 15.5 to 124.5).

1.1.2 SSD cream compared with biosynthetic dressing with human fibroblast skin substitute (Transcyte on Biobrane mesh) (one trial)

Noordenbos\textsuperscript{69} enrolled 14 patients, each with two partial-thickness burns of similar size, and compared SSD cream on one burn with a biosynthetic dressing combined with human fibroblasts on the other.

*Primary outcome: infection rate*

The trial report defined wound infection as cellulitis. Six of the 14 burns in the SSD group, and none in the biosynthetic dressing group developed cellulitis. The number of burns that developed cellulitis was significantly lower in the biosynthetic dressing group (RD 0.43; 95% CI 0.16 to 0.70) (Analysis 1.1). The number needed to treat (NNT) with biosynthetic dressings was two, in order to prevent one additional patient developing cellulitis.

*Primary outcome: wound healing rate*

The report defined healing as 90% re-epithelialisation. The mean time to 90% healing in the SSD group was 18.14 days, compared to 11.14 days in the biosynthetic dressing group (Analysis 1.2). The mean time to healing was significantly shorter in the biosynthetic dressing group. Time to healing is a time-to-event outcome, however, the trialists did not analyse it as such and, therefore, this effect estimate may be inaccurate.

1.1.3 SSD cream with chlorhexidine-impregnated gauze (Bactigras\textsuperscript{®}) compared with hydrocolloid dressing (Duoderm\textsuperscript{®} Hydroactive) (one trial)

Afilalo\textsuperscript{49} enrolled 48 patients with partial-thickness burns and compared a layer of SSD cream covered by chlorhexidine-impregnated gauze (Bactigras) with a hydrocolloid dressing (Duoderm Hydroactive).

*Primary outcome: infection rate*

Wound infection was not defined in this trial, but was based on the unblinded, subjective opinion of the investigator or the plastic surgeon, and, therefore, was subject to bias. One participant out of 24 in the SSD with chlorhexidine-impregnated gauze group developed an infection, and 2/24 in the hydrocolloid dressing group. There was no statistically significant difference in the number of patients that developed a wound infection (RD: -0.04, 95% CI -0.18 to 0.09) (Analysis 1.1).

*Primary outcome: wound healing rate*

The trialists defined wound healing as complete re-epithelialisation. The mean time to complete healing was 11.2 days in the SSD with chlorhexidine-impregnated gauze group, and
10.7 days in the hydrocolloid group (Analysis 1.2). There was no statistically significant difference in the mean time to complete healing. Again, this time-to-event outcome had been inappropriately analysed as a continuous variable rather than by survival analysis, and, therefore, was inaccurate.

**Secondary outcome: pain**
The pain scores at baseline and the second visit (24 hours after the initial visit) were assessed. Pain was measured on a scale from 1 to 10. There was no statistically significant difference in the groups for the median pain score at baseline or at the second visit.

**Secondary outcome: patient satisfaction**
Overall satisfaction was reported as excellent or satisfactory for all patients, and there was no statistically significant difference between the groups.

**1.1.4 SSD cream compared with hydrocolloid dressing (DuoDerm® Hydroactive) (one trial)**
Wyatt\(^74\) enrolled 50 patients with minor, second-degree burn injuries in order to compare the effects of SSD cream with hydrocolloid dressings.

**Primary outcome: infection rate**
Wound infection was defined on clinical grounds, but how exactly was unclear. None of the patients developed a wound infection (RD 0.00; 95% CI -0.09 to 0.09) (Analysis 1.1).

**Primary outcome: wound healing rate**
Healing was defined as complete healing. The mean time to complete healing was 15.59 days in the SSD group, and 10.23 days in the hydrocolloid dressing group. The mean time to complete healing was significantly shorter in the hydrocolloid group (Analysis 1.2). Again, this time-to-event outcome was inappropriately analysed as a continuous variable, and is, therefore, inaccurate.

**Secondary outcome: pain**
Pain was measured on a scale from one (no pain) to 10 (maximum pain). The mean pain score was 2.28 in the SSD group, and 1.09 in the hydrocolloid dressing group. The mean reported pain score was significantly lower in the hydrocolloid group (MD 1.19; 95% CI 0.56 to 1.82).

**1.1.5 SSD cream compared with honey (two trials)**
Mashhood\(^66\) enrolled 50 patients with superficial and partial-thickness burns. Subrahmanyam\(^71\) enrolled 50 patients with superficial thermal burns. Both compared the effects of SSD cream with pure, unprocessed, undiluted honey. Mashhood described it as ‘traditional medicine honey’ and Subrahmanyam stated only that the honey was obtained from hives.
Primary outcome: infection rate

While Mashhood defined wound infection on clinical grounds, and via swabs for bacterial density and culture, infection rate was not reported. For Subrahmanyam wound infection was defined clinically (presence of pus or slough), and by means of bacterial cultures. There was no statistically significant difference between the two groups in this trial with respect to clinical evidence of wound infection in the short term (day 7), but in the longer term (day 21), the honey group demonstrated significantly fewer infections (RD 0.20; 95% CI 0.03 to 0.37) (Analysis 1.1). The NNT with honey was five, in order to prevent one wound infection.

Primary outcome: wound healing rate

In the Mashhood trial healing was defined as 100% epithelialisation. The number of wounds completely healed was reported after two, four and six weeks’ treatment. At the two and four weeks’ treatment time-points, the honey group did significantly better. The number of wounds completely healed after two weeks was 5/25 in the SSD group and 13/25 in the honey treated group (RD -0.32; 95% CI -0.57 to -0.07) (Analysis 1.3). The number of wounds completely healed after four weeks was 15/25 in the SSD group and 25/25 in the honey treated group (RD -0.40; 95% CI -0.60 to -0.20). The NNT with honey was three, in order to promote the healing of one extra wound. All wounds were completely healed after six weeks.

In the Subrahmanyam trial healing was defined as “patients with clinical and histological evidence of epithelialisation”. The number of patients with clinical evidence of wound healing was reported on days 21 and 30, with histological evidence of wound healing reported for days 7 and 21. There was no statistically significant difference between the two groups for the clinical evidence on day 30. For the other time points, the honey group...
performed significantly better than the SSD group. The number of patients with clinical
evidence of wound healing on day 21 was 21/25 in the SSD group and 25/25 in the honey
group (RD -0.16; 95% CI -0.31 to -0.01) (Analysis 1.3). The NNT with honey was six, in order
to promote the healing of one extra wound.

Secondary outcome: pain
Mashhood reported pain on the basis of the number of participants who were free of
pain after one, two, three and four weeks of treatment. While there was no statistically
significant difference between the two groups at the start and end of the trial (i.e. weeks
1 and 4), there was a statistically significant difference between groups in the middle (i.e.
weeks 2 and 3), with more patients free of pain in the honey group (RD -0.36; 95% CI
-0.61 to -0.11). We calculated the Mann-Whitney U test: z = -2.823, P value = 0.005.

Secondary outcome: costs
Mashhood reported the cost of dressing material for one percent of body surface area
burnt. The cost of dressing material for each percent of body surface area burnt was
PKR 0.10/2 g for SSD, and PKR 0.75/5 ml for honey. No SDs were reported, so no mean
difference could be calculated.

1.1.6 SSD cream compared with liposome hydrogel containing polyvinyl-pyrrol-
idone iodine (PVP-I) (one trial)
Homann\textsuperscript{58} enrolled 47 patients with 94 partial-thickness burns (degree IIa).

Primary outcome: infection rate
Wound infection was defined using clinical criteria such as inflammation. When wound
infection was suspected, wound swabs were taken for microbiological investigation. None
of the patients developed a wound infection (RD 0.00; 95% CI -0.04 to 0.04) (Analysis 1.1).

Primary outcome: wound healing rate
Healing was defined as 95% to 100% re-epithelialisation. There was no statistically
significant difference in the mean time to complete healing (11.3 days for the SSD group,
9.9 days for the liposome hydrogel containing polyvinyl-pyrrolidone iodine (PVPI) group)
(Analysis 1.2). Again, this time-to-event outcome was inappropriately analysed as a
continuous variable rather than by means of survival analysis.

Secondary outcome: adverse events
There was no statistically significant difference between the groups with respect to wound
necrosis and wound itching (RD 0.02; 95% CI -0.05 to 0.10).

Secondary outcome: pain
Pain was measured, but the method the trialists used was not reported. There was no
statistically significant difference in the number of patients reporting wound pain (RD
-0.02; 95% CI -0.16 to 0.12).
1.1.7 SSD cream compared with collagenase ointment applied with polymyxin B sulfate/bacitracin (Santyl®) (two trials)

Soroff\textsuperscript{70} enrolled 15 patients with 30 partial-thickness burns. Hansbrough\textsuperscript{57} enrolled 79 patients with 158 partial-thickness burns.

**Primary outcome: infection rate**

Soroff did not report infection rate. Hansbrough did not define wound infection, but the number of patients with cellulitis was reported. There was no statistically significant difference in the number of patients who developed cellulitis between the groups (11/79 in the SSD group; 12/79 in the collagenase ointment applied with polymyxin B sulfate/bacitracin (Santyl®) group), (RD -0.01; 95% CI -0.12 to 0.10) (Analysis 1.1).

**Primary outcome: wound healing rate**

Soroff defined healing as complete re-epithelialisation and time to a clean wound bed (determined by the disappearance of injured dermis), while Hansbrough defined healing as complete re-epithelialisation and time to a clean wound bed (determined by the absence of retained dermis). In both trials, healing was significantly better in the Santyl® group. In Soroff the median time to complete epithelialisation was 15 days in the SSD group and 10 days in the Santyl® group (P value 0.00007). In the Hansbrough trial, the mean time to epithelial closure was 22.1 days in the SSD group, and 19.0 days in the Santyl® group (no SD was reported) (P value < 0.001). Again, this time-to-event outcome was inappropriately analysed as a continuous variable.

**Secondary outcome: pain and adverse events**

Hansbrough reported pain as an adverse event and described it as burning or stinging. The number of patients reporting pain was significantly lower in the SSD group (RD -0.19; 95% CI -0.31 to -0.07). The NNT with SSD was five, in order to prevent one patient from experiencing pain. Soroff reported three patients who described a burning sensation at the wound site in the Santyl® group.

1.1.8 SSD cream/chlorhexidine (Silverex) compared with diphenylhydantoin (Phenytoin) (one trial)

Carneiro\textsuperscript{50} enrolled 64 patients with second degree burns.

**Primary outcome: infection rate**

Bacterial cultures were obtained on days 5 and 10. Negative cultures were defined as the absence of pathogens. The number of positive bacterial cultures on both days was significantly lower in the diphenylhydantoin group. At day 10 15/32 cultures were positive in the SSD/chlorhexidine group compared with 3/32 in the diphenylhydantoin group (RD 0.38; 95% CI 0.17 to 0.58) (Analysis 1.1). The NNT with diphenylhydantoin was three, in order to prevent one additional positive culture.
Primary outcome: wound healing rate
Wound healing was defined as complete healing. There was no statistically significant difference between the groups in the rate of complete healing; 24/32 wounds in the SSD/chlorhexidine group were completely healed, and 29/32 in the diphenylhydantoin group (RD -0.16; 95% CI -0.34 to 0.02) (Analysis 1.3).

Secondary outcome: pain
Pain was measured in categories: moderate to severe pain or discomfort; mild; or no pain or discomfort. Statistically significantly more patients reported moderate to severe pain or discomfort in the SSD/chlorhexidine group (17/32), than in the diphenylhydantoin group (7/32) (RD 0.31; 95% CI 0.09 to 0.54).

Secondary outcome: length of hospital stay
The mean length of hospital stay was 16.3 days in the SSD/chlorhexidine group and 14.2 days in the diphenylhydantoin group (not statistically significant). No SDs were reported; therefore no mean difference could be calculated.

Summary for burns: SSD versus no silver
Eleven trials compared SSD with a range of non-silver comparators in participants with superficial or partial-thickness burns. Only four of the eleven trials reported adequate sequence generation, and only two described allocation concealment, therefore these trials were generally of at least moderate, (or unknown), risk of bias and the findings should be interpreted with this in mind.

Infection rate was reported in nine trials. Six trials found no statistically significant differences, and three trials found a statistically significant increase in infection with SSD compared with the non-silver comparators.

Time to complete healing was reported in eight trials, though in each trial this had been inappropriately analysed as a continuous variable ("mean time") rather than as a time-to-event outcome. Six trials showed a statistically significant difference in favour of non-silver dressings, and two trials showed no differences. However, these data would be inaccurate if not all the participants were followed to complete healing.

The proportions of wounds healed and unhealed at specific time points were reported in three trials. Two trials showed a statistically significant difference in favour of non-silver dressings, and one trial showed no difference.

Pain was reported in eight trials. While one trial showed a statistically significant difference in favour of SSD, five trials showed a statistically significant difference is favour of non-silver dressings, and two trials showed no difference.
1.2 Dressings containing silver compared with any dressings without silver (silver versus no silver)

1.2.1 Nanocrystalline silver coated dressing (Acticoat®) compared with hydrophilic polyurethane dressing (Allevyn®) (one trial)

Innes\textsuperscript{61} enrolled 17 patients, with 18 paired adjacent burn sites, who required a split-thickness skin graft.

*Primary outcome: infection rate*

Wound infection was defined clinically by criteria such as erythema, induration, purulent discharge, and malodour. Every third day, swabs were taken and were rated as 1 (light growth), 2 (medium growth), or 3 (heavy bacterial growth). There was no statistically significant difference in the number of patients who developed an infection, or in the number of positive cultures at any time point. None of the patients developed a wound infection (RD 0.00; 95% CI -0.11 to 0.11) (Analysis 1.1).

*Primary outcome: wound healing rate*

Healing was defined as 90% or more re-epithelialisation. Healing was significantly faster in the hydrophilic polyurethane dressing group (Allevyn\textsuperscript{®}) (14.5 days for the nanocrystalline silver coated dressing (Acticoat\textsuperscript{®}) group, and 9.1 days for the Allevyn\textsuperscript{®} group) (Analysis 1.2). Again, this time-to-event outcome was inappropriately analysed as a continuous variable. The number of wounds healed by day of discharge showed a statistical significance in favour of Allevyn\textsuperscript{®} (RD -0.69; 95% CI -0.92 to -0.45) (Analysis 1.3). The NNT with Allevyn\textsuperscript{®} was six, in order to promote one additional wound to heal.

*Secondary outcome: cost*

The mean cost per cm\textsuperscript{2} was USD 0.088 in the Acticoat\textsuperscript{®} group and USD 0.059 in the Allevyn\textsuperscript{®} group. No SDs were reported, so no mean difference could be calculated.

1.2.2 Silver nitrate (0.5%) compared with Ringer’s lactate (one trial)

Livingston\textsuperscript{65} enrolled 52 patients with burns who required skin grafting. The trial had three treatment groups; silver nitrate (0.5%) (19 participants), Ringer’s lactate (15 participants), and neomycin with bacitracin (18 participants).

*Primary outcome: infection rate*

Wound infection was defined as present when there were more than 10\textsuperscript{5} organisms per gram of tissue. The silver nitrate group showed significantly fewer infections (2/19 infections in the silver nitrate group; 8/15 in the Ringer’s lactate group) (RD -0.43; 95% CI -0.72 to -0.14) (Analysis 1.1). The NNT with silver nitrate was two, in order to prevent one wound infection. Mean time to development of wound infection was significantly shorter in the Ringer’s lactate group (13.7 days in the silver nitrate group, versus 5.5 days in the Ringer’s lactate group). Again, the outcome was inappropriately analysed as a continuous variable.
Secondary outcome: length of hospital stay
Length of hospital stay was only reported for subgroups, and was reported as being significantly shorter for patients in the silver nitrate group with wounds covering 20% to 40% TBSA.

1.2.3 Silver nitrate (0.5%) compared with neomycin with bacitracin (one trial)
In the same trial, the comparison arm of silver nitrate (0.5%) (19 participants) was compared with the neomycin with bacitracin arm (18 participants).

Primary outcome: infection rate
Wound infection was defined as present when there were more than $10^5$ organisms per gram of tissue. There was no statistically significant difference in the number of patients who developed an infection (2/19 in the silver nitrate group and 6/18 in the neomycin with bacitracin group) (RD -0.23; 95% CI -0.49 to 0.03) (Analysis 1.1). Mean time to development of wound infection was significantly shorter in the neomycin with bacitracin group (13.7 days in the silver nitrate group versus 5.5 days in the neomycin with bacitracin group). Again, this time-to-event outcome was inappropriately analysed as a continuous variable.

Secondary outcome: length of hospital stay
Length of hospital stay was only reported for subgroups, and there were no statistically significant differences between them.

Summary for burns: silver versus no silver
Both trials investigated burns requiring skin grafting. Only one of the trials reported adequate sequence generation, and neither trial reported adequate allocation concealment.

Infection rate was reported in both trials with a total of three dressing comparisons. Two comparisons showed no differences, and one comparison showed a statistically significant difference in favour of silver nitrate.

Time to complete healing was reported in one trial, which showed a statistically significant difference in favour of non-silver dressings however it had been wrongly analysed as a continuous variable (with mean healing time calculated) whereas time to healing is a time-to-event outcome which should be subject to analysis by survival methods.

The number of wounds healed was reported in one trial, which showed a statistically significant difference in favour of non-silver dressings. An overview of the number of patients who developed a wound infection for all trials comparing SSD/silver versus no silver is given in Analysis 1.1. A funnel plot revealed no evidence of publication bias for wound infection.
1.3 Comparisons between alternative topical preparations of silver, e.g. SSD cream (SSD versus silver)

1.3.1 SSD cream compared with nanocrystalline silver-coated dressing (Acticoat®) (one trial)
Muangman\textsuperscript{68} enrolled 50 patients, with partial-thickness burns.

Primary outcome: infection rate
Wound infection was defined as the presence of erythema, induration, purulent discharge and malodour. There was no statistically significant difference in the number of patients who developed an infection (4/25 in the SSD group; 3/25 in the nanocrystalline silver-coated dressing (Acticoat®) group) (RD 0.04; 95% CI -0.15 to 0.23).

Secondary outcome: pain
Pain was measured on a visual analogue pain scale from 1 (no pain) to 10 (extreme pain). Background pain, between dressings, was significantly lower in the Acticoat® group (5 in the SSD group, 4 in the Acticoat® group) (MD 1.00; 95% CI 0.64 to 1.36).

Secondary outcome: length of hospital stay
The mean length of hospital stay was 21 days in both groups (MD 0.00; 95% CI -6.43 to 6.43).

1.3.2 SSD cream compared with hydrofibre dressing containing ionic silver (Aquacel® Ag) (one trial)
Caruso\textsuperscript{51} enrolled 82 patients, with superficial, mid-dermal or mixed partial-thickness burns.

Primary outcome: infection rate
Wound infection was not defined. There was no statistically significant difference in the number of patients who developed an infection (6/40 in the SSD group; 8/42 in the hydrofibre dressing containing ionic silver (Aquacel® Ag) group) (RD -0.04; 95% CI -0.20 to 0.12).

Primary outcome: wound healing rate
Healing was defined as either 100% re-epithelialisation, including open areas; less than 1 cm fully re-epithelialized area; or re-epithelialisation less than 100% but to the extent that surgical interventions were not required. There were no differences in healing within 21 days (24/40 in the SSD group; 31/42 in the Aquacel® Ag group) (RD -0.14; 95% CI -0.34 to 0.06). For the time to complete re-epithelialisation only median values were given: 17 days in the SSD group and 16 days in the Aquacel® Ag group (P value 0.517). No MD could be calculated. The time to complete re-epithelialisation was analyzed using life table methods. Kaplan Meier survival curves for each treatment group were plotted.
Secondary outcome: adverse events
Adverse events were defined as any untoward medical occurrence that was new or worsened during the trial. There were no statistically significant differences between SSD and Aquacel® Ag for adverse events (RD -0.03; 95% CI -0.24 to 0.19).

Secondary outcome: use of systemic antibiotics
There was no statistically significant difference between groups in the number of patients that used antibiotics (RD -0.04; 95% CI -0.20 to 0.12).

Secondary outcome: pain
Pain was measured on a visual analogue scale from 1 (no pain) to 10 (extreme pain). The mean pain score per week was 4.77 in the SSD group and 3.63 in the Aquacel® Ag group (P value 0.003). No SDs were reported, so no mean difference could be calculated. Pain was also measured on an observational scale. Patients were able to grade the extent to which the dressings reduced pain from “extremely well” to “not very well at all”. Patients reported statistically significantly less pain associated with the Aquacel® Ag dressing (P value 0.002).

Secondary outcome: costs
Different components of costs were measured and combined later to be able to calculate cost effectiveness. For most components no SDs were reported, so no mean difference could be calculated. All costs were expressed as US dollars. There was no statistically significant difference in the mean total costs of clinical care ($1181 for the SSD group and $1040 for the Aquacel® Ag group) (MD $141; 95% CI -$216 to $498). The average cost effectiveness, calculated from the total cost of clinical care, divided by the proportion of patients with full epithelialisation, was $1968 (95% CI $1483 to $2690) in the SSD group and $1409 (95% CI $1050 to $1858) in the Aquacel® Ag group.

1.3.3 SSD cream compared with synthetic dressing containing silver (Hydron-AgSD) (one trial)
Fang54 enrolled 27 patients with 54 second degree burns, with areas of similar size and injury matched.

Primary outcome: infection rate
Wound infection was determined by taking swabs for bacterial colonisation and reporting on the number of positive cultures. The time-point(s) at which the swabs were taken was not reported. The number of positive culture swabs was significantly higher in the SSD group (46/98 swabs in the SSD group; 32/98 in the synthetic dressing containing silver (Hydron-AgSD) group) (RD 0.14; 95% CI 0.01 to 0.28). The NNT with Hydron-AgSD was seven, in order to prevent one positive culture.
Primary outcome: wound healing rate
No definition of healing was reported. Fang stated that wounds healed equally in both groups, no data were reported to support this statement.

1.3.4 SSD cream (Flamazine®) compared with 1% SSD plus 0.2% chlorhexidine digluconate cream (Silvazine®) (one trial)
Inman\textsuperscript{60} enrolled 121 patients with fresh, full-thickness burns.

Primary outcome: infection rate
Wound infection was defined by clinical criteria such as softening of eschar, erythema, or colour change accompanied with a quantitative culture with $10^5$ or more organisms per gram of burn tissue. There was no statistically significant difference between the groups in the number of patients that developed an infection (12/67 in the SSD group; 10/54 in the SSD with chlorhexidine digluconate cream group) (RD -0.01; 95% CI -0.14 to 0.13).

Secondary outcome: use of systemic antibiotics
There was no statistically significant difference between groups in the use of antibiotics during the in-hospital period (RD 0.10; 95% CI -0.03 to 0.24).

Secondary outcome: pain
Pain was not defined. There was no statistically significant difference between groups in the number of patients who experienced extreme pain at the time when cream was being applied (RD -0.02; 95% CI -0.07 to 0.03).

1.3.5 SSD cream compared with SSD cream containing cerium nitrate (SSD-CN) (one trial)
De Gracia\textsuperscript{52} enrolled 60 patients with moderate and severe burns.

Primary outcome: infection rate
In the De Gracia trial, wound sepsis was defined as wound deterioration with severe inflammation. Wound biopsies were taken and bacterial growth on culture media was reported. De Gracia found no statistically significant difference between the groups for any infection outcome. The number of patients developing sepsis after ten days was 3/30 in the SSD group and 0/30 in the SSD-cerium nitrate (SSD-CN) group (RD 0.10; 95% CI -0.02 to 0.22).

Primary outcome: wound healing rate
The De Gracia trial defined healing as complete re-epithelialisation, or wounds being ready for skin grafting. Re-epithelialisation was categorised into four groups: ‘quick’ (0 to 14 days), ‘moderate’ (15 to 21 days), ‘slow’ (22 to 35 days), and ‘very slow’ (more than 35 days). We calculated the Chi\textsuperscript{2} statistic as 5.233, and the P value as 0.155. There were no
statistically significant differences between the groups. The mean number of days until complete re-epithelialisation was significantly shorter in the SSD-CN nitrate group (25.1 days in the SSD group; 17.2 days in the SSD-CN group). The mean time to readiness to accept a skin graft was significantly shorter in the SSD-CN group (24.6 days in the SSD group (17 participants); 13.6 days in the SSD-CN group (nine participants). Once again, these were time-to-event outcomes that had been inappropriately analysed as continuous data.

Secondary outcome: adverse events
In the De Gracia trial skin rashes were observed in both groups, but did not differ significantly between the groups. A subjective stinging effect was significantly higher in the SSD-CN group (RD -0.37; 95% CI -0.58 to -0.15). The NNT with SSD was three, in order to prevent one participant experiencing a stinging effect.

Secondary outcome: use of systemic antibiotics
There was no statistically significant difference between groups in the number of patients who received oral antibiotics for at least seven days (RD -0.03; 95% CI -0.20 to 0.13).

Secondary outcome: length of hospital stay
There was no statistically significant difference between groups in the mean length of hospital stay (MD 7.4; 95% CI -1.69 to 16.49).

1.3.6 SSD cream compared with Dimac containing SSD (Sildimac®) (one trial)
Miller\textsuperscript{67} enrolled 59 patients with two separate, comparable, sustained full-thickness burns.

Primary outcome: infection rate
Wound infection was defined as present when there were more than $10^5$ organisms per gram of tissue. Wound biopsies were obtained before treatment, and every seven days thereafter until the last day of treatment. Positive cultures were defined as any growth of any organism. Wound infection was based on clinical judgement. There was no statistically significant difference between the groups in the number of patients who developed an infection at any time point. Clinical wound infection occurred in 2/51 patients in the SSD group and 1/51 patients in the Dimac SSD group (RD 0.02; 95% CI -0.05 to 0.09).

Secondary outcome: adverse events
There was no statistically significant difference between groups in the number of patients reporting local adverse effects (such as burning and stinging) (RD 0.03; 95% CI -0.10 to 0.16). Six patients reported adverse effects at both the SSD site and the Dimac SSD site.

Summary for burns: SSD versus silver
Two trials investigated partial-thickness burns and four trials full thickness or severe burns. Only two out of six trial reports described adequate sequence generation,\textsuperscript{51,67} and none described adequate allocation concealment.
Infection rates were reported in six trials. No statistically significant differences were found in five trials, though one trial showed a statistically significant difference for the number of positive-culture swabs in favour of the synthetic silver dressings.

Time to complete healing was reported in two trials. One trial used appropriate analysis methods and showed no statistically significant differences, and the second trial analysed a time-to-event outcome (time to complete healing) inappropriately as a continuous variable and showed a statistical significance in favour of the SSD cerium nitrate group.

The number of wounds healed was reported in three trials. None of the trials showed statistically significant differences.

Pain was reported in three trials. One trial showed no statistically significant differences, while two trials showed a statistically significant difference in favour of the silver-containing dressings Acticoat® and Aquacel® Ag.

1.4 Comparisons between alternative silver-containing dressings including dose comparisons (silver versus silver)

1.4.1 Nanocrystalline silver-coated dressing (Acticoat®) compared with fine-mesh gauze with silver nitrate (0.5%) (one trial)

Tredget enrolled 30 patients with 60 deep partial- and full thickness burns.

*Primary outcome: infection rate*

Wound infection was defined as present when there were more than $10^5$ organisms per gram of tissue present. Bacteraemia was defined as the presence of the same bacterium isolated from the blood and the burn wound at concentrations of more than $10^5$ organisms per gram of tissue. Significantly fewer patients developed a wound infection in the nanocrystalline silver-coated (Acticoat®) group (5/17 in the Acticoat® group; 16/17 in the fine-mesh gauze with silver nitrate group) (RD -0.65; 95% CI -0.89 to -0.40). The NNT with nanocrystalline silver was two, in order to prevent one infection. There was no statistically significant difference between groups in the number of patients who developed bacteraemia (1/17 in the Acticoat® group and 5/17 fine-mesh gauze with silver nitrate group) (RD -0.24; 95% CI -0.48 to 0.01).

*Primary outcome: wound healing rate*

Healing was defined as complete re-epithelialisation; the authors reported there was no difference between the treatments, but no data were reported to support this statement.

*Secondary outcome: pain*

Pain was measured on a visual analogue scale from 1 (not painful) to 5 (very painful). Only the mean pain score on dressing removal was significantly lower in the Acticoat® group, but not the mean overall pain score (MD -0.28; 95% CI -0.93 to 0.37).
2. Acute wounds: other wounds

2.1 Topical silver-containing agents compared with topical agents without silver (SSD versus no silver)

Dire\textsuperscript{33} enrolled 465 patients with minor, uncomplicated, soft tissue wounds requiring sutures into a study that compared three antimicrobial regimens with paraffin-impregnated gauze. Data from 39 enrolled participants were excluded for protocol violations, so only 426 participants were included in the analysis (i.e. not analysed by intention-to-treat). The trial had four treatment groups in which the following numbers of participants completed the trial; SSD cream (99 participants), bacitracin zinc ointment (109 participants), neomycin sulfate (110 participants), and petrolatum (108 participants). We compared each of these antimicrobial alternatives with SSD cream.

Wound infection was defined as any subjective or objective sign or symptom of infection, e.g. fever, erythema, oedema, induration, tenderness, heat, exudate, adenopathy, and lymphangitis. Wounds were classified into one of five categories based upon clinical assessment, ranging from no signs of infection (384 participants), simple stitch abscess (25 participants), surrounding cellulitis (14 participants), accompanying lymphangitis (three participants), and systemic symptoms (no participants).

2.1.1 SSD cream compared with bacitracin zinc ointment

Primary outcome: infection rate

There was no statistically significant difference between groups in the number of patients who developed wound infections (12/99 in the SSD group; 6/109 in the bacitracin zinc group) (RD 0.07; 95% CI -0.01 to 0.14) (Analysis 1.1).

2.1.2 SSD cream compared with neomycin sulfate

Primary outcome: infection rate

Significantly fewer patients developed wound infections in the neomycin sulfate group (12/99 in the SSD group; 5/110 in the neomycin sulfate group) (RD 0.08; 95% CI 0.00 to 0.15) (Analysis 1.1). The NNT with neomycin sulfate was 13, in order to prevent one infection.

2.1.3 SSD cream compared with petrolatum

Primary outcome: infection rate

There was no statistically significant difference between groups in the number of patients who developed wound infections (12/99 in the SSD group; 19/108 in the petrolatum group) (RD -0.05; 95% CI -0.15 to 0.04) (Analysis 1.1).
2.2 Dressings containing silver compared with dressings without silver (silver versus no silver)

2.2.1 Hydrofibre dressing containing ionic silver (Aquacel® Ag) compared with povidone iodine gauze (one trial)

Jurczak\(^64\) enrolled 67 patients with open surgical wounds or open traumatic wounds all healing by secondary intention to a randomised controlled trial comparing silver-containing hydrofibre (hydrofibre-Ag) with povidone iodine gauze.

*Primary outcome: infection rate*

Wound infection was defined on clinical criteria such as warmth, redness, increased tenderness, swelling, increased exudate or purulent discharge, and malodour. There was no statistically significant difference in the number of patients who developed a wound infection during the trial period (4/35 in the Aquacel®Ag group; 4/32 in the povidone iodine group) (RD -0.01; 95% CI -0.17 to 0.14) (Analysis 1.1).

*Primary outcome: wound healing rate*

Healing was defined as epithelialisation, but also reduction in wound area in mm\(^2\), and reduction in wound depth in mm were reported. The mean time to complete healing was 14.1 days in the Aquacel® Ag group and 13.9 days in the povidone iodine group (log-rank test: not statistically significant). There was no statistically significant difference in the number of patients with complete wound healing at two weeks (8/35 in the Aquacel® Ag group; 3/32 in the povidone iodine group) (RD 0.13; 95% CI -0.04 to 0.31) (Analysis 1.2).

The authors stated that the adjusted mean reduction in wound area was 551 mm\(^2\) in the Aquacel®Ag group and 401 mm\(^2\) in the povidone iodine group. The adjusted mean reduction in wound depth was 9 mm in the Aquacel® Ag group and 10 mm in the povidone iodine group. How, and why, the adjustment was made was not reported. The authors stated that both reductions were statistically significant when compared with baseline, but, when compared with each other, no statistically significant difference was found. No SDs were reported; therefore the mean difference could not be calculated.

*Secondary outcome: adverse events*

Adverse events were defined as any event that occurred during the trial period, e.g. allergy, skin burn, haemorrhage. There was no statistically significant difference between the groups (RD -0.09; 95% CI -0.21 to 0.02).

*Secondary outcome: pain*

Pain was measured on a visual analogue scale from 1 (no pain) to 10 (worst pain imaginable). Although no statistically significant differences were found for the pain score at dressing removal and application, the decrease in mean pain score from baseline when the dressings were in place was -0.7 for Aquacel® Ag versus 0 for povidone iodine gauze, though no SD was given. The overall ability to manage pain could be scored as excellent, good, fair
or poor. The pain management was evaluated at the final visit (i.e. when the wound was completely healed or at week 2). Overall 70.6% of participants rated pain management as excellent in the Aquacel®Ag group compared with 22.6% in the povidone iodine gauze group. There was a statistically significant difference in the ability to manage pain in favour of the Aquacel® Ag group; P value < 0.001.

**Summary for acute wounds: SSD/silver versus no silver**

One of the two trials reported adequate sequence generation and adequate allocation concealment. Infection rate was reported in both trials with a total of four different dressing comparisons. Three comparisons were not statistically significantly different, and one comparison showed a statistically significant difference in favour of neomycin sulfate. Time to complete healing was reported in one trial, and was not statistically significant. The number of wounds healed was reported in one trial, and was not statistically significant. Pain was reported in one trial and showed a statistically significant difference in favour of hydrofibre dressing containing ionic silver.

**3. Chronic wounds**

**3.1 Topical silver-containing agents compared with topical agents without silver (SSD versus no silver)**

**3.1.1 SSD cream compared with Bensal HP with QRB7 (one trial)**

Jacobs enrolled 40 patients with Wagner grade 1 or 2 diabetic foot ulcers in a trial comparing SSD with Bensal HP with QRB7, which is a mixture of 6% benzoic acid, 3% salicylic acid and 3% extract of Q rubra (an extract of oak (Quercus rubra) bark).

*Primary outcome: infection rate*

Wound infection was defined on the basis of clinical signs (foul odour, exudation, or erythema) and bacterial cultures. None of the treated wounds demonstrated growth of pathogenic bacteria at six weeks (Analysis 1.1).

*Primary outcome: wound healing rate*

Healing was defined as the percentage reduction in total wound size (derived by adding the individual wound areas for each participant in each group) at two, four and six weeks. Complete healing was not defined. The “collective” wound diameter of the Bensal HP-treated patients had decreased by 72.5%, whereas the collective diameter of the SSD group had reduced by 54.7% (Student t test: P value 0.059). There was no statistically significant difference in the number of patients with complete wound healing within six
weeks (6/20 in the SSD group; 8/20 in the Bensal HP group) (RD -0.10; 95% CI -0.39 to 0.19) (Analysis 1.3).

Secondary outcome: adverse events
None of the patients experienced adverse effects.

3.2 Dressings containing silver compared with non-silver dressings (silver versus no silver)

3.2.1 Activated-charcoal dressing containing silver (Actisorb Plus®) compared with conventional phase-adapted therapy using diverse topical modalities (one trial)
Wunderlich\textsuperscript{73} enrolled 40 patients with venous leg ulcers of whom 38 were followed to study completion.

Primary outcome: infection rate
Every two weeks swabs were taken and were rated as 0 (no bacterial growth), 1 (light bacterial growth), 2 (medium bacterial growth), or 3 (heavy bacterial growth). The authors reported no differences in infection rates, but no actual data were reported.

Primary outcome: wound healing rate
Healing was defined as granulation (on an ordinal scale from 0 to 3), epithelialisation (on an ordinal scale from 0 to 3), and also as the reduction of the mean ulcer area in cm\textsuperscript{2}. There was no statistically significant difference in the number of patients healed after six weeks of treatment (6/19 patients in the charcoal-silver group; 2/19 patients in the conventional phase-adapted therapy using diverse topical modalities group) (RD 0.21; 95% CI -0.04 to 0.46) (Analysis 1.3).

3.2.2 Hydrofibre dressing containing ionic silver (Aquacel® Ag) compared with calcium alginate dressing (Algosteril®) (one trial)
Jude\textsuperscript{63} enrolled 434 patients with diabetic foot ulcers (Wagner grade 1 and 2). Although, at baseline, the calcium alginate dressing group (Algosteril®) seemed to have larger ulcers, and more patients in the hydrofibre dressing containing ionic silver (Aquacel® Ag) group were receiving antibiotics, the authors stated that the groups were comparable.

Primary outcome: infection rate
Wound infection was defined on the basis of clinical signs and/or bacterial cultures. There was no statistically significant difference in the number of patients who developed wound infection (11/67 in the Aquacel® Ag group; 8/67 in the Algosteril® group) (RD 0.04; 95% CI -0.07 to 0.16) (Analysis 1.1).

Primary outcome: wound healing rate
Healing was defined as complete re-epithelialisation, and as the reduction of the mean ulcer area in percentage and ulcer depth. Healing speed was defined as a weekly reduction in
absolute and percentage ulcer area. Only the mean time to complete healing was significantly lower in the Aquacel® Ag group (52.6 days +/-1.8 days (SD) Aquacel® Ag group; 57.7 days +/- 1.7 days (SD) Algosteril® group) (MD -5.1; 95% CI -5.69 to -4.51) (Analysis 1.2). Time in days to 100% healing was estimated by Kaplan-Meier survival analysis. The number of patients with complete wound healing within eight weeks was 21/67 in the Aquacel® Ag group and 15/67 in the Algosteril® group (RD 0.09; 95% CI -0.06 to 0.24) (Analysis 1.3). The mean percentage ulcer area reduction by eight weeks was 58.1% in the Aquacel® Ag group and 60.5% in the Algosteril® group (MD -2.4; 95% CI -18.72 to 13.92). The reduction in mean ulcer depth at eight weeks was 0.25 cm in the Aquacel® Ag group and 0.13 cm in the Algosteril® group (MD 0.12; 95% CI -0.05 to 0.29).

Secondary outcome: adverse events
Adverse events were not clearly defined. One of the events mentioned was infection. There was no statistically significant difference in the number of patients who experienced adverse effects (25/67 in the Aquacel® Ag group; 26/67 in the Algosteril® group) (RD -0.01; 95% CI -0.18 to 0.15).

Summary for chronic wounds: SSD/silver versus no silver
Two of the three trials reported adequate sequence generation, and none adequate allocation concealment.

Infection rate was reported in three trials, and showed no statistically significant differences.

Time to complete healing was reported in one trial, and was significantly faster with the silver hydrofibre (Aquacel® Ag) dressing. Time to healing was appropriately analysed using survival analysis.

The number of wounds healed was reported in all three trials, and showed no statistically significant difference.

4. Mixed wounds

4.1 Topical silver-containing agents compared with topical agents without silver (SSD versus no silver)
Hutchinson enrolled 292 patients with venous leg ulcers, partial-thickness burns or partial-thickness donor sites. The trial had three treatment groups; SSD cream/hydrocolloid (58 participants), hydrocolloid alone (108 participants), and non-occlusive paraffin impregnated gauze (126 participants). The results are presented comparing SSD cream to each of the comparators. Wound infection was defined using clinical criteria such as erythema, oedema, pain and purulent discharge.
4.1.1 SSD cream/hydrocolloid compared with hydrocolloid alone (one trial)

Primary outcome: infection rate
There was no statistically significant difference in the number of patients who developed a wound infection (0/58 in the SSD/hydrocolloid group, and 2/108 in the hydrocolloid group) (RD -0.02; 95% CI -0.06 to 0.02) (Analysis 1.1).

4.1.2 SSD cream/hydrocolloid compared with non-occlusive paraffin impregnated gauze

Primary outcome: infection rate
Significantly fewer patients in the SSD/hydrocolloid group developed a wound infection when compared with the non-occlusive paraffin impregnated gauze group (0/58 in the SSD/hydrocolloid group; 7/126 in the non-occlusive paraffin impregnated gauze group) (RD -0.06; 95% CI -0.10 to -0.01) (Analysis 1.1). The NNT with SSD/hydrocolloid was 18, in order to prevent one infection.

Summary for mixed wounds: SSD versus no silver
This trial did not report adequate sequence generation or adequate allocation concealment, therefore effect estimates may be biased.

Infection rate was reported in this trial with a total of two different dressing comparisons. One comparison showed a statistically significant difference in favour of SSD/hydrocolloid, and the other showed no differences.

Summary for all wounds: SSD/silver versus no silver

Infection rate
Infection rates were reported in 17 trials with a total of 21 different dressing comparisons. One comparison showed a statistically significant difference in favour of silver nitrate dressings, 15 comparisons showed no differences, and five comparisons using SSD showed a statistically significant difference in favour of non-silver dressings. In most cases, time to complete wound healing was inappropriately regarded as a continuous outcome and the analysis of these outcomes was, therefore, flawed, leading to potentially misleading results. Eight trials reported the number of wounds completely healed. Five trials showed no differences, and three trials showed a statistically significant difference in favour of non-silver dressings.
Adverse events
Adverse events were reported in four trials. None of them showed statistically significant differences.\textsuperscript{58,62-64}

Pain
Pain was reported in nine trials, but was expressed in different ways, e.g. the need for analgesia, or on a visual analogue scale (VAS). Overall, the reported pain scores were low in the majority of these trials, and the absolute differences in pain scores between the studied interventions were minimal. Two trials showed a statistically significant difference in favour of silver-containing dressings,\textsuperscript{57,64} two trials found no differences,\textsuperscript{49,58} and five trials showed a statistically significant difference in favour of non-silver dressings.\textsuperscript{50,55,56,66,74}

Patient satisfaction
Patient satisfaction was reported in one trial,\textsuperscript{49} and showed no statistically significant differences.

Length of hospital stay
Length of hospital stay was reported in two trials, with a total of three dressing comparisons. Only one patient group treated with silver nitrate for burns covering 20% to 40% of the total body surface area experienced significantly shorter hospital stay compared with participants who received Ringer’s lactate.\textsuperscript{65} No statistically significant differences were present for any of the other groups,\textsuperscript{65} or trial.\textsuperscript{50}

Costs
Costs were reported in four trials. One trial,\textsuperscript{61} found that the mean costs per cm\textsuperscript{2} of dressing - based on price lists supplied by the manufacturers - were lower in the non-silver dressings group, compared with the silver-containing dressing group. One trial reported costs of dressings per percent of body surface burnt,\textsuperscript{66} but differences were not reported. Both of the remaining two trials showed a statistically significant difference in favour of non-silver dressings.\textsuperscript{55,56}

DISCUSSION
This review highlights the lack of conclusive evidence on the effects of silver-containing dressings or agents to prevent wound infection and to promote wound healing. In particular, there was no evidence to support the use of SSD for prevention of wound infection in patients with partial-thickness burns. None of the trials indicated a beneficial effect for SSD for other outcomes when compared with other silver-containing or non-silver dressings. Furthermore, there was evidence that SSD may delay wound healing, may be more expensive, and may be more painful when applied to burns. The few trials on full-thickness burns and acute, chronic, or mixed wounds showed insufficient evidence for a beneficial
effect of silver-containing dressings to decrease infection rates and to aid wound healing. Only one trial showed significantly better results in terms of infection rates when another agent was added to the silver-containing dressing: infection rates were significantly lower than with SSD cream alone when a synthetic dressing was added to SSD cream (Hydron-SSD). The nanocrystalline form of silver present in the Hydron-SSD dressing, which releases silver ions faster, might explain the better results in burns. Furthermore, most trials used 1% SSD cream, but its effect might be dose-related. On the other hand, higher doses could also result in higher toxicity and more adverse effects.

Recently published literature had already suggested the lack of evidence of effectiveness for silver-containing dressings and topical agents in burns. Hussain published a Best Evidence Topic report on burns, including evidence from RCTs and CCTs. The authors concluded that there was little evidence for using silver-containing dressings to prevent wound infection, and that such products tend to delay wound healing. Furthermore, silver may have serious cytotoxic activity on various host cells.

In minor thermal burns (less than 15% TBSA) SSD cream was found to delay healing time and increase pain when compared with other treatments. Wasiak also evaluated different dressings for burn wounds and found evidence for a delayed healing time for SSD. Similarly, Bergin found no RCTs that evaluated the effects of silver-containing dressings for the treatment of diabetic foot ulcers, and Vermeulen found three RCTs and concluded that there was insufficient evidence of effectiveness for silver-containing dressings as a treatment for infected wounds.

The following limitations of this review should be noted

Firstly, the methodological quality of the 26 included trials was relatively low, and a large proportion of the evidence presented here is accrued from trials which demonstrate a high or uncertain risk of bias. Most of the studies had small sample sizes and were, therefore, at risk of not detecting any existing differences, and of incurring chance baseline imbalances for important prognostic factors. Only one-third of the trials reported adequate sequence generation, and even fewer reported allocation concealment.

Blinding of participants and care providers was not really possible, but outcome assessors could have been blinded, or healing confirmed by blinded assessment of photographs. This was almost never achieved or reported. Similarly the drop-out rate or reasons for drop-out were not always described.

The duration of follow-up of the included studies ranged from a few days to more than three months, whilst in only five studies was follow-up continued until complete wound re-epithelialisation was achieved. In some trials the length of follow-up was unclear, or too short, and almost half of the trials were supported financially by a single manufacturer. If this caused publication bias - which was shown to be present in studies on negative pressure wound therapy - the real effect is likely to be even less favourable.
Secondly, one of the strengths of a systematic review is the ability to pool data from several - often small - trials to achieve greater statistical power and a more precise overall effect size estimate. In this review few data could be pooled because the trials did not compare similar interventions, and there was considerable heterogeneity in the wounds being compared. Therefore, the lack of conclusive evidence for the effects of silver-containing dressings remains.

Thirdly, some trials used repeated measurements, for example, healing rate or swabs taken (e.g. at three, six, or nine days for one endpoint). This may illustrate the eagerness of the investigators (or the sponsors) to identify any sign of a treatment difference, at the cost of an increased chance of false positive results, while the shorter intervals are not relevant to patients. Furthermore, outcome parameters were measured in different ways and on different scales. Many secondary outcomes were based on subjective concepts such as “ease of use”, “comfortable to wear”. These subjective findings can hardly help in clinical practice and should be measured with standardised objective measurements whenever possible. Also, some trials measured “time per dressing”, or “costs per cm²”. These measures alone are meaningless and should be reported in combination with other aspects of costs.

Fourthly, the majority of studies that reported outcomes such as time to healing or time to skin grafting, incorrectly reported and analysed these outcomes as continuous - rather than time-to-event - variables. The problem with this approach is that the time to the event is only known for those people who actually experienced it (in this case healing, or grafting), and no information is obtained from those who were observed, but did not experience the event. This approach may introduce bias. Time-to-event data, such as time to wound healing, should be analysed using survival analysis in which the treatment effect is expressed as a hazard ratio.

Finally, eight trials did not attempt to define infection. Some trials defined infection only on clinical grounds and others merely on the presence of bacterial cultures. It is clearly difficult to interpret the results of studies that do not define their main outcomes. We reported the definition of infection and healing as used by the study authors and were unable to conduct any pooling due to heterogeneity.

Apart from the definition used, Sibbald\textsuperscript{82} stated that chronic wounds always contain bacteria and a diagnosis of infection should be based on clinical signs and not solely on bacterial cultures.

AUTHORS’ CONCLUSIONS

Implications for practice

There is currently insufficient evidence that silver-containing dressings prevent wound infection or promote wound healing; the available evidence is low both in volume and
quality. There is some evidence from small, poor-quality trials, that SSD does not reduce wound infection and slows down wound healing in people with partial-thickness burns.

**Implications for research**

More studies, and particularly studies with a low risk of bias, are needed to confirm any effect of silver-containing dressings in full thickness burns and other wound groups. Future research must develop clear, valid, and reliable measures of wound infection. The use of common, quantifiable, and clinically-relevant endpoints (time to complete wound healing, number and time to wound infection, pain, adverse events, 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. Future research must adopt a survival approach for the analysis of time-to-event data, such as time to healing. Finally, a sufficiently long follow-up period of at least six months is essential if treatment effects in chronic wounds are to be detected. Interventions under evaluation should be thoroughly, and clearly, described. For this purpose use of the revised CONSORT statement is recommended in order to report these trials adequately.
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