Silver delivery approaches in the management of partial thickness burns: A systematic review and indirect treatment comparison

Leo Nherera, MSc; Paul Trueman, MA; Christopher Roberts, PhD; Leena Berg, PhD, MD

1. Smith & Nephew Advanced Wound Management, Hull, United Kingdom, 2. Clinical Resolutions, Hessle, East Yorkshire, United Kingdom, and 3. Department of Plastic Surgery, Kuopio University Hospital, Kuopio, Finland

Reprint requests:
Leo Nherera, Smith & Nephew Global Market Access, 101 Hessle Road, Hull HU3 2BN, United Kingdom. Email: leo.nherera@smith-nephew.com

Manuscript received: March 1, 2017
Accepted in final form: July 13, 2017
DOI:10.1111/wrr.12559

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

ABSTRACT

Silver-containing products play an important role in the management of burn wound infections. We sought to compare the efficacy of commonly used silver delivery approaches including nanocrystalline silver, silver-impregnated hydrofiber dressing, and silver-impregnated foam dressing as the main products in the management of partial thickness burns. A systematic review was performed by searching PubMed, EMBASE, Cochrane, and other databases to identify relevant randomized controlled trials and observational studies. Due to the paucity of direct head-to-head trials, an indirect treatment comparison was performed. The use of nanocrystalline silver was associated with a statistically significant reduction in length of stay when compared to silver-impregnated hydrofiber dressing (p = 0.027) and a shorter time to healing when compared to silver-impregnated foam dressing (p = 0.0328). There were no statistically significant differences in infection rates and surgical procedures between nanocrystalline silver, silver-impregnated hydrofiber dressing, and silver-impregnated foam dressing; however, nanocrystalline silver was found to be the most beneficial for all the outcomes, including infection rates and surgical procedures, according to the Monte Carlo simulation method. In conclusion, current evidence from the published literature suggests that where the clinical and microbiological priority is to get in control of infection quickly it would seem prudent to use the most potent silver delivery system, which is nanocrystalline silver. Nanocrystalline silver may offer both clinical and economic benefits compared to alternative treatments in the management of patients with mixed burns that are at high risk of infection.

Burns are a common injury that can be a significant health burden to both patients and clinical practitioners. In particular, wound infections are a serious complication of burns and a major cause of morbidity and mortality. Infections can result in delayed wound healing, an increased need for surgical procedures and extended hospital stay. In many cases, the development of systemic infection and sepsis can be the main causes of mortality in burns patients. The risk of wound infection is related to the extent of the injury, including the total body surface area (TBSA) affected and the thickness of the burn wound.

Silver-containing creams and dressings are widely used in the management of burn wound infections, with the antimicrobial properties of silver having long been established. While silver sulfadiazine (SSD) cream has been a mainstay of burns management for many years, it has some limitations including being short-acting and requiring frequent re-application. Many other improved silver delivery approaches have become available over the past few decades, which include nanocrystalline silver, silver-impregnated hydrofiber dressing and silver-impregnated foam dressings. These dressings have been designed to provide a more sustained availability of silver over extended...
time periods resulting in less frequent dressing changes.\textsuperscript{9} These silver delivery methods are achieved through the use of different substrates and types of silver incorporated into the overall architectural structure of the dressing. Other older technologies for the prevention and management of infection in burn wounds include silver nitrate. There is no clear evidence on the clinical superiority of each dressing in providing wound coverage to burnt areas of skin.

According to the European Burns Association’s clinical practice guidelines for burn care, the choice of wound care dressing should be based on the cause, size, depth and location of the burn, amount of exudate, and contamination level. However, it has advised that clinicians should “be creative because there is no clinical directive evidence to support the choice of one dressing over another.”\textsuperscript{10} Overall, there is a need for more evidence-based information to help clinicians decide on the most appropriate approach to facilitate healing.

We report the findings of a systematic review and indirect treatment comparison to determine the comparative efficacy of commonly used silver delivery approaches including but not exclusive to nanocrystalline silver, silver-impregnated hydrofiber dressing, and silver-impregnated foam dressing in the management of partial thickness burns. As far as we are aware this is the first published indirect treatment comparison of different silver-delivery approaches.

**METHODS**

**Systematic review**

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.\textsuperscript{11}

**Literature search**

Studies were identified by searches of the following electronic databases with no restrictions in language: PubMed, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) Database, ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), and the European Trials Register. A search strategy, which included both free text and MeSH terms, was used to identify studies indexed on PubMed, and this was modified for searches of the other databases to account for differences in syntax and thesaurus headings. The search terms are shown in Appendix I (Supporting Information). The searches included citations from 1990 (when most of the commonly used silvers became available) to May 2015. A pearl-growing technique, whereby the references of relevant papers identified in the original search are searched, was used to identify further publications of interest.

**Eligibility criteria**

The Population, Intervention, Comparator, and Outcomes (PICO) eligibility criteria are outlined in Table 1. Studies which included adults and children with deep partial and superficial partial thickness burns were selected. The interventions included nanocrystalline silver (ACTICOAT\textsuperscript{\textregistered}; Smith & Nephew Healthcare Ltd, Hull, United Kingdom), silver-impregnated hydrofiber dressing (AQUACEL AG, ConvaTec, Skillman, NJ) and silver-impregnated foam dressing (MEPILEX MG, Mölnlycke Health Care, Göteborg, Sweden). These were chosen as silver delivery products associated with burn wound covers available in

**Table 1. Inclusion and exclusion criteria.**

| Criteria                  | Inclusion                                                                                     | Exclusion                                                                                     |
|---------------------------|----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Type of study             | RCTs, retrospective, and prospective comparative observational studies                        | Systematic reviews, conference abstracts, case series, case reports, narrative reviews, editorials, opinions; studies performed in animals |
| Population                | Adults and children with deep partial and superficial partial thickness burns                 | Full thickness burns                                                                         |
| Geographical location     | Publications from any country                                                                 | None                                                                                          |
| Interventions             | Nanocrystalline silver (ACTICOAT), silver-impregnated hydrofiber dressing (AQUACEL AG), and silver-impregnated foam dressing (MEPILEX) | Other silver dressings other than nanocrystalline silver (ACTICOAT), silver-impregnated hydrofiber dressing (AQUACEL AG), and silver-impregnated foam dressing (MEPILEX) |
| Comparators               | All silver delivery approaches including SSD, silver nitrate, nanocrystalline silver, silver-impregnated hydrofiber dressing, and silver-impregnated foam dressing | None                                                                                          |
| Outcomes of interest      | Infection, LOS, time to healing/reepithelialization, incidence of surgical procedures (defined as debridement and skin grafting) and pain |                                                                                               |

LOS, length of stay (in hospital); SSD, silver sulfadiazine; RCT, randomized controlled trial.
Europe and the United States, although other silver delivery approaches are available. The outcomes of interest were infection, length of stay (LOS), incidence of surgical procedures, and pain. Both randomized controlled trials (RCTs) and observational studies were included. We used evidence from both study designs to maximize all the available data as well as exploit the advantages offered by the different designs such as the internal validity provided by RCTs and greater external validity offered by observational studies.

Data extraction

Two reviewers independently assessed the full text papers of the studies identified during the abstract assessment stage for inclusion, based on the PICO eligibility criteria. Initially, five papers were fully independently data extracted by two reviewers using a standardized data extraction form and validated by one reviewer; however, because agreement between the two reviewers was high, the remaining papers were extracted by one reviewer and validated by a second reviewer. Any discrepancies were resolved through discussion, with involvement of a third reviewer if necessary.

Quality assessment

Two reviewers assessed the methodological quality of the studies independently. RCTs were assessed using the Cochrane risk of bias tool, which addresses seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and “anything else.” The Good ReseArch for Comparative Effectiveness (GRACE) checklist, which is an 11-item tool, was used to assess the quality of data and methods of the observational studies.

Statistical analysis

To compare treatments when they have not been evaluated directly in head-to-head trials, a type of statistical analysis called an adjusted indirect treatment comparison (ITC) can be used. The technique of ITC is often used when there is no evidence or insufficient evidence from head-to-head trials, or when more than two treatments are of interest. For example, we found studies that compared the effectiveness of “nanocrystalline silver vs. SSD” and others compared the effectiveness of “silver-impregnated hydrofiber dressing vs. SSD,” but no trials or inadequate studies that compared the effectiveness of “nanocrystalline silver vs. silver-impregnated hydrofiber dressing.” In order to learn about the relative effectiveness of “nanocrystalline silver vs. silver-impregnated hydrofiber dressing,” we can compare them indirectly by contrasting trials of “nanocrystalline silver vs. SSD” with trials of “silver-impregnated hydrofiber dressing vs. SSD.”

An ITC is therefore when the results of two separate meta-analyses are combined, and the adjustment is made using direct evidence from a common comparator, in this case via SSD because it was the most frequent comparator in the studies (see Figure 2). One study of silver nitrate was included as an additional historical control as it still represents part of standard care pathways for infection management in some burn units worldwide. Using the method outlined by Bucher 1997 of adjusted indirect comparisons, comparisons were made between nanocrystalline silver vs. silver-impregnated hydrofiber dressing and vs. silver-impregnated foam dressing and silver-impregnated hydrofiber dressing vs. silver-impregnated foam dressing for the outcomes of interest that were reported in the pairwise analysis. The method used for the ITC is a standard approach that has been used for many years in different therapeutic areas, as reviewed by Kim et al.

For dichotomous outcomes, the odds ratio (OR) was reported as the summary statistic, and for continuous outcomes using the Mantel–Haenszel methods, the (weighted) mean difference (MD) was reported using the generic inverse variance method. We calculated the probability that each dressing would be the most effective (ranking of treatments), that is, the first best, second best and so on using Monte Carlo simulation methods and these probabilities sum to one for each treatment and each rank. In each Monte Carlo cycle (2000 simulations were done), each treatment is ranked according to the estimated effect size. The proportion of the cycles in which a given treatment ranks first out of the total gives the probability that a treatment ranks first, that is, “is the best” among the available treatment options. Similar probabilities were calculated for being the second best, and so on.

We assessed the clinical similarity assumption in the data by considering the baseline characteristics reported in the studies, definition of outcomes to check if the results could meaningfully be combined in a meta-analysis. Statistical heterogeneity (variation in study outcomes or results) was analyzed using $I^2$. $I^2$ describes the percentage of variation across studies that is due to heterogeneity rather than chance and was classified to be substantial if $I^2 > 50\%$. In case of substantial heterogeneity, we used a statistical model called the random effects otherwise we used the fixed effects model. No tests for inconsistency were done for the indirect treatment comparison as we did not have a complete loop in our data set, that is, we only had data from the indirect comparison and no direct comparison data were available for the comparators of interest (nanocrystalline silver vs. silver-impregnated hydrofiber dressing and vs. silver-impregnated foam dressing and silver-impregnated hydrofiber dressing vs. silver-impregnated foam dressing). Inconsistency tests are done to assess the agreement between direct and indirect results.

RESULTS

Study selection

The electronic database searches initially identified 1,587 articles, of which 1,057 were screened after the removal of duplicates (Figure 1). After the initial screening, a total of 52 articles were retrieved for full-text assessment, of which nineteen met the inclusion criteria.

Summary of included studies

A summary of the study characteristics and results are shown in Table 2. Nanocrystalline silver was reported in twelve of the included studies, that is, six RCTs and six observational studies (Table 2). The
nanocrystalline silver studies ranged in patient sample size from 14 to 596 patients, with four studies conducted in a pediatric population alone. Six studies were in comparison to SSD; two were vs. silver-impregnated hydrofiber dressing, and one each vs. silver-impregnated foam dressing, silver nitrate, and silicone rubber. The mean TBSA across the studies ranged from 1% (in a study comparing nanocrystalline silver to silver-impregnated foam dressing) to 54%; the mean TBSA was >10% in four studies.

Silver-impregnated hydrofiber dressing was reported in seven studies, that is, four RCTs, and three observational studies. The patient population sizes ranged from 20 to 805. One study included only pediatric cases. When reported, the mean TBSA across the studies ranged from 2% (in a study vs. nanocrystalline silver) to 15% (in a study compared to gauze), with a mean TBSA >10% in two studies.

Silver-impregnated foam dressing was reported in three RCTs, two of which were vs. SSD, and one vs. nanocrystalline silver. The patient population sizes ranged from 96 to 153, with one study (vs. nanocrystalline silver) in pediatric cases only. The mean TBSA was <5% in all studies.

Two studies evaluated both nanocrystalline silver and silver-impregnated hydrofiber dressing, and one study compared nanocrystalline silver vs. silver-impregnated foam dressing (Table 2). The RCT by Verbelen et al., which was conducted in 100 patients with partial thickness burns and a mean TBSA of 2.2%, found no statistically significant differences for signs of infection, bacterial control and healing time between nanocrystalline silver and silver-impregnated hydrofiber dressing. However, a statistically significant difference in favor of silver-impregnated hydrofiber dressing was found for patient pain (p < 0.001). The observational study by Gravante and Montone reported that nanocrystalline silver resulted in shorter LOS compared to silver-impregnated hydrofiber dressing.

All of the RCTs were rated as having an unclear risk of bias, generally due to a lack of information being reported in the methods. The majority of the observational studies were deemed to be of adequate quality.

**Indirect treatment comparison**

Due to the paucity of head-to-head studies directly evaluating the treatments identified, indirect comparisons were made using SSD/silver nitrate as the common comparator. The analysis therefore included direct (vs. SSD/silver nitrate) and indirect comparisons (nanocrystalline silver vs. silver-impregnated hydrofiber dressing, nanocrystalline...
Table 2. Characteristics of the studies

| Author, year and country | Study design and sample size | Mean age ± SD (range), years | Mean TBSA ± SD (range), % | Summary of results |
|--------------------------|-----------------------------|-----------------------------|--------------------------|-------------------|
| **Nanocrystalline silver vs. silver-impregnated hydrofiber dressing studies** | | | | |
| Verbelen 2014, Belgium | RCT of silver-impregnated hydrofiber dressing (n = 50) vs. nanocrystalline silver (n = 50) in patients with partial thickness burns | 31 | 2.2 | Silver-impregnated hydrofiber dressing vs. nanocrystalline silver
Infection: $p = 0.965$ (only $p$-values were provided for difference between groups for infection)
Mean healing time for epithelialization: 15.06 ± 3.42 vs. 16.16 ± 7.19 days ($p = 0.941$)
Pain: $p = 0.039$ and $p = 0.006$ in favor of silver-impregnated hydrofiber dressing for first dressing application pain and pain during dressing inspection, respectively. Dressings were comparable for worst pain score and comfort with dressing |
| Gravante 2010, UK | Retrospective study for period November–December 2005 and January–February 2006 in 347 ambulatory patients with mixed superficial and partial thickness burns. Patients were treated with many dressings, including nanocrystalline silver, silver-impregnated hydrofiber dressing and SSD | 48 ± 20.5 | 4 ± 2 | Superficial wounds: 64% |
| **Nanocrystalline silver vs. silver-impregnated foam dressing studies** | | | | |
| Gee-Kee 2015, Australia | RCT of silver-impregnated foam dressing (n = 33) vs. nanocrystalline silver (n = 31) and nanocrystalline silver + silicone wound contact layer (Mepitel™) (n = 32) in patients with superficial partial to deep partial thickness burns | Silver foam: 3.0 (1.0–4.0) | Silver foam: 1.0 (0.50–2.0) | Nanocrystalline silver vs. silver-impregnated foam dressing
Median time to full epithelialization: 9.5 vs. 7.0 days
Pain (VAS scores): 25% lower in the silver foam group at dressing removal ($p = 0.04$) vs. nanocrystalline silver. There was no statistically significant difference in VAS scores between the silver foam and nanocrystalline silver in pain scores after dressing application and in the overall VAS pain score |
| Author, year and country | Study design and sample size | Mean age ± SD (range), years | Mean TBSA ± SD (range), % | Summary of results |
|--------------------------|-----------------------------|-----------------------------|--------------------------|-------------------|
| Other nanocrystalline silver studies | | | | |
| Muangman 2006 24 Thailand | RCT of nanocrystalline silver (n = 25) in patients with partial thickness burns | 30 | 36 (18-54) | Pain (FLACC scale scores): 32% lower in the silver foam group at dressing removal (p = 0.01), 37% lower at new dressing application (p = 0.04), and 22% lower overall FLACC score vs. nanocrystalline silver | |
| Huang 2007 23 China | RCT of nanocrystalline silver (n = 10) vs. SSD (n = 10) in patients with residual wounds post burn | 41 (25-68) | 41.6 (4.5-27) | Infection: 3/25 (12%) vs. 4/25 (16%) | |
| Vargas 2005 26 USA | RCT of nanocrystalline silver (n = 14 wounds) vs. SSD (n = 14 wounds) in 28 patients with partial thickness burns, 2 burn wounds each | 35.2 ± 3.2 | 14.6 ± 1.5 | Pain (mean VAS pain scores at dressing changes [scale 0-10]): 3.2 ± 2.6 vs. 7.9 ± 1.5 | |
| Tedgjet 1998 25 Canada | RCT in 30 patients of nanocrystalline silver (14 wounds) vs. 0.5% solution of silver nitrate | 41 (25-68) | 41.6 (4.5-27) | Pain (mean VAS pain scores at dressing removal [scale 0-10]): 3.2 ± 2.6 vs. 7.9 ± 1.5 | |
| Fong 2005 29 Australia | A series of audits (observational study) nanocrystalline silver (n = 19) vs. SSD (n = 51) in a convenience sample of people with burn injuries | NR | 9 | Infection: 2/19 (10.5%) vs. 5/51 (9.8%) | |
| Cuttle 2007 28 Australia | Retrospective cohort study in 569 pediatric cases with partial or full thickness burn comparing nanocrystalline silver (n = 241) and SSD (n = 328) | 50 months | 5 | Mean time to reepithelialization: 14.9 ± 9.7 vs. 18.3 ± 22.3 days (p = 0.047) | |

| Table 2. Continued. | | | | |

**Comparison of silver delivery approaches in partial thickness burns**

Nherera et al.
| Author, year and country | Study design and sample size | Mean age ± SD (range, years) | TBSA ± SD (range, %) | Summary of results |
|--------------------------|------------------------------|-----------------------------|----------------------|-------------------|
| Peters and Verchere 2006 31 Canada | Retrospective cohort study in 103 pediatric cases with partial or full thickness burn. Nanocrystalline silver patients (n = 30) were managed as outpatients while SSD patients (n = 73) were managed as inpatients | 3.23 ± 3.99 | 6.72 ± 4.13 | Nanocrystalline silver vs. SSD LOS (mean LOS in hospital): 0.83 ± 2.34 vs. 13.85 ± 10.29 days (p < 0.001) Surgical procedures (mean number of debride- ments/graft procedures): 9/30 (30%) vs. 34/73 (47%) (p = 0.18) |
| Tonkin & Wood 2005 33 Australia | A combination of retrospective and prospective cohort study comparing SSD (n = 36) and nanocrystalline silver (n = 36) in patients with mixed burns with deep partial being most common (41%) | 36 | 9 | Nanocrystalline silver vs. SSD LOS (mean LOS in hospital): 8.8 ± 5.6 vs. 15.5 ± 7.8 days (p = 0.045) Surgical procedures: 9/36 (25%) vs. 24/36 (66.7%) |
| Strand 2010 32 Sweden | Retrospective case review of the use of nanocrystalline silver (n = 57 in 2007) compared with previous protocol of silicone rubber dressing (n = 48 in 2001) in pediatric burns for periods 2001, 2004, and 2007 Only data for inpatients were reported | 2.47 in 2001 vs. 5.13 in 2007 | | Nanocrystalline silver vs. silicone rubber LOS (mean LOS in hospital): 4.5 vs. 12.47 days (p < 0.001) |
| Other silver-impregnated hydrofiber dressing studies | | | | |
| Caruso 2006 35 USA | RCT comparing silver-impregnated hydrofiber dressing (n = 42) with SSD (n = 40) in patients with mixed partial-thickness burns | 27 | 11 | Silver-impregnated hydrofiber dressing vs. SSD Infection: 6/42 (14.3%) vs. 8/40 (20%) Median time to reepithelialization: 16 ± 8 vs. 17 ± 8.5 days Surgical procedures (skin grafting): 5/42 (11.9%) vs. 7/40 (17.5%) Pain (mean VAS score during dressing changes for those >4 years [scale 0–10]): 3.63 vs. 4.77 (p = 0.003) |
| Muangman 2010 34 Thailand | RCT comparing silver-impregnated hydrofiber dressing (n = 35) vs. SSD (n = 35) in patients with superficial second-degree burns in an outpatient clinic | 36 | 3 | Silver-impregnated hydrofiber dressing vs. SSD Mean wound healing time: 10 ± 3, vs. 13.7 ± 4.3 days (p < 0.02) There was less pain during dressing change with hydrofiber dressing (p < 0.02) |
| Dokter 2013 37 Netherlands | A retrospective study of silver-impregnated hydrofiber dressing (n = 302) and SSD | 1.3 (1.06) | 5.2 (2.47) | Silver-impregnated hydrofiber dressing vs. SSD LOS (mean time in hospital): 7.5 (6.46) vs. 9.7 (7.60) days (p < 0.01) |
| Author, year and country | Study design and sample size | Mean age ± SD (range), years | Mean TBSA ± SD (range), % | Summary of results |
|--------------------------|-----------------------------|-----------------------------|--------------------------|--------------------|
| Saba 2009 USA 38         | Retrospective study of silver-impregnated hydrofiber dressing (n = 10) vs. Xeroflo gauze with bacitracin zinc ointment (n = 10) in partial thickness burns | Hydrofiber dressing: 37 ± 51 Gauze: 46 ± 66 | Hydrofiber dressing: 15 ± 4.7 Gauze: 17 ± 10 | Surgical procedures (skin grafting): 35/302 (11.6%) vs. 34/164 (20.7%) (p < 0.01) Silver-impregnated hydrofiber dressing vs. gauze |
| Yarboro 2013 USA 36      | Nonrandomised trial of silver-impregnated hydrofiber dressing (n = 12) vs. SSD (n = 12) in superficial thickness burns | 34 | Not reported but excluded >25% | Pain (mean VAS score [scale 0–10]): 2.92 ± 1.12 vs. 4.7 ± 2.22 (p = 0.02) |
| Silverstein 2011 USA 39  | RCT of silver-impregnated foam dressing (n = 49) vs. SSD (n = 50) partial thickness burns | 38 | 5 | Silver-impregnated foam dressing vs. SSD |
| Tang 2015 China 40       | RCT of silver-impregnated foam dressing (n = 71) vs. SSD (n = 82) in partial thickness burns | 36.2 (12.8) | 4.48 (4.93) | Silver-impregnated foam dressing vs. SSD Infection: 8/71 (11.3%) vs. 14/82 (17.1%) Median healing time: 15 ± 5.25 days Surgical procedures (grafting): 3/71 (4.2%) vs. 4/82 (4.9%) (nonsignificant) Pain (mean VAS score during dressing removal [scale 0–100]): 9.2 (13.6) vs. 19.1 (23.9) (p = 0.005) |

FLACC, Face, Legs, Activity, Cry, Consolability scale; LOS, length of stay; RCT, randomized controlled trial; SSD, silver sulfadiazine; VAS, visual analog scale.
Figure 2. Network of evidence for the newer antimicrobials and SSD/silver nitrate. All the new antimicrobials were compared directly with SSD/silver nitrate as shown by solid lines with double arrows. A connected “star” network for the three newer antimicrobials and SSD/silver nitrate was formed for all the outcomes, allowing a comparison between all three to be undertaken shown by broken lines with double arrows. LOS, length of stay; RCT, randomized controlled trial; obs, observational study. [Color figure can be viewed at wileyonlinelibrary.com]

silver vs. silver-impregnated foam dressing and silver-impregnated hydrofiber dressing vs. silver-impregnated foam dressing) (Figure 2).

Pain was reported by eight studies that compared the new antimicrobials with SSD/silver nitrate. Pain was assessed using either a 10-point or 100-point visual analog or face pain rating scale in small children in the included studies; however, reported results ranged from a week after treatment initiation to when the studies were completed at between three to six weeks. The ITC showed a high degree of statistical heterogeneity, and it was decided against pooling the results in accordance with guidance from the Cochrane methods handbook. Therefore, the results of pain from the individual studies alone are summarized (Table 2). The ITC showed a low degree of heterogeneity for the other outcomes of interest, that is, infection control, LOS, time to healing/reepithelialization and surgical procedures, and the results are reported below.

Infection control

Infection was reported by six studies that compared the new antimicrobial delivery systems with SSD/silver nitrate, five of which were RCTs and one observational study. Of the five RCTs, two evaluated nanocrystalline silver, one evaluated silver-impregnated hydrofiber dressing, and the other two comprised silver-impregnated foam dressing. One observational study reported on nanocrystalline silver.

Of the new silver dressings only nanocrystalline silver resulted in a statistically significant reduction in the incidence of infections compared to SSD/silver nitrate (Table 3; Figure 3a). Although silver-impregnated hydrofiber dressing and silver-impregnated foam dressing resulted in a reduction of the incidence of infection, it did not reach statistical significance. The indirect evidence showed that there were no statistically significant differences in infection rates with nanocrystalline silver compared to silver-impregnated hydrofiber dressing (OR [95% CI]: 0.31 [0.06, 1.54]) and silver-impregnated foam dressing (OR: 0.32 [0.07, 1.53]) (Table 3). However, the Monte-Carlo method, which allows further exploration of the uncertainty, suggested that nanocrystalline silver was the most effective intervention in 71% of the simulations compared to 16 and 13% for silver-impregnated hydrofiber dressing and silver-impregnated foam dressing, respectively.

Length of stay

LOS was reported in six studies comparing the new antimicrobial with SSD, including two RCTs and three observational studies. Of these, four included nanocrystalline silvers and one each included silver-impregnated hydrofiber dressing and silver-impregnated foam dressing. However, one study of nanocrystalline silver was not considered in the meta-analysis as it contributed to significant heterogeneity.

Compared to SSD, nanocrystalline silver and silver-impregnated hydrofiber dressing resulted in a statistically significant reduction in LOS, while there was no statistical difference for silver-impregnated foam dressing (Table 3; Figure 3b). In addition, nanocrystalline silver resulted in a statistically significant reduction in LOS when compared to silver-impregnated hydrofiber dressing ($p = 0.027$). There were no statistically significant differences in LOS with nanocrystalline silver compared to silver-impregnated foam dressing ($p = 0.207$) and silver-impregnated hydrofiber dressing with silver-impregnated foam dressing.
Table 3. Direct pairwise comparison with SSD and indirect treatment comparison for infection control, LOS, and surgical procedures.

### Infection control

| Intervention                  | Comparator                           | OR\(^a\) (95% CI)      | p-Values |
|-------------------------------|--------------------------------------|-------------------------|----------|
| Nanocrystalline silver        | SSD/silver nitrate                   | 0.21 (0.07, 0.62)       | 0.005    |
| Silver-impregnated hydrofiber dressing | SSD/silver nitrate                   | 0.67 (0.21, 2.13)       | 0.49     |
| Silver-impregnated foam dressing   | SSD/silver nitrate                   | 0.65 (0.27, 1.57)       | 0.34     |
| Nanocrystalline silver        | Silver-impregnated hydrofiber dressing | 0.31 (0.06, 1.54)       | 0.1534   |
| Silver-impregnated foam dressing   | Silver-impregnated hydrofiber dressing | 0.32 (0.07, 1.53)       | 0.1549   |

### LOS

| Intervention                  | Comparator                           | MD\(^b\) (95% CI)      | p-Values |
|-------------------------------|--------------------------------------|-------------------------|----------|
| Nanocrystalline silver        | SSD/silver nitrate                   | -5.17 (-7.42, -2.92)    | <0.00001 |
| Silver-impregnated hydrofiber dressing | SSD/silver nitrate                   | -2.20 (-3.57, -0.83)    | 0.002    |
| Silver-impregnated foam dressing   | SSD/silver nitrate                   | -2.69 (-5.80, 0.42)    | 0.09     |
| Nanocrystalline silver        | Silver-impregnated hydrofiber dressing | -2.97 (-5.60, -0.34)    | 0.027    |
| Silver-impregnated foam dressing   | Silver-impregnated hydrofiber dressing | -2.48 (-6.32, -1.36)    | 0.207    |

### Time to healing/reepithelialization

| Intervention                  | Comparator                           | MD\(^b\) (95% CI)      | p-Values |
|-------------------------------|--------------------------------------|-------------------------|----------|
| Nanocrystalline silver        | SSD/silver nitrate                   | -4.47 (-5.63, -3.30)    | <0.00001 |
| Silver-impregnated hydrofiber dressing | SSD/silver nitrate                   | -3.18 (-4.75, -1.62)    | <0.0001  |
| Silver-impregnated foam dressing   | SSD/silver nitrate                   | -1.85 (-3.96, 0.26)    | 0.09     |
| Nanocrystalline silver        | Silver-impregnated hydrofiber dressing | -1.29 (-3.24, 0.66)    | 0.1964   |
| Silver-impregnated foam dressing   | Silver-impregnated hydrofiber dressing | -2.62 (-5.03, -0.21)    | 0.0328   |
| Silver-impregnated hydrofiber dressing | Silver-impregnated foam dressing     | -1.33 (-3.96, 1.30)    | 0.3259   |

### Surgical procedures

| Intervention                  | Comparator                           | OR\(^a\) (95% CI)      | p-Values |
|-------------------------------|--------------------------------------|-------------------------|----------|
| Nanocrystalline silver        | SSD/silver nitrate                   | 0.40 (0.28, 0.56)       | <0.00001 |
| Silver-impregnated hydrofiber dressing | SSD/silver nitrate                   | 0.52 (0.32, 0.84)       | 0.007    |
| Silver-impregnated foam dressing   | SSD/silver nitrate                   | 0.67 (0.21, 2.10)       | 0.49     |
| Nanocrystalline silver        | Silver-impregnated hydrofiber dressing | 0.77 (0.42, 1.39)       | 0.3937   |
| Silver-impregnated foam dressing   | Silver-impregnated hydrofiber dressing | 0.60 (0.18, 1.99)       | 0.4078   |
| Silver-impregnated hydrofiber dressing | Silver-impregnated foam dressing     | 0.78 (0.22, 2.70)       | 0.7038   |

*Numbers in bold indicate statistically significant results.

CI, confidence interval; LOS, length of stay; MD, mean difference; OR, odds ratio; SSD, silver sulfadiazine.

\(^a\)The OR represents the ratio of being the most effective treatment compared to another. An OR of <1 favors the intervention compared to the comparator.

\(^b\)An MD of <0 favors the intervention compared to the comparator.

(p = 0.790) (Table 3). Nanocrystalline silver had the highest probability (88%) of being the most efficacious treatment for LOS according to the Monte Carlo simulation method described earlier followed by silver-impregnated foam dressing (11%) and silver-impregnated hydrofiber dressing (1%).

### Time to healing/reepithelialization

Time to healing/reepithelialization was reported by six studies comparing the newer silver delivery systems with SSD. Three studies, one RCT and two observational studies, included nanocrystalline silver;\(^{23,28,30}\) two RCTs...
Figure 3. Impact of the newer silver delivery approaches nanocrystalline, silver-impregnated hydrofiber dressing, and silver-impregnated foam dressing compared to SSD/silver nitrate on (A) incidence of infection, (B) length of stay, (C) time to healing/reepithelialization, and (D) incidence of surgical procedures. The forest plot shows the odds ratio (OR) calculated by the random effects model or the mean difference (MD) calculated by the fixed effects model. Squares represent individual study effects and diamonds represent the summary effect from the meta-analysis. Horizontal bars represent 95% CIs, and the vertical line in plot is at 1 for OR and 0 for MD, corresponding to the null hypothesis of no effect. An OR of <1 or an MD of <0 (depicted on the left hand side of the plot) favors the newer silver delivery approach vs. the older silver delivery approach. There was evidence of low or moderate statistical heterogeneity ($I^2$ = test of heterogeneity). CI, confidence interval; df, degree of freedom; M–H, Mantel–Haenszel; SSD, silver sulfadiazine. [Color figure can be viewed at wileyonlinelibrary.com]
included silver-impregnated hydrofiber dressing, and one RCT included silver-impregnated foam dressing.

Nanocrystalline silver and silver-impregnated hydrofiber dressing resulted in a statistically significant reduction in time to healing/reepithelialization compared to SSD; there was no statistical difference for silver-impregnated foam dressing compared to SSD (Table 3 and Figure 3c). Nanocrystalline silver was associated with a significantly shorter time to healing when compared to silver-impregnated foam dressing, whereas there was no significant difference when compared to silver-impregnated hydrofiber dressing (Table 3). According to the Monte Carlo simulation method, nanocrystalline silver had the highest probability (88%) of resulting in a shorter time to healing/reepithelialization compared to 10 and 2% for silver-impregnated hydrofiber dressing and silver-impregnated foam dressing, respectively.

Surgical procedures

The incidence of surgical procedures was reported by nine studies that compared the newer silver delivery systems with SSD: four RCTs and five observational studies. Two of the RCTs compared SSD with silver-impregnated foam dressing, one with nanocrystalline silver, and one with silver-impregnated hydrofiber dressing. Four of the observational studies compared nanocrystalline silver with SSD, and one compared silver-impregnated hydrofiber dressing with SSD.

Nanocrystalline silver and silver-impregnated hydrofiber dressing resulted in a statistically significant reduction in the incidence of surgical procedures compared to SSD, and there was no statistical difference for silver-impregnated foam dressing compared to SSD (Table 3 and Figure 3d). There were no statistically significant differences in surgical procedures between nanocrystalline silver, silver-impregnated hydrofiber dressing, and silver-impregnated foam dressing, although nanocrystalline silver was found to be the most efficacious in 59% of the simulations according to the Monte Carlo simulation method compared to 24 and 17% for silver-impregnated foam dressing and silver-impregnated hydrofiber dressing, respectively.

DISCUSSION

This systematic review summarizes the best available evidence mainly relating to the effects of nanocrystalline silver, silver-impregnated hydrofiber dressing, and silver-impregnated foam dressing in the management of partial thickness burns. The number of studies with direct head-to-head evidence was limited, and therefore, we performed an adjusted indirect treatment comparison to indirectly compare the three silver delivery approaches, which to the best of our knowledge is the first of its kind. The products chosen covered what were considered commonly used approaches for infection prevention management and offered a range of silver levels available for release and replenishment of this antiseptic within the barrier dressing.

In the only RCT that compared nanocrystalline silver and silver-impregnated foam dressing, 90% of the patients treated with silver-impregnated foam dressing and 77% treated with nanocrystalline silver had superficial wounds with a mean TBSA of 1%. The conclusions of this study, that is, that silver-impregnated foam dressing was more effective in terms of accelerated wound reepithelialization time and decreased pain during dressing changes compared to nanocrystalline silver, can therefore not be generalized to both superficial and deep second degree burns, rather they are applicable to superficial burn patients. As might be expected from these low risk burns, no infections were detected in the course of the study. One RCT compared nanocrystalline silver with silver-impregnated hydrofiber dressing in partial thickness burns with a mean TBSA of 2% and concluded that there was no difference in all clinical outcomes (healing time and bacterial control), except for pain, which favored silver-impregnated hydrofiber dressing.

Overall, the available data were of sufficient quality to allow an ITC to be conducted. Only nanocrystalline silver resulted in a statistically significant reduction in the incidence of infection when compared to SSD. In addition, nanocrystalline silver was associated with a statistically significant reduction in LOS and time to healing. It is accepted that definitions of time to healing varied between some of the identified articles subjected to analysis and was reported as mean time to healing in some studies, and mean time to reepithelialization in others. Furthermore, it is recognized that LOS defined as “mean time in hospital” may depend on local habits and infrastructure. Data on infection rates and surgical procedures was less clear and in most cases the differences between dressing types was not statistically significant. However, Monte Carlo techniques reported that nanocrystalline silver remained the most clinically effective dressing after repeated sampling. Of course, there may be associations between the outcomes considered in the analysis. Because burn wound infections are associated with an increased hospital LOS, the statistically significant reduction in LOS may be a consequence of the improved rate of infections.

Nanocrystalline silver is the most potent silver delivery system, which may be particularly advantageous to help prevent the development of infection in the higher risk burns. The use of this architecturally unique silver delivery system ensures the release and replenishment of the highest levels of positively charged silver ions from a microcrystalline structure of nanoproporions. A key advantage relates to the exposure of silver being directly in contact with the burn wound surface which will facilitate faster kill of surface and invading organisms. This may also be an important contributor to reducing the potential of resistance development that is frequently associated with the use of both topical and oral antibiotics. Despite the widespread use of silver in open wounds over centuries, the global problems associated with resistance following antibiotic use has not been realized. The development of silver resistance in the laboratory has been documented sporadically, but to date the theoretical risk of resistance development in clinical practice remains
low. In the other advanced dressings included in this review, lower levels of silver are released within the dressings, which may keep the dressing microbiologically clean but have little impact on the bacteria involved in tissue invasion which ultimately will culminate in the development of infection. This is less important in superficial lower risk wounds where silver-impregnated hydrofiber dressing and silver-impregnated foam dressing appear to have benefits, as shown in the head-to-head RCTs,25,27 mainly based on the dressing attributes and not antimicrobial component of the product. There continues to be debate over the benefits of the carrier dressing in managing exudate, reducing pain and facilitating rapid closure in superficial burns compared to the need for interventional antibacterial delivery where the priority addresses the need to control or prevent infection.43,49

The ITC was conducted to a high standard using classical statistical methods outlined by Bucher et al.,17 and one of the strengths of the approach is that the estimation of the relative effect between two treatments used all the information available from the network of evidence, that is, both RCT and observational evidence. For this systematic review and ITC, a comprehensive search was performed using several electronic databases and a pearl-growing technique (i.e., searching references of relevant papers identified in the original search). Due to the absence of direct evidence between interventions that met the inclusion criteria, we were unable to conduct tests of consistency. However, our meta-analysis to a large extent satisfied the homogeneity and similarity assumptions, which are important for the validity and robustness of the results. Similarity assumption for ITC assumes that the comparators included in the meta-analysis are sufficiently similar for moderators of relative treatment effect, while the homogeneity assumption assumes that studies are sufficiently homogeneous to be quantitatively combined.21

Including both RCTs and observational studies was done to tap into the advantages that are offered by both study designs. RCTs have strength in internal validity, which is achieved through balancing confounding factors and treatment effect modifiers between treatment groups at baseline. Inclusion of observational studies increases the external validity of the analysis and also the number of studies and individuals within a meta-analysis, thus increasing power. However, we note that this advantage may be eroded by concerns regarding bias in observational studies especially when the observational studies are not well conducted. Observational studies included in our analysis were of moderate-to-good quality as assessed by the GRACE checklist.15 Although we reported the results of the combined analysis of RCT and observational data, the study data were analyzed separately to produce study-design level estimates and results of the two study designs were in agreement. This in line with other published analysis, which found that meta-analyses based on well-designed observational studies generally produce estimates of effect similar to those from meta-analyses based on RCTs, and therefore, this should be a valid approach.30,51

Limitations of the systematic review and ITC should also be highlighted. The definition of surgical intervention was not consistent across studies, with some studies referring to skin grafting while others referred to surgical debridement followed by skin grafting. The same was true of healing time, with studies analyzing time to re-epithelialization or healing time. This heterogeneity in the methods used to measure the outcomes could potentially have an impact on the reliability of the results for the comparison of the different dressings. In addition, in some of the studies the assessment of burn wound depth was either not reported or there was no formal assessment; therefore it is possible that some studies may have included a mixture of various burn depths. Furthermore, the quality of the evidence provided by some of these studies was low and relatively limited, which may potentially bias the results. The analysis, which focussed on three commonly used silver delivery approaches, was not exhaustive, and other silver products are also available. As with any ITC, additional studies verifying the results drawn solely from indirect comparisons are warranted—in this case studies comparing nanocrystalline silver to the other silver delivery approaches in deep and/or widespread burns, which are more prone to infection. Finally, while this analysis concentrated on deep partial and superficial partial thickness burns, it would also be of interest to include full thickness burns in future analyses, as this depth of burn may benefit most from efficacious antimicrobials. However, treatment of full thickness burns includes early excision to remove a number of barriers to infection followed by use of skin substitutes/dermal regeneration templates and skin grafting. With such severe injuries systemic antibiotics can be administered which was thought to be a major complication in evaluating any benefits associated with the use of nanocrystalline silver alone.

In conclusion, current evidence from the published literature suggests that where the clinical and microbiological priority is to get in control of infection quickly it would seem prudent to use the most potent silver delivery system which is nanocrystalline silver. Nanocrystalline silver is an evidence-based superior antimicrobial in reducing LOS and healing time even though definitions of such outcomes and perhaps local practices need refinement when conducting future studies. Nanocrystalline silver also resulted in reduction infection rates and in surgical procedures compared to silver-impregnated hydrofiber dressing or silver-impregnated foam dressing when Monte Carlo simulation techniques were applied. Silver-impregnated foam dressing and silver-impregnated hydrofiber dressing may have benefits in terms of accelerated wound reepithelialization time and/or pain in burns that are of lower risk for infection such as superficial burns.

ACKNOWLEDGMENTS

Dr Amanda Prowse provided editorial assistance in the preparation of the manuscript.

Source of Funding: None.

Conflicts of Interest: LN and PT are employees of Smith & Nephew. CDR provides consultancy support to Smith and Nephew. LB has no conflicts of interest.

Author contributions: Mr L. M. Nherera conducted the meta-analysis and contributed to the interpretation of results, writing, and commenting on the manuscript. Mr P. Trueman contributed to the interpretation of results, writing, and commenting on the manuscript. Dr Christopher D. Roberts (PhD) contributed to the interpretation of results, writing, and commenting on the manuscript. Dr Leena
Berg (MD, PhD, plastic surgeon) contributed to the interpretation of results, writing, and commenting on the manuscript.

REFERENCES

1. World Health Organization. Burns. Fact Sheet No. 365. Available at http://www.who.int/medicinedocuments/factsheets/fs365/en/ (accessed August 2016).

2. Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn wound infections. Clin Microbiol Rev 2006; 19: 403–34.

3. Gomez R, Murray CK, Hospenthal DR, Cancio LC, Renz EM, Holcomb JB, et al. Causes of mortality by autopsy findings of combat casualties and civilian patients admitted to a burn unit. J Am Coll Surg 2009; 208: 348–54.

4. Rosanova MT, Stamboulian D, Lede R. Risk factors for mortality in burn children. Braz J Infect Dis 2014; 18: 144–9.

5. Shahrokhi S. Infections in burns. In: Jeschke MG, Kamolz L-P, ShahVrokhi S, editors. Burn care and treatment: a practical guide. Vienna: Springer, 2013: 43–55.

6. Williams FN, Herndon DN, Hawkins HK, Lee JO, Cox RA, Kulp GA, et al. The leading causes of death after burn injury in a single pediatric burn center. Crit Care 2009; 13: R183.

7. Rodgers GL, Mortensen J, Fisher MC, Lo A, Cresswell A, Long SS. Predictors of infectious complications after burn injuries in children. Pediatr Infect Dis J 2000; 19: 990–5.

8. Yurt RW, McManus AT, Mason AD, Jr, Pruitt BA, Jr., Increased susceptibility to infection related to extent of burn injury. Arch Surg 1984; 119:183–8.

9. International Consensus. Appropriate use of silver dressings in wounds. An expert working group consensus. London: Wounds International, 2012. Available at http://www.woundinternational.com/media/issues/567/files/content_10381.pdf (accessed September 2016).

10. European Burns Association. European practice guidelines for burn care, 2015. Available at http://euroburn.org/wp-content/uploads/2015/04/EBEA-Guidelines-Version-3-2015.pdf (accessed September 2016).

11. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 349: g7647.

12. Schillaci G, Battista F, Pucci G. Are observational studies more informative than randomized controlled trials in hypertension? Con side of the argument. Hypertension 2013; 62: 470–6.

13. Cameron C, Fireman B, Hutton B, Clifford T, Coyle D, Wells G, et al. Network meta-analysis incorporating randomized controlled trials and non-randomized comparative cohort studies for assessing the safety and effectiveness of medical treatments: challenges and opportunities. Syst Rev 2015; 4: 147. doi: 10.1186/s13643-015-0133-0.

14. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.

15. Dreyer NA, Velentgas P, Westrich K, Dubois R. The GRACE checklist for rating the quality of observational studies of comparative effectiveness: a tale of hope and caution. J Manag Care Spec Pharm 2014; 20: 301–8.

16. Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, Wong DK, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. Gastroenterology 2010; 139: 1218–29.

17. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50: 683–91.

18. Kim H, Gurrin L, Ademi Z, Liew D. Overview of methods for comparing the efficacies of drugs in the absence of head-to-head clinical trial data. Br J Clin Pharmacol 2014; 77: 116–21.

19. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011; 64: 163–71.

20. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statist. Med 2002; 21: 1539–58. DOI: 10.1002/sim.1186

21. Song F, Loke YK, Walsh T, Glenny AM, Eastwood AJ, Altman DG. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: a survey of published systematic reviews. BMJ 2009; 338: b1147.

22. Gee Kee EL, Kimble RM, Cuttle L, Khan A, Stockton KA. Randomized controlled trial of three burns dressings for partial-thickness burns in children. Burns 2015; 41: 946–55.

23. Huang Y, Li X, Liao Z, Zhang G, Liu Q, Tang J, et al. A randomized comparative trial between Acticoat and SDF-Ag in the treatment of residual burn wounds, including safety analysis. Burns 2007; 33: 161–6.

24. Muangman P, Chumrarakul C, Silthram S, Suvanchote S, Benjathanang R, Kittidacha S, et al. Comparison of efficacy of 1% silver sulfadiazine and Acticoat for treatment of partial-thickness burn wounds. J Med Assoc Thai 2006; 89: 953–8.

25. Tredget EE, Shankowsky HA, Groeneveld A, Burrell R. A matched-pair, randomized study evaluating the efficacy and safety of Acticoat silver-coated dressing for the treatment of burn wounds. J Burn Care Rehabil 1998; 19: 531–7.

26. Varas RP, O’Keefe T, Namias N, Pizano LR, Quintana OD, Herrero Tellachea M, et al. A prospective, randomized trial of Acticoat versus silver sulfadiazine in the treatment of partial-thickness burns: which method is less painful? J Burn Care Rehabil 2005; 26: 344–7.

27. Verbeelen J, Hoeksema H, Heyneman A, Pirayesh A, Monstrey S, Aqaciel R. Ag dressing versus Acticoat dressing in partial thickness burns: a prospective, randomized, controlled study in 100 patients. Part 1: burn wound healing. Burns 2014; 40: 416–27.

28. Cuttle L, Naidu S, Mill J, Hoskins W, Das K, Kimble RM. A retrospective cohort study of Acticoat versus Silvazine in a paediatric population. Burns 2007; 33: 701–7.

29. Fong J, Wood F, Fowler B. A silver coated dressing reduces the incidence of early burn wound cellulitis and associated costs of inpatient treatment: comparative patient care audits. Burns 2005; 31: 562–7.

30. Gravante G, Montone A. A retrospective analysis of ambulatory burn patients: focus on wound dressings and healing times. Ann R Coll Surg Engl 2010; 92: 118–23.

31. Peters DA, Verchere C. Healing at home: comparing cohorts of children with medium-sized burns treated as outpatients with in-hospital applied Acticoat to those children treated as inpatients with silver sulfadiazine. J Burn Care Res 2006; 27: 198–01.
32. Strand O, San Miguel L, Rowan S, Sahlqvist A. Retrospective comparison of two years in a paediatric burns unit, with and without Acticoat as a standard dressing. *Ann Burns Fire Disasters* 2010; 23: 182–5.

33. Tonkin C, Wood F. Nanocrystalline silver reduces the need for antibiotic therapy in burn wounds. *Primary Intention* 2005; 13: 163–8.

34. Muangman P, Pundee C, Opasanon S, Muangman S. A prospective, randomized trial of silver containing hydrofiber dressing versus 1% silver sulfadiazine for the treatment of partial thickness burns. *Int Wound J* 2010; 7: 271–6.

35. Caruso DM, Foster KN, Blome-Eberwein SA, Twomey JA, Herndon DN, Luterman A, et al. Randomized clinical study of hydrofiber dressing with silver or silver sulfadiazine in the management of partial-thickness burns. *J Burn Care Res* 2006; 27: 298–09.

36. Yarboro DD. A comparative study of the dressings silver sulfadiazine and Aquacel Ag in the management of superficial partial-thickness burns. *Adv Skin Wound Care* 2013; 26: 259–62.

37. Dokter J, Boxma H, Oen IM, van Baar ME, van der Vlies CH. Reduction in skin grafting after the introduction of hydrofiber dressings in partial thickness burns: a comparison between a hydrofiber and silver sulphadiazine. *Burns* 2013; 39: 130–5.

38. Saba SC, Tsai R, Glat P. Clinical evaluation comparing the efficacy of Aquacel Ag hydrofiber dressing versus petrolatum gauze with antibiotic ointment in partial-thickness burns in a pediatric burn center. *J Burn Care Res* 2009; 30: 380–5.

39. Silverstein P, Heimbach D, Meites H, Latenser B, Mozingo D, Mullins F, et al. An open, parallel, randomized, comparative, multicenter study to evaluate the cost-effectiveness, performance, tolerance, and safety of a silver-containing soft silicone foam dressing (intervention) vs silver sulfadiazine cream. *J Burn Care Res* 2011; 32: 617–26.

40. Tang H, Lv G, Fu J, Niu X, Li Y, Zhang M, et al. An open, parallel, randomized, comparative, multicenter investigation evaluating the efficacy and tolerability of Mepilex Ag versus silver sulfadiazine in the treatment of deep partial-thickness burn injuries. *J Trauma Acute Care Surg* 2015; 78: 1000–7.

41. Deeks J, Higgins J, Altman D. Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions* Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011. Available from: www.handbook.cochrane.org (accessed October 2016).

42. Thomas S, McCubbin P. An in vitro analysis of the antimicrobial properties of 10 silver-containing dressings. *J Wound Care* 2003; 12: 305–8.

43. Roberts C, Ivins N, Widgerow A. ACTICOAT™ and ALLEVYN™ Ag made easy. *Wounds International* 2011; 2: S7–12.

44. Nadworny PL, Burrell RE. A review of assessment techniques for silver technology in wound care. *J Wound Technol* 2008; 2: 6–22.

45. Roberts CD, Leaper DJ, Assadian O. The role of topical antimicrobial agents within antimicrobial stewardship strategies for prevention and treatment of surgical site and chronic open wound infection. *Adv Wound Care* 2017; 6: 63–71.

46. Roberts C. Antimicrobial agents used in wound care. In: Edwards-Jones V, editor. *Essential microbiology for wound care*. Oxford: Oxford University Press, 2016: 103–21.

47. Percival SL, Bowler PG, Russell D. Bacterial resistance to silver in wound care. *J Hosp Infect* 2005; 60: 1–7.

48. Woods EJ, Cochrane CA, Percival SL. Prevalence of silver resistance genes in bacteria isolated from human and horse wounds. *Vet Microbiol* 2009; 138: 325–9.

49. Queen D, Walker M, Parsons D, Rondas A. AQUACEL® Ag dressings made easy. *Wounds Int* 2011; 2: 1–6.

50. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev* 2014; 4: MR000034.

51. Concato J, Shah N, Horowitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000; 342: 1887–92.

**Supporting Information**

Additional supporting information may be found in the online version of this article at the publisher’s web-site

**Appendix 1.** Search strategy for PubMed