



**TITLE: Silver Dressings for the Treatment of Patients with Infected Wounds: A Review of Clinical and Cost-Effectiveness**

**DATE:** 7 July 2010

**CONTEXT AND POLICY ISSUES:**

Silver is a broad-spectrum antimicrobial agent with activity against bacteria, fungus, and yeast.<sup>1</sup> In the presence of moisture and wound fluid, silver is released in its ion form ( $\text{Ag}^+$ ).<sup>1,2</sup> The ion binds to tissue proteins and causes damage to the bacterial cell membrane which in turn causes bacterial death.<sup>3,4</sup> It also prevents bacterial replication by denaturing the cell's DNA and RNA.<sup>3,4</sup> When used therapeutically, silver is available as a cream, as a solution, and as a dressing.

Silver dressings are used to promote healing and to treat chronic (for example diabetic foot ulcer, venous leg ulcer, and pressure sore) and acute (for example burn, surgical wound, and skin graft donor site) infected wounds.<sup>4,5</sup> Health Canada's Medical Devices website lists 26 active licenses for silver dressings.<sup>6</sup> The dressings are made of foam, hydrofibre, or other material.<sup>2,7</sup> Silver may be inorganic, nanoparticles, or nanocrystalline.<sup>8</sup> Nanocrystalline silver dressings release silver in the wound, whereas other dressings absorb wound fluid and microbes into the dressing.<sup>8</sup> These differences may affect the efficacy of the silver.<sup>7</sup> Hence, evidence for efficacy of one type of silver dressing cannot be extrapolated to another type of silver dressing.<sup>2</sup>

This report reviews the clinical effectiveness, the cost-effectiveness, and the indications for the use of silver dressings compared to other dressings in patients treated for acute or chronic infected wounds.

**RESEARCH QUESTIONS:**

1. What is the comparative clinical effectiveness of silver dressings versus other antimicrobial or non-antimicrobial dressings for the treatment of patients with acute or chronic infected wounds?

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2. What is the comparative cost-effectiveness of silver dressings versus other antimicrobial or non-antimicrobial dressings for the treatment of patients with acute or chronic infected wounds?
3. What are the recommended indications for silver dressings?

#### **METHODS:**

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 5, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and June 14, 2010. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic studies, and guidelines.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, systematic reviews and meta-analyses are presented first. These are followed by randomized controlled trials (RCTs) and evidence-based guidelines.

#### **SUMMARY OF FINDINGS:**

Considering only silver-releasing dressings used in the treatment of infected wounds, we found four systematic reviews (Appendix, Table 1),<sup>9-12</sup> one RCT,<sup>13</sup> and one set of guidelines.<sup>14</sup> Two of the four systematic reviews included a meta-analysis.<sup>9,10</sup> There were no relevant health technology assessments, non-randomized studies, or economic evaluations retrieved.

#### **Systematic reviews and meta-analyses**

A Cochrane review was conducted to evaluate the effects of topical silver on the healing of infected wounds.<sup>12</sup> RCTs that included patients with open wounds of any etiology were considered for inclusion. Studies had to compare silver-releasing dressings or dressings with added silver to other silver dressings, to dressings with antiseptics, to non-medicated dressings, to silver cream, or to silver solution. The primary and secondary outcomes were objective measures of healing rate and days of wound infection, respectively. Various databases and sources were searched for relevant studies. Three studies, all of four-week duration, met their inclusion criteria. One study of 129 patients with chronic venous or mixed leg ulcers (Jørgensen 2005) compared silver-releasing foam dressing to hydrocellular foam dressing. It found no statistically significant differences in the rates of complete healing and in the median ulcer area. The median relative reduction in ulcer area was statistically significantly greater in the silver dressing group than the control group. The second study (Meaume 2005) compared silver-containing alginate dressing to plain alginate dressing and included 99 patients with leg ulcers and pressure ulcers. The treated and control groups in this study differed in age (more elderly patients in the control group), in co-morbidities (more diabetic patients in the treated group), and in wound size (larger in the treated group). There were no statistically significant differences in the number of ulcers completely healed, in the absolute wound area decrease, in the relative wound area decrease, and in the healing rate measured in cm<sup>2</sup> per day at week 4. The third study (Münter 2006) compared silver-containing foam to best local practice (any type of

dressings) in 619 patients with delayed healing ulcers, burns, donor sites, and post-operative wounds. The median relative reduction in ulcer area was statistically significantly greater in the treated group than the control group. In sub-group analyses, treated patients with pressure ulcers and venous leg ulcers had similar ulcer area reduction to control groups. None of the studies reported days of wound infection as an outcome. All studies suffered from detection bias (no blinding). The authors stated that the study duration was short (four weeks), that the ways healing was measured were surrogate end-points (complete healing would be a more relevant end-point), and that multiple measurements of wound healing increase the chance of obtaining false positive results. Furthermore, all three studies were financed by a single manufacturer and they questioned the objectivity of the results. The authors concluded that there are few high-level studies supporting the use of silver-releasing dressings to treat infected wounds.<sup>12</sup>

Silver treatments for leg ulcers or wounds were evaluated in two systematic reviews, and both included a meta-analysis.<sup>9,10</sup> In 2007, Chambers et al.<sup>10</sup> obtained RCTs of patients with venous, arterial, or mixed etiology leg ulcers that examined the benefits of silver treatments compared to other treatments without silver including placebo or no dressing. The outcomes of interest included the proportion of ulcers completely healed, time to complete healing, and change in ulcer size. Various databases and sources were searched for relevant studies. Nine studies were included in the systematic review, of which six were on silver dressings. Three of the six studies (Jørgensen 2005, Meaume 2005, Münter 2006) are summarized in the Cochrane review.<sup>12</sup> A fourth study (Chaloner 2004) compared two different types of silver dressings in 40 patients with venous leg ulcers. It found no statistically significant difference in percentage median reduction in ulcer size and in the proportion of ulcers completely healed. The fifth study (Ivins 2005) re-randomized 45 patients from the Jørgensen study, but it was unclear as to why re-randomization was necessary. No statistically significant differences were found between the silver-releasing foam dressing and the hydrocellular foam dressing for mean relative reduction in ulcer area and proportion of ulcers completely healed. The last study (Wunderlich 1991) compared silver-impregnated activated charcoal dressing to conventional therapy in 40 patients with venous leg ulcers. There was no statistically significant difference in reduction of ulcer area and in the proportion of ulcers completely healed. Data from two studies (Jørgensen 2005, Wunderlich 1991) were meta-analyzed and the results showed no statistically significant difference between the treated and control group in the proportion of ulcers completely healed. The authors concluded that there is a lack of evidence to support the use of silver products for wound care.<sup>10</sup>

Carter et al.<sup>9</sup> considered RCTs of patients with leg ulcers or wounds, comparing topical silver preparations to placebo or conservative wound treatment, and reported complete wound healing, wound size reduction, wound depth reduction, healing rate, or time to heal. Various databases and sources were searched for relevant studies. Ten studies met their inclusion criteria, and seven were on silver-releasing dressings. Four studies were also included in the other summarized systematic reviews (Jørgensen 2005, Meaume 2005, Münter 2006, Wunderlich 1991). One study (Jude 2007) compared hydrofiber dressing with ionic silver to calcium alginate dressing in 134 patients with diabetic foot ulcers. All healing parameters (complete healing, healing rate, mean time to heal, and wound size reduction) were not statistically different between the silver and non-silver dressings. A study on 67 patients with open surgical or traumatic wounds (Jurczak 2007) comparing hydrofiber dressing with ionic silver to povidone-iodine gauze dressing found no statistically significant differences in complete wound healing, mean time to heal, wound size reduction, or adjusted wound size depth. The

seventh study (Lazareth 2008) enrolled 102 patients with venous ulcers to compare a polyester textile mesh with hydrocolloid and sustained silver release to the same dressing without the silver. In favor of the silver group, the percent wound size reduction was statistically significant at four weeks (28.1% versus 8.6%,  $p=0.04$ ) and at eight weeks (36.5% versus 6.2%,  $p=0.02$ ), and the absolute decrease in area was statistically significantly different at four weeks ( $p=0.02$ ) and at eight weeks ( $p=0.01$ ). The daily healing rate and the complete wound healing at eight weeks were not statistically significantly different between groups. When the data were meta-analyzed, there were no statistically significant differences in complete wound healing (seven trials) and in healing rate per day (three trials). Wound size reduction favored silver dressing when pooling the results of five trials ( $p=0.002$ ). The authors concluded that there is no evidence that silver-containing dressings are effective in promoting complete wound healing due to a lack of studies with adequate follow-up.<sup>9</sup>

The use of silver-containing dressings for infected chronic wounds was examined by Lo et al. in a systematic review that included RCTs and non-randomized studies.<sup>11</sup> The control group could be any treatment not containing silver and the outcomes included improved wound infection such as a reduction in the size of the ulcer, a change in exudate level, a reduction in odor, or a change in the composition of the wound bed tissues. Fourteen studies met the inclusion criteria. A narrative review was provided and the findings summarized with few details. The efficacy of silver dressing on wound bed improvement proved to be difficult to measure because the outcome measures were varied. Four studies reported a statistically significant reduction in infection in the treated groups. Six studies reported that silver dressing reduced wound exudate. Thirteen studies showed that silver dressings reduced the overall wound area. The authors concluded that silver dressings had an overall positive effect in the management of infected chronic wounds.<sup>11</sup>

### **Randomized controlled trial**

One prospective, open-label RCT, not included in the five systematic reviews summarized, was found.<sup>13</sup> It compared the efficacy of silver-containing alginate dressing to plain alginate dressing in 20 women (mean age, standard deviation  $68.9\pm 18.8$  years) and 22 men (mean age, standard deviation  $66.5\pm 15.7$  years) with pressure ulcers, venous or mixed etiology leg ulcers, diabetic foot ulcers, or acute wounds, with signs and symptoms of local infection. The outcome of interest was the change in the local infection score, an 18-point scale specifically developed for the purpose of the study (Appendix, Table 2). An infection with more serious signs and symptoms obtained a higher score. The study was sponsored by the manufacturer of the silver dressing. At baseline and at the end of the study period (15 days), there was no statistically significant difference in clinical infection scores between the treated group and the control group. When sub-group analyses were conducted for the different types of wounds, the results were also not statistically significant. The authors concluded that there was no difference between the two dressings in treating infected wounds.<sup>13</sup>

### **Guidelines**

One set of Canadian guidelines on the diagnosis and treatment of infected non-surgical skin ulcers was found.<sup>14</sup> The authors searched the Cochrane database, Medline, and Google for relevant articles on skin ulcer infections. They also considered international guidelines and best practice reports developed by various organizations, and obtained expert opinions. Based on

their findings, topical preparations, such as silver-based preparations or iodine-containing products, are recommended to treat skin ulcers with overt signs of infection but without cellulitis or a deep space infection (*level II evidence: other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study*).<sup>14</sup>

No guidelines were identified that recommended indications for use of silver dressings.

### **Limitations**

The systematic reviews were conducted according to accepted standards. One systematic review<sup>11</sup> gave a narrative review of the results without providing details and as such, it had a weaker conclusion.

The results of the RCT<sup>13</sup> were limited by the use of an infection scoring system that was not a validated tool. Another limitation was the fact that the study was underpowered to detect a statistical difference.

The guidelines<sup>14</sup> did not indicate which criteria were used for selecting the relevant studies, and the methods used to formulate the recommendations were not described.

### **CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:**

RCTs and non-randomized controlled trials on the use of silver dressings for infected wounds were captured in four systematic reviews. These studies, and the additional RCT, considered various outcomes in mixed populations. The current evidence showed no differences in various healing parameters when comparing silver dressings to other types of dressings. Canadian guidelines recommended the use of topical silver preparations for non-surgical infected skin ulcers but they did not describe how this recommendation was made. No information on cost-effectiveness nor on recommended indications were found.

Overall, the literature reported that silver dressings have similar efficacy to non-silver dressings in the treatment of infected wounds. Studies looking at specific wound-types, with adequate follow-up, with adequate power, and with similar outcomes may be helpful to aid in decision-making about the use of silver dressings.

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**APPENDIX; TABLE OF FINDINGS**

<b>Table 1: Details of the Systematic reviews and meta-analyses</b>				
<b>First author</b>	<b>Literature search</b>	<b>Inclusion criteria</b>	<b>Relevant outcomes</b>	<b>Results</b>
Carter, 2010 <sup>9</sup> (meta-analysis)	Cochrane Library, Scopus, Medline, grey literature, hand-searching of journals; no restriction on year of publication or language	RCTs of patients with leg ulcer or wound (includes venous ulcer, arterial ulcer, diabetic foot ulcer, pressure ulcer) comparing topical silver-based agent vs. placebo or any conservative wound care or treatment	wound-healing parameters such as complete wound healing, wound size reduction or depth reduction, healing rate, time to heal	7 studies on silver dressings compared to other non-silver dressings; n=40 to 619; no statistical difference in wound healing (7 trials) and in healing rate (3 trials); wound size reduction favors silver dressing [WMD 10.29%, (95%CI: 3.86, 16.71), p=0.002, (5 trials)]
Chambers, 2007 <sup>10</sup> (meta-analysis)	Cochrane Library, Medline, Embase, CINAHL to May 2006; hand-searching of wound journals; conference proceedings; manufacturers; no language restriction	RCTs of patients with venous, arterial, or mixed etiology leg ulcers, comparing silver dressing or topical agent vs. non silver treatment, placebo, or no dressing	proportion of ulcers completely healed during follow-up, time to complete healing, change in size of ulcer over duration of trial	6 studies on silver dressings; n=40 to 619; no statistical difference in proportion of ulcers completely healed (2 trials)
Lo, 2008 <sup>11</sup>	PubMed (1950-May 2007), CINAHL (1982-May 2007), Cochrane (1991-May 2007), Medline (1951-May 2007), British Nursing Index (1994-May 2007), EBSCO Host (May 2007), OCLC (1967-May 2007), Proquest (1950-May 2007), and PsychInfo (?-May 2007); grey lit; conference proceedings; hand-searching of journals; no language restriction	RCTs and non-RCTs of patients with infected chronic wound (includes venous ulcer, arterial ulcer, diabetic foot ulcer, pressure ulcer), comparing silver dressing vs. non silver treatment or placebo	objective indicators of improved wound infection (reduction in ulcerated area)	14 studies; n=19 to 619; efficacy of wound bed improvement not assessed because outcome measures were too varied; a statistically significant reduction in: infection (4 studies); in wound exudate (6 studies); and in the overall wound area (13 studies) all in favor of the treated groups (no values reported)

**Table 1: Details of the Systematic reviews and meta-analyses**

First author	Literature search	Inclusion criteria	Relevant outcomes	Results
Vermeulen, 2007 <sup>12</sup>	Cochrane Wounds Group Specialized Register (2006), Cochrane Library (2006), Medline (2002- Sep 06), Embase (2002-Sep 06), CINAHL (2002-Sep 06), digital dissertations (2006), manufacturers; no language restrictions	RCTs of patients with open wounds of any etiology (ischemia, diabetes, burns, trauma, chronic pressure, or after an operation, but not ostomies), comparing silver dressing vs. dressing without silver, dressing with other antiseptics, dressing with different dosages of silver, or other topical preparation of silver (cream or solution)	<i>primary</i> : objective measure of healing (time to complete healing, rate of change in wound area and volume, proportion of infected wounds healed within a trial period)  <i>secondary</i> : days of wound infection	3 studies; <i>Study 1</i> : n=99, comparing silver-containing alginate vs. non silver alginate; no statistical difference in any of the measures of wound healing. <i>Study 2</i> : n=129, comparing silver-containing foam vs. non silver foam; no statistical difference in complete rate of healing and median ulcer area; median relative reduction in ulcer area statistically better with silver dressing [WMD - 15.70 cm <sup>2</sup> , (95%CI: -29.5, -1.90), p=0.034]. <i>Study 3</i> : n=619, comparing silver-containing foam to various dressings; median relative wound area reduction superior with silver dressing (47% vs. 32%, p=0.0019)

CCT=controlled clinical trials; CI=confidence interval; MA=meta-analysis; RCT= randomized controlled trials; sd=standard deviation; WMD=weighted mean difference

**Table 2: Clinical infection scoring system according to Trial et al.<sup>13</sup>**

Sign or symptom	Score
fever	yes=1; no=0
local heat	yes=1; no=0
peri-lesional erythema	yes=1; no=0
persistent pain between dressing changes	recorded on a visual analog scale (0-10) stated as 0, 1, 2, or, 3
edema, malodour, pus, exudate production	nil=0; low=1; moderate=2; important=3
<b>TOTAL SCORE</b>	<b>0-18</b>