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Abstract

Introduction: Prosthetic joint infection (PJI) is a potentially catastrophic complication of total joint replacement. Our purpose was to determine whether the use of a silver dressing reduces the incidence of superficial and deep PJI following primary total hip replacement and total knee replacement.

Methods: A case-control study of primary total hip replacement and total knee replacement was performed to compare the incidence of superficial and deep PJI in patients who received a silver nylon dressing with patients who received a standard dressing.

Results: The incidence of infection was significantly lower in the study group compared with the control group. There were no deep PJIs in the silver dressing group. Twelve patients (2.3%) in the control group developed PJI.

Discussion: The use of a silver dressing significantly reduced the incidence of superficial and deep PJI following total joint replacement (P = 0.010). Given the financial impact of PJI, the application of silver dressings may result in considerable cost savings, and a formal cost-benefit analysis could be investigated.

Prosthetic joint infection (PJI) is a potentially catastrophic complication of total hip replacement (THR) and total knee replacement (TKR) surgeries that is associated with significant morbidity and mortality. Infection is the most common cause of failure of TKR surgery and the third most common cause of failure following THR surgery. The treatment of PJI often necessitates prolonged antimicrobial regimens and repeat surgical procedures that may include temporary or permanent removal of the implant. Despite contemporary treatment protocols, the incidence of PJI continues to rise. In the setting of multidrug-resistant organisms and immunocompromised hosts, these infections may result in loss of limb or life resulting from sepsis.

Because the number of patients having arthritis of the hip and knee continues to rise, the numbers of joint replacements are projected to increase 673% and 174% by the year 2030 for primary TKR and THR, respectively. This would amount to approximately 4 million total joint
replacements (TJRs) performed each year. Although the rate of infection reported following TJR is low (0.58%–2.4%), the increase in the volume of TJR procedures has resulted in 5,310 to 21,240 infections per year. As the magnitude of patient suffering increases, so does the economic burden associated with prolonged antibiotic treatments, repeat surgical procedures, and extended admissions to hospital and postacute care facilities, as well as lost wages because of prolonged patient disability. The financial impact of PJI in the United States was $566 million in 2009 and is projected to increase to $1.62 billion in 2020. Strategies to reduce the incidence of deep PJI are imperative.

The antimicrobial properties of silver ion have been known for centuries. Historically, topical silver was used in the 1800s in the treatment of infected traumatic battle wounds, burns, venereal diseases, and leg ulcers. The recent increase in infections resulting from resistant microorganisms has led to the development of contemporary silver–containing dressings designed to treat and prevent infections. Silver-impregnated dressings have been shown to be safe and effective in reducing the incidence of surgical site infections (SSIs) following colorectal, cardiothoracic, lumbar spine, and foot and ankle surgeries. A retrospective study has also shown silver-impregnated dressings to reduce infection risk following cesarean sections. Others have shown silver dressings to be associated with improved wound analgesia and incisional cosmesis. A retrospective review of patients who underwent TJR with the use of a silver dressing (Aquacel Ag with Hydrofiber; Convatec) demonstrated a significant reduction in the incidence of acute PJI compared with a standard nonsilver dressing.

To our knowledge, the performance and efficacy of a silver nylon dressing (Silverlon) as it pertains specifically to the incidence of PJI following primary THR and TKR surgeries have not been evaluated in a nonindustry–supported study. We sought to determine whether the use of a silver nylon dressing reduces the incidence of both superficial infection and deep PJI within 1 year following primary THR and TKR surgeries and whether this dressing can be used safely in this patient population.

### Methods

A case-control study was conducted for quality assurance purposes to evaluate the efficacy of a silver nylon dressing (Silverlon Island Dressing) in patients who presented to our institution for primary THR and TKR surgeries. The study group was followed prospectively and compared with historic controls. Permission to perform this quality assurance study was granted by the institutional review board.

Inclusion criteria included all male and female patients aged 18 years and older who were consecutively scheduled to undergo primary TKR and THR surgeries. Patients were treated by two surgeons at a single institution. Exclusion criteria included revision THR and TKR, bilateral joint replacement, and prior or active infection of the operative extremity. Patient characteristics were collected, including age at surgery, sex, tobacco use, body mass index, and immunocompromised status. Patients were considered to be immunocompromised when they had uncontrolled diabetes, presence of HIV, liver disease, active cancer with ongoing chemotherapy, and/or latent tuberculosis, or were currently using corticosteroids or methotrexate. Current steroid use, diabetes, presence of HIV, and liver disease were also evaluated as independent risk factors for infection. Patients’ surgical risk was measured using the American Society of Anesthesiologists (ASA) physical status classification (ASA 1 or 2 as low risk and ASA ≥3 as high risk).

This study consisted of two groups. The study group received a Silverlon dressing at the time of surgery and consisted of all patients who had primary THR and TKR between 2013 and 2014 after both surgeons started to use silver-impregnated dressings for all TJR cases. The Silverlon dressing was placed on the incision at the time of surgery and removed on the seventh postoperative day, as initially scheduled. The control group consisted of all patients who had primary THR and TKR performed by the same two surgeons from 2011 to 2013, prior to the time the surgeons started to use the silver-impregnated dressing. The patients in the control group received what will be referred to as a “standard” dressing consisting of a non-adherent layer (Xeroform) and dry gauze. The standard dressing was changed to a second standard dressing on postoperative day 2 and then changed daily until the wound remained dry.

All surgical incisions were treated with a primary closure using staples in the skin and a sterile dressing placed at the time of surgery. The
postoperative protocol was consistent between both surgeons and compliant with an institutional standardized protocol for all patients undergoing TJR. All patients received perioperative antibiotics, specifically cefazolin 2 g intravenous (IV) Q8H for a 24-hour period. Patients with a body weight greater than 100 kg were given cefazolin 3 g IV Q8H for a 24-hour period. Patients who had a penicillin allergy or a positive methicillin-resistant Staphylococcus aureus preoperative nasal swab screening were administered vancomycin 15 mg/kg IV Q12H for a 24-hour period. Venous thromboembolism (VTE) prophylaxis was accomplished with enoxaparin subcutaneously for 4 weeks postoperatively in all patients. Patients received a dose of tranexamic acid 10 mg/kg preoperatively unless contraindications were present. Contraindications for tranexamic acid administration at our institution are as follows: a glomerular filtration rate <60 mL/min, known colorblindness, history of deep vein thrombosis or pulmonary embolism, known thrombophilia (including, but not limited to, factor V Leiden and protein S or C deficiency), and anesthesiologist concern regarding specific coagulation issues, commonly including recent stroke, myocardial infarction, or multiple intracoronary stents. All patients received low-molecular-weight heparin for prevention of VTE. If low-molecular-weight heparin was contraindicated, VTE prophylaxis was in the form of warfarin. All patients participated in physical therapy starting on postoperative day 1 and continued a standardized regimen postoperatively. All patients had staples removed 2 weeks postoperatively.

Study patients were followed prospectively to determine the onset of superficial infection (including wound infection, stitch abscess, and cellulitis) and deep PJI. These data were extracted retrospectively for the control group based on chart review. Data were collected until the 12-month annual follow-up visit for all study and control subjects. Diagnosis for deep PJI was based on the criteria defined by the workgroup convened by the Musculoskeletal Infection Society. Patients with deep PJI were further subcategorized into acute deep PJI, defined as <3 weeks between symptom onset and treatment, and chronic PJI, defined as >3 weeks between symptom onset and treatment. The diagnosis of superficial infection was made by the treating surgeon and included superficial incisional infections (wound drainage, erythema, or dehiscence), stitch abscesses, and cellulitis (acute erythema extending beyond the limits of the surgical wound on the operative extremity). The decision to aspirate the knee to rule out the presence of deep PJI in the setting of a wound complication or cellulitis was left to the discretion of the treating surgeon and was based on the presence of joint pain with range of motion, active drainage, fever, and/or elevated serum inflammatory markers.

Statistical Analysis

The primary outcome measure of this study included the combined rate of postsurgical superficial and deep infections that occurred within 1 year following surgery. Secondary outcomes included the individual incidence of deep and superficial infections. Subgroup prespecified analysis included analysis by immunocompetence status. Continuous variables with normal distribution are presented as mean (±SD) and compared using the Student t-test. Continuous variables with non-normal distributions are presented as medians and interquartile ranges and compared using the Mann-Whitney test. Dichotomous or nominal categorical variables are compared with the use of the chi-square test with normal approximation or Fisher exact test, as appropriate.

We used a generalized estimating equation (GEE) approach for the univariate and multivariate analyses of the outcomes to account for the individual surgeon clustering. We used an interchangeable correlation matrix and logistic regression as a link function. The variables were introduced to the model based on the clinical and statistical significance (P < 0.1 in univariate analysis). The final model included the following variables: patient age at the time of surgery, ASA class (ASA 1 or 2 as low risk and ASA 3 as high risk), immunocompromised status, and the use of a silver dressing.

In a subgroup analysis among those who had any infection, superficial infection and deep infection were stratified by the immunocompetence status. A univariate logistic regression model using GEEs to account for the individual surgeon clustering was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Statistical analysis was performed using IBM SPSS Statistics software package (version 20.0; IBM). Two-tailed values of P < 0.05 were considered statistically significant.

Results

The study group consisted of 309 consecutive TJR cases performed in 309 patients (219 TKRs and 90 THRPs) from November 1, 2013, to November 30, 2014. The control group consisted of 525 consecutive TJRs performed in 525 patients (382 TKRs and 143 THRPs) who underwent surgery from November 1, 2011, to November 30, 2013. The study and control patients were compared with respect to demographics and risk factors for infection (Table 1). There were no patients who were
lost to follow-up at the final follow-up interval of 12 months in either the control group or the study group.

The incidence of any infection was significantly lower in the silver dressing group in comparison with the control group (Table 2). There were no deep PJIs in the group treated with the silver nylon dressing. There were 12 deep PJIs (2.3%) in the control group, including 11 TKRs and 1 THR. The interval from the date of surgery until the onset of infection was a median of 58 days (range, 11–147 days). Most deep infections were acute infections that presented within 3 weeks of the onset of symptoms4 (Figure 1). All cases of deep PJI were treated surgically and received parenteral antibiotic treatment; eight required irrigation and débridement with liner exchange and four required two-stage revision. The organisms isolated included the following: methicillin-susceptible \textit{S. aureus}, \textit{Corynebacterium}, \textit{Streptococcus viridans}, \textit{Mycobacterium tuberculosis}, \textit{Aggregatibacter}, \textit{Pseudomonas aeruginosa}, \textit{Peptostreptococcus}, and mixed flora (\textit{Proteus mirabilis} and \textit{Enterobacter cloacae}). No organisms were identified in four cases.

There were a total of 46 superficial infections, including 12 in the study group (3.9%: 10 TKRs and 2 THRs) and 32 in the control group (6.1%: 28 TKRs and 4 THRs). The types of superficial infection are displayed in Figure 2. In all cases of superficial infection, the clinical signs of infection resolved following a course of oral antibiotic treatment. At final follow-up, none of the superficial infections recurred or progressed to deep PJI.

The ORs for the tested variables are summarized in Table 3. The odds of any infection were significantly less in the silver dressing group compared with the control group (OR, 0.382; 95% CI, 0.250–0.583; \(P = 0.0001\)), as were the odds of superficial infection (OR, 0.546; 95% CI, 0.343–0.870; \(P = 0.011\)). The odds of any infection, as well as superficial infection, were lower in the silver dressing group in both immunocompetent and immunocompromised patients.

The results of a GEE logistic regression analysis are displayed in Table 4. The odds of any infection were significantly less with the use of a silver dressing, independent of immunocompromised status high ASA score, and age at surgery (OR, 0.396; 95% CI, 0.273–0.573; \(P < 0.001\)).

### Table 1

<table>
<thead>
<tr>
<th>Baseline Characteristics of the Patients</th>
<th>No Silver: 62.9% (n = 525)</th>
<th>With Silver: 37.1% (n = 309)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery, yrs, mean ± SD</td>
<td>63.40 ± 10.98</td>
<td>62.53 ± 11.57</td>
<td>0.280</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, % (n)</td>
<td>62.9 (330)</td>
<td>68 (210)</td>
<td></td>
</tr>
<tr>
<td>Male, % (n)</td>
<td>37.1 (195)</td>
<td>32 (99)</td>
<td>0.136</td>
</tr>
<tr>
<td>ASA high score (3–5), % (n)</td>
<td>51 (268)</td>
<td>46.3 (143)</td>
<td>0.183</td>
</tr>
<tr>
<td>Tobacco use, % (n)</td>
<td>13.9 (73)</td>
<td>21.7 (67)</td>
<td>0.004</td>
</tr>
<tr>
<td>Body mass index, median (interquartile range)</td>
<td>31 (27–36)</td>
<td>31 (27–36.5)</td>
<td>0.814</td>
</tr>
<tr>
<td>Immuno compromised, % (n)</td>
<td>41.9 (220)</td>
<td>31.7 (98)</td>
<td>0.003</td>
</tr>
<tr>
<td>Steroids, % (n)</td>
<td>3.4 (18)</td>
<td>2.6 (8)</td>
<td>0.500</td>
</tr>
<tr>
<td>Diabetes, % (n)</td>
<td>27 (142)</td>
<td>20.4 (63)</td>
<td>0.031</td>
</tr>
<tr>
<td>HIV, % (n)</td>
<td>2.7 (14)</td>
<td>1 (3)</td>
<td>0.094</td>
</tr>
<tr>
<td>Liver disease, % (n)</td>
<td>7.2 (38)</td>
<td>6.5 (20)</td>
<td>0.675</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>No Silver: 62.9% (n = 525)</th>
<th>With Silver: 37.1% (n = 309)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection, % (n)</td>
<td>8.4 (44)</td>
<td>3.9 (12)</td>
<td>0.012</td>
</tr>
<tr>
<td>Infection type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep infection, % (n)</td>
<td>2.3 (12)</td>
<td>0 (0)</td>
<td>0.010</td>
</tr>
<tr>
<td>Superficial infection, % (n)</td>
<td>6.1 (32)</td>
<td>3.9 (12)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td>0.032</td>
</tr>
<tr>
<td>Medical alone, % (n)</td>
<td>5.9 (31)</td>
<td>3.2 (10)</td>
<td></td>
</tr>
<tr>
<td>Surgery, % (n)</td>
<td>2.5 (13)</td>
<td>0.6 (2)</td>
<td></td>
</tr>
<tr>
<td>Expired patients, % (n)</td>
<td>2.5 (13)</td>
<td>1 (3)</td>
<td>0.126</td>
</tr>
</tbody>
</table>

The incidence of any infection was significantly lower in the silver dressing group in comparison with the control group (Table 2). There were no deep PJIs in the group treated with the silver nylon dressing. There were 12 deep PJIs (2.3%) in the control group, including 11 TKRs and 1 THR. The interval from the date of surgery until the onset of infection was a median of 58 days (range, 11–147 days). Most deep infections were acute infections that presented within 3 weeks of the onset of symptoms4 (Figure 1). All cases of deep PJI were treated surgically and received parenteral antibiotic treatment; eight required irrigation and débridement with liner exchange and four required two-stage revision. The organisms isolated included the following: methicillin-susceptible \textit{S. aureus}, \textit{Corynebacterium}, \textit{Streptococcus viridans}, \textit{Mycobacterium tuberculosis}, \textit{Aggregatibacter}, \textit{Pseudomonas aeruginosa}, \textit{Peptostreptococcus}, and mixed flora (\textit{Proteus mirabilis} and \textit{Enterobacter cloacae}). No organisms were identified in four cases.

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The ORs for the tested variables are summarized in Table 3. The odds of any infection were significantly less in the silver dressing group compared with the control group (OR, 0.382; 95% CI, 0.250–0.583; \(P < 0.0001\)), as were the odds of superficial infection (OR, 0.546; 95% CI, 0.343–0.870; \(P = 0.011\)). The odds of any infection, as well as superficial infection, were lower in the silver dressing group in both immunocompetent and immunocompromised patients.

The results of a GEE logistic regression analysis are displayed in Table 4. The odds of any infection were significantly less with the use of a silver dressing, independent of immunocompromised status high ASA score, and age at surgery (OR, 0.396; 95% CI, 0.273–0.573; \(P < 0.001\)).
Discussion

Infection following THR and TKR surgeries is a devastating complication with tremendous implications pertaining to patient morbidity and mortality. This is further compounded by the astronomical health care costs associated with the treatment of PJI. As the number of joint replacements performed in the United States continues to rise, so do the numbers of patients affected by infection. The downstream effects of these infections on patients’ lives include poor functional outcome and disability, patient dissatisfaction, lost wages because of work absence, and general depreciation in health-related quality of life. To circumvent the adverse effects of PJI, prevention is paramount.

Silver nylon dressings have been found to reduce SSI in a number of surgical procedures, including cardiothoracic surgery, colorectal surgery, cesarean sections, spinal surgery, and recently in the field of arthroplasty. These prior reports have shown that silver ion dressings are safe to be used in the surgical setting and are furthermore effective in reducing SSI. In a prior retrospective study, the use of a dressing that combines silver with a hydrofiber layer that gels on contact with the wound (Acquacel Hydrofiber) was found to reduce the incidence of acute PJI following hip and knee arthroplasty. We sought to determine whether a silver nylon dressing can reduce SSI following THR and TKR. The Silverlon dressing differs from the Acquacel dressing in silver content (546 mg/100 cm² versus 8.3 mg/100/cm², respectively) and absence of the hydrofiber gel layer. The silver ion is in direct contact with the skin in the Silverlon dressing, unlike other contemporary silver-containing dressings, and thus we sought to determine whether this dressing with more than 5-fold increased silver content, and direct silver contact with the skin, could be used safely in this population. Furthermore, at our institution, the Silverlon dressing was less expensive than Acquacel ($30 per dressing versus $39 of the similar size).

Our study found that the use of a silver nylon dressing significantly reduced the incidence of both superficial infection and deep PJI following THR and TKR in all subjects. The odds of any infection were all significantly lower in the silver nylon dressing group. The strengths of this study include its prospective nature, use of a control group, and follow-up duration of 1 year. We did not identify any adverse reaction to the silver dressing in our population. This article is the first to our knowledge to evaluate the effect of a silver nylon dressing on SSI following TJR surgery of the hip and knee in a nonindustry-supported study. Furthermore, this is the first study to specifically investigate the use of the Silverlon dressing in this patient population.

Superficial wound infections have been demonstrated to be a risk factor for deep prosthetic infection. It stands to reason that topical agents...
aimed at reducing superficial infections may in turn prove to successfully decrease the incidence of PJI. In this study, the use of a silver nylon dressing was associated with significantly lower odds of developing a superficial wound infection compared with a traditional dressing.

The use of silver-impregnated dressings has been shown to improve the length of the primary dressing wear time, decrease the number of dressing changes, decrease the length of hospital stay, and avoid skin blistering.22 Although the beneficial effects of silver dressing use are multifactorial, minimizing the risk of superficial wound complications is likely a major step toward lessening the risk of subsequent PJI.

As expected, immunocompromised patients displayed higher odds of developing any infection following THR and TKR compared with immunocompetent individuals. However, there were no deep infections in any study patients, including immunocompromised patients. Although the control group contained significantly greater immunocompromised patients (Table 1), a multivariate logistic regression analysis determined that the use of a silver nylon dressing was independently associated with significantly lower odds of developing postoperative infection following TJR, regardless of the immunocompetence or ASA score (Table 4).

The organisms isolated in the cases of deep PJI were nearly all atypical pathogens. Gram-positive cocci are the most common pathogens typically involved in hip and knee PJI. S aureus and coagulase-negative Staphylococcus account for 50% to 60% of PJIs, whereas streptococci and enterococci contribute to approximately 10% of cases.23 In our series, only one case of deep PJI had cultures that grew methicillin-sensitive S aureus. Furthermore, most of the patients with deep infections were immunocompromised subjects. We attribute the atypical organisms isolated in the cases of deep PJI to the greater number of immunocompromised and complex patients cared for at our tertiary care center. Four of 12 patients with deep PJI had cultures that yielded no growth. This is consistent with previous reports in the literature, in which 5% to 34% of PJIs were found to be culture negative.24,25

The cost per unit of silver dressing exceeds that of a standard dressing ($30 for Silverlon versus approximately $2 for a standard gauze dressing). The cost of medical and

### Table 3

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Type of Infection</th>
<th>No Silver, 62.9% (n = 525)</th>
<th>With Silver, 37.1% (n = 309)</th>
<th>P</th>
<th>Odds Ratio for Infection (With Silver) and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>Any infection</td>
<td>8.4 (44)</td>
<td>3.9 (12)</td>
<td>&lt;0.0001</td>
<td>0.382 (0.250–0.583)</td>
</tr>
<tr>
<td>Immunocompetent: N = 59.1% (305) and N = 40.9% (211) without and with silver</td>
<td>Any infection</td>
<td>7.5 (23)</td>
<td>3.3 (7)</td>
<td>0.016</td>
<td>0.327 (0.131–0.811)</td>
</tr>
<tr>
<td>Deep infections</td>
<td>1.3 (4)</td>
<td>0 (0)</td>
<td>0.149</td>
<td>—</td>
<td>0.413 (0.152–1.123)</td>
</tr>
<tr>
<td>Superficial infections</td>
<td>6.2 (19)</td>
<td>3.3 (7)</td>
<td>0.083</td>
<td>—</td>
<td>0.543 (0.492–0.600)</td>
</tr>
<tr>
<td>Immunocompromised: N = 69.2% (220) and N = 30.8% (98) without and with silver</td>
<td>Deep infections</td>
<td>3.6 (8)</td>
<td>0 (0)</td>
<td>0.113</td>
<td>—</td>
</tr>
<tr>
<td>Superficial infections</td>
<td>5.9 (13)</td>
<td>5.1 (5)</td>
<td>0.301</td>
<td>0.935 (0.824–1.061)</td>
<td></td>
</tr>
</tbody>
</table>

The values in parentheses are the number of subjects in that category. CI = confidence interval.

### Table 4

<table>
<thead>
<tr>
<th>Population Characteristics</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery, yrs</td>
<td>0.989</td>
<td>0.975–1.002</td>
<td>0.102</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>1.304</td>
<td>1.092–1.556</td>
<td>0.003</td>
</tr>
<tr>
<td>ASA high score (3–5)</td>
<td>1.390</td>
<td>0.944–2.047</td>
<td>0.095</td>
</tr>
<tr>
<td>Silver dressing</td>
<td>0.396</td>
<td>0.273–0.573</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval.
surgical treatment for 1 patient with PJI is estimated between $30,000 and $70,000.26,27 Thus, the use of silver-impregnated dressings at the time of primary THR and TKR may result in considerable cost savings. A cost-benefit analysis is beyond the scope of the current study and could be the subject of future investigation.

Our study is limited because of the short follow-up duration; however, our follow-up interval is sufficient to detect early PJI, which was the primary intent of the study. A longer follow-up duration would be needed to determine the effect of silver dressings on late PJI. Another limitation is the lack of randomization of patients to specific treatment arms. The study groups were generated based on the initiation of silver dressing use in our institution. Although the burden of illness associated with PJI is substantial and the overall national prevalence of PJI continues to rise, the overall infection rates of PJI remain low and are typically in the range of 0.5% to 2%. Thus, our sample size in a single institution may not have been sufficiently large to detect significant differences with certain subgroups, such as the ASA score. This study was conducted as a quality assurance assessment in our specific patient population, and thus results may not be generalizable to the population as a whole.

In conclusion, we demonstrated a significant decrease in superficial and deep PJIs associated with the use of the Silverlon silver nylon dressing in primary total hip and knee arthroplasty. To our knowledge, this is the first non–industry-supported report on the use of silver-impregnated dressings in joint replacement surgery and the first to specifically investigate the use of the Silverlon dressing. We hope that this study will serve as a pilot to facilitate a power calculation for a subsequent multicentered randomized controlled trial to further evaluate the efficacy of silver dressings in total hip and knee arthroplasty.

Acknowledgments

The authors acknowledge Dr. Robert G. Davis for the involvement of his patients in the study.

References

Exhibit 2 - Tampa Gen IVCD Study
Review of a Large Clinical Series
Reduction in Central Line–Associated Bloodstream Infections Correlated With the Introduction of a Novel Silver-Plated Dressing for Central Venous Catheters and Maintained for 6 Years

Rachel Karlnoski, PhD1, Elia Charbel Abboud, MD1, Peggy Thompson, BSN, CIC, FAPIC2, Asa Z. Oxner, MD3, John T. Sinnott, MD, FACP4, and Jorge E. Marcet, MD, FACS, FASCRS1

Abstract
Objective: To assess a novel silver-plated dressing (SD) for central venous catheters in comparison to chlorhexidine gluconate–impregnated sponge (CHGIS) dressings in preventing central line–associated bloodstream infections (CLABSIs) in adult intensive care unit (ICU) patients. Design: Retrospective cohort study. Setting: Tampa General Hospital, an academic medical tertiary care center. Patients: All adult ICU patients of an academic medical tertiary care center from January 2009 to December 2010. Measurements and Main Results: A total of 3189 patient records were studied from 7 different ICUs during the 2-year period. Patients received either CHGIS dressings (January 2009-December 2009) or SDs (January 2010-December 2010). Primary outcomes measured were CLABSI rates per 1000 catheter days and ICU length of stay. There were 30 696 catheter days with CHGIS dressings and 31 319 catheter days with SDs. There was a statistically significant decrease in the rate of CLABSI per 1000 catheter days in the SD group, from 2.38 to 1.28 (P = .001), with an absolute risk reduction of 1.1. There was a significantly lower incidence in the rate of CLABSI per 1000 catheter days in the SD group (incidence rate ratio [IRR] = 0.54, 95% confidence interval [CI]: 0.36-0.80). The relative risk of CLABSI in the SD group was 0.502 (95% CI: 0.340-0.730; P < .001). If SDs are used on all catheters, the decreased rate of CLABSIs observed would calculate to a cost savings of US$4070 to US$39 600 per 1000 catheter days. After successful implementation of the SD, we observed significant reductions in CLABSI rates and a sustained reduction in the subsequent 6 years. Conclusion: Use of SDs is associated with a significant decrease in CLABSI rates in adult ICU patients compared to CHGIS dressings, with an estimated cost savings of US$4070 to US$39 600 per 1000 catheter days.

Keywords
silver-plated dressing, central venous catheter, central line–associated bloodstream infection, intensive care unit, reduced infection rate, chlorhexidine gluconate–impregnated sponge dressing

Introduction
Patients admitted to intensive care units (ICUs) often require the placement of central venous catheters (CVCs). In 2013, 48% of ICU patients had CVCs, accounting for approximately 9.2 million CVC days, and an estimated 30 100 central line–associated bloodstream infections (CLABSIs).1-4 Patient mortality rates associated with CLABSIs range from 12% to 25%,4 and the cost of CLABSIs per episode of care ranges from US$3700 to US$36 000.5 The average infection rate for adult ICUs reported in 2013 by the National Healthcare Safety Network (NHSN) ranged from 0.8 to 2.9 per 1000 catheter days.1 Central line–associated bloodstream infection prevention is clearly of prime importance.

Several strategies have been studied and developed in an attempt to prevent CLABSIs, varying from the more expensive...
technologic innovations, such as coated catheters, to lower-cost interventions, including aseptic insertion technique and reduced catheter time. The Centers for Disease Control and Prevention (CDC) reported a 50% reduction in ICU CLABSI rates in the United States from 2008 to 2014. Currently, it is thought that most CLABSI are preventable.

Use of chlorhexidine gluconate–impregnated sponge (CHGIS) dressings has been associated with reduced rates of CLABSI. A multicenter randomized controlled trial found that CHGIS dressings significantly decreased the rates of catheter colonization and CLABSI. Another trial found that use of these dressings in hematological–oncological patients reduced the rate of CLABSI by 46%. Silver has a broad spectrum of antimicrobial activity. The extensive coverage that silver provides against bacteria, fungi, and viruses, including the notorious nosocomial pathogens methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci, makes it a valuable adjunct in the prevention and treatment of infection. Silver has both bactericidal effects via oxidation of the cell membrane and bacteriostatic effects by inhibiting bacterial replication through damage to DNA. Fortunately, toxicity of silver to human cells is considerably less than to bacteria. Unlike antibiotics, resistance to silver is very rare; instead of targeting a specific cellular process, silver ions directly interact with proteins and other organic molecules and disrupt electrolyte balances. Silver’s affinity to multiple microbial molecules and structures further decreases the risks of resistance. A variety of silver dressings are commercially available today. Silver impregnated dressings have been shown to be effective in preventing surgical site infections even in the contaminated context of colorectal surgery, where infection rates reach 30%. There are few studies evaluating non-CHGIS dressings for CVCs. The objective of this observational study was to describe the outcomes of Silverlon Lifesaver Ag (Cura Surgical, LLC; Geneva, IL) a novel silver-plated dressing (SD), in comparison to CHGIS dressings in preventing CLABSI in adult ICU patients.

Materials and Methods

This study was approved by the institutional review board of University of South Florida (IRB#Pro00015734) and was carried out in an academic medical tertiary care center (Tampa General Hospital, Tampa, FL). Our hospital’s Department of Infection Prevention (DIP) collects prospective data on CLABSI in ICUs for ongoing quality improvement. In each ICU, a staff member is designated to take daily record of each patient’s number of central line days. These data are forwarded to the DIP office for entry into a spreadsheet to facilitate calculation of CLABSI rates per central line days, which allows for comparison of rates with ICU-specific NHSN data. For this study, the DIP database was queried to reveal data of 3189 patients with central line days who had an ICU stay between January 2009 and December 2010 from 7 different ICUs: medical, coronary care, neurological, burn, surgical trauma, cardiothoracic, and vascular. The center’s billing records were queried to identify the medical record numbers of those 3189 patients. Medical records were retrospectively reviewed to capture demographic information. Between January and December 2009, all patients received a CHGIS dressing on their CVC as per hospital policy. From January to December 2010, all patients received the novel SD on their CVC as per hospital policy. After the study ended in December 2010, our hospital policy continued to enforce the use of the novel SD on all CVCs.

Catheter site dressing regimens were the same in all patients within each group. Other than implementation of the SD, the center’s ICU CVC protocols remained the same in 2010 compared to 2009 and continue to remain the same. Per hospital policy, the antiseptic used to prepare the skin prior to CVC insertion was 2% chlorhexidine in 70% isopropyl alcohol. In patients who could not tolerate chlorhexidine, a 1% tincture of iodine was used. Following manufacturer’s instructions, CHGIS dressings were applied at the insertion site with the blue side up, and SDs were moistened with sterile water or saline and applied silver side down. All CVC dressings were covered with a transparent adhesive film. If there was bleeding from the puncture site, gauze was placed over the antimicrobial dressing. The gauze was removed at 24 hours, and a new antimicrobial patch (CHGIS or SD) was placed and covered with a transparent adhesive film. The transparent films and antimicrobial patches were changed if they became compromised or when inspection of the site was necessary. Dressings were otherwise replaced every 7 days. In order to maintain consistency with insertion practices, all necessary materials were combined in a bundled kit and placed on a designated cart for line insertion. In order to measure compliance, completion of an insertion checklist was required by all clinicians and monitored regularly by the DIP. These quality improvement measures were in place prior to the study period.

Central line–associated bloodstream infection rates are compared with the CDC’s NHSN data in analogous ICUs for benchmarking. The DIP is supported by an electronic surveillance system that allows review of all laboratory data on ICU patients. These results are reviewed daily and specific criteria are used to define device-associated infections. A CLABSI in the study period was defined as meeting at least 1 of the following 2 CDC/NHSN-defined criteria:

1. Patient has a recognized pathogen (eg, Staphylococcus aureus, Enterococcus subspecies, Escherichia coli, Pseudomonas subspecies, Klebsiella subspecies, Candida subspecies, and others), but not a common skin contaminant, cultured from 1 or more blood cultures, and the organism cultured from the patient’s blood is not related to an infection at another site.
2. Patient has at least 1 of fever (>38°C), chills, or hypotension; a common skin contaminant (diphtheroids Corynebacterium subspecies), Bacillus subspecies (not Bacillus anthracis), Propionibacterium subspecies, coagulase-negative staphylococci (including Staphylococcus
epidermidis], viridans group streptococci, *Aerococcus* subspecies, and *Micrococcus* subspecies) is cultured from 2 or more blood cultures drawn on separate occasions within 2 days of each other; and signs and symptoms and positive laboratory results are not related to an infection at another site.

Bloodstream infections that developed within 48 hours of discharge from the ICU were considered CLABSIs. There was no minimum time period that the CVC had to be in place in order for the bloodstream infection to be considered central line associated.

The primary outcomes measured were CLABSI rates per 1000 catheter days and length of stay in the ICU. Statistical analysis was performed using the χ² test for categorical data and Student t test for continuous data. A P value of less than .05 was considered significant.

Published estimates of attributable cost per CLABSI for studies performed in the United States (US$3700-US$36 000) were used to calculate cost savings. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting our results.

## Results

There were 1524 adult ICU patients between January and December 2009 (the CHGIS dressing period), with a total of 30 696 catheter days. Between January and December 2010 (the SD time frame), there were 1665 adult patients in the center’s ICUs, totaling 31 319 catheter days. Age and gender demographics were similar between the 2 groups (Table 1). The length of stay in the ICU was not significantly different (CHGIS: 13.1 days vs SD: 12.6 days; P = .85). However, the distribution of patients across ICUs was not homogenous (P < .001).

There were 73 infections in the CHGIS group during a total of 30 696 catheter days, and 40 infections in the SD group during 31 319 catheter days. These results correspond to a statistically significant decrease in CLABSI in the SD group: 2.38 infections per 1000 catheter days versus 1.28 infections per 1000 catheter days (P = .001), with an absolute risk reduction of 1.1 per 1000 catheter days. There was a significantly lower incidence in the rate of CLABSI per 1000 catheter days in the SD group, with an IRR of 0.54 (95% confidence interval [CI]: 0.36-0.80). The relative risk of CLABSI in the SD group was 0.502 (95% CI: 0.340-0.730; P < .001). We have sustained low rates of CLABSI in our ICU in the subsequent period of time since the study period ended, which is tracked as part of our ICU quality improvement process (Figure 1).

Using the estimates of attributable cost per CLABSI (US$3700 to US$36 000), the absolute risk reduction of 1.1 per 1000 catheter days observed for the rate of CLABSI in the SD group translates to an estimated cost savings of US$4070 to US$39 600 per 1000 catheter days. For our center, there were 33 fewer CLABSIs in the 12-month period when SDs were implemented (despite an increase in the total number of catheter days), and this translates to a cost savings estimate of US$122 100 to US$1 188 000 over the 1-year study period.

## Discussion

The antimicrobial and wound healing properties of silver have been exploited for centuries. Drinking from silver vessels was practiced as early as 4000 BC, and the Roman civilization documented silver nitrate as a therapeutic agent in their medical books. Silver is used in various forms in medicine today. Examples of commonly used silver products include silver salts, such as silver sulfadiazine topical creams, and silver sustained release products, such as the SD used in this study.

Hospital-acquired infections are a significant cause of patient morbidity and mortality, prolonged hospital stay, and increased costs. A number of clinical trials have shown silver-impregnated dressings to reduce these iatrogenic infection rates and improve wound healing. For this reason, silver dressings are commonly used in the treatment of a wide variety of wounds today, including burns, traumatic lacerations, ulcers, and surgical sites. The study presented here is the first to demonstrate the use of silver nylon dressings for the purpose of reducing CLABSIs. In this cohort study, SDs were found to significantly decrease CLABSIs in adult ICU patients compared to patients using CHGIS dressings. This reduction in CLABSI rates was found to be associated with significant cost savings.

The results of this study in reduction of CLABSIs and expected cost savings are very encouraging. This study does have limitations, however, which must be taken into consideration. For example, we did not collect data on significant risk factors for CLABSI, such as preexisting bloodstream infections, fever within 24 hours of catheter placement, concurrent indwelling catheters, immunodeficiency, and dialysis. We also did not account for patients with preexisting CVCs prior to ICU
transfer or the location of the line placement. This leads to the inability to match the groups. Also, it was assumed that the overall population of the hospital did not change significantly during the study time period and thus the comorbidities and indications for CVCs were comparable in the 2 groups across time. Cost data were not collected individually for the patients in this study, and the calculated cost savings are estimates, using values obtained from published reports in the medical literature.5 Because this study was a before-and-after design, it is limited by confounding factors related to changes in environmental variables, such as changes in clinical management or quality improvement. There is a possibility that increased awareness of the problem of CLABSI could have theoretically led to improved medical practice (Hawthorne effect). However, a bundle approach and clinical protocol have been implemented prior to the initial year of the study, with the type of CVC dressing being the only difference between the groups. A well-designed prospective randomized controlled trial will ensure homogenous stratification of patients across the different ICUs and will control for confounding variables between the groups. A prospective, controlled trial will also allow for the collection of more accurate data for cost.

Much success has been achieved over the past decade in reducing the rate of CLABSIs in ICUs.4 However, it should be noted that CVCs are also used in a range of other health-care settings and increasingly in the outpatient setting and long-term care facilities.7 As well, peripherally inserted central catheter (PICC) lines are frequently used for long-term intravenous access and are often replacing inpatient CVCs.32 This leads to additional questions which deserve to be studied: Will SDs be as effective in reducing infection and related cost in PICC lines and in pediatric populations?

Despite the reduction in central line infections owing to the improvement with insertion and maintenance techniques in recent years, CLABSIs still occur today.33 Continued success in prevention of these infections requires strict adherence to current prevention recommendations and the development and implementation of novel prevention strategies in daily practice.4 We believe that the positive results we have obtained in this study for SDs reducing CLABSIs deserve serious consideration for the routine use of the SD in CVC care protocols in adult ICUs.

Conclusion
This study demonstrates that the use of SD for CVCs is associated with a significant decrease in CLABSIs in adult ICU patients compared to patients receiving the CHGIS dressing. The observed reduction in CLABSIs calculates to an estimated cost savings of US$122 100 to US$1 188 000 per 1000 catheter days. This leads to an estimated cost saving of over a million dollars for our hospital center during the 1-year study period.

Authors’ Note
Preliminary data for this study were presented as a poster at the 49th Annual Meeting of the Infectious Diseases Society of America (IDSA)—Boston, Massachusetts—October 20-23, 2011. The work was performed at Tampa General Hospital, University of South Florida.

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data provision and ongoing efforts to prevent infection and improve patient safety.

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References
26. Alimov V, Lovecchio F, Sinha M, Foster KN, Drachman D. Use of a silver-containing hydrofiber dressing for filling abscess cavities following incision and drainage in the emergency department:
Exhibit 2 - Tampa General Study Cont.


Exhibit 3 - Duke SSI Cost Study
Clinical and Financial Outcomes Due to Methicillin Resistant *Staphylococcus aureus* Surgical Site Infection: A Multi-Center Matched Outcomes Study

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Abstract

**Background:** The clinical and financial outcomes of SSIIs directly attributable to MRSA and methicillin-resistance are largely uncharacterized. Previously published data have provided conflicting conclusions.

**Methodology:** We conducted a multi-center matched outcomes study of 659 surgical patients. Patients with SSI due to MRSA were compared with two groups: matched uninfected control patients and patients with SSI due to MSSA. Four outcomes were analyzed for the 90-day period following diagnosis of the SSI: mortality, readmission, duration of hospitalization, and hospital charges. Attributable outcomes were determined by logistic and linear regression.

**Principal Findings:** In total, 150 patients with SSI due to MRSA were compared to 231 uninfected controls and 128 patients with SSI due to MSSA. SSI due to MRSA was independently predictive of readmission within 90 days (OR = 35.0, 95% CI 17.3–70.7), death within 90 days (OR = 7.27, 95% CI 2.83–18.7), and led to 23 days (95% CI 19.7-26.3) of additional hospitalization and $61,681 (95% CI 23,352-100,011) of additional charges compared with uninfected controls. Methicillin-resistance was not independently associated with increased mortality (OR = 1.72, 95% CI 0.70–4.20) nor likelihood of readmission (OR = 0.43, 95% CI 0.21–0.89) but was associated with 5.5 days (95% CI 1.97–9.11) of additional hospitalization and $24,113 (95% CI 4,521–43,704) of additional charges.

**Conclusions/Significance:** The attributable impact of *S. aureus* and methicillin-resistance on outcomes of surgical patients is substantial. Preventing a single case of SSI due to MRSA can save hospitals as much as $60,000.

Introduction

Surgical site infections (SSIs) are well known to lead to adverse clinical and financial outcomes for patients. The average SSI leads to approximately one week of additional hospitalization and increases the risk of death 2- to 11-fold compared to uninfected surgical patients [1,2,3]. In addition, SSIs lead to significant hospital costs. Each SSI costs approximately $12,000–$35,000 (2007 USD), depending on the type of procedure. In total, SSIs cost the US healthcare system approximately $10 billion annually [4].

Methicillin resistant *Staphylococcus aureus* (MRSA) has become the leading cause of SSI in community hospitals [5] and leads to 15% of SSIs reported to the NHSN [6]. To date, only a few studies have specifically examined outcomes related to SSI due to MRSA [7,8,9]. These studies have been limited to single institutions, small numbers, and/or a single surgical procedure. The authors of these studies reached conflicting conclusions regarding the impact of methicillin resistance on outcomes among patients with *S. aureus* SSI. Furthermore, only one of these studies [7] evaluated financial outcomes directly attributable to SSI due to MRSA. Thus, financial outcomes due to MRSA SSI are not well described.

An accurate assessment of the financial and human costs of SSI due to MRSA is a necessary first step in justifying and allocating resources for the prevention of MRSA SSI. Indeed, it is important to first develop metrics to assess costs and outcomes before designing studies that assess the benefits and impact of prevention programs. Thus, we conducted a large, multi-center study of
multiple surgical procedure types to determine clinical and financial outcomes of SSIs directly attributable to MRSA and methicillin-resistance.

**Methods**

**Ethics Statement.**
All work included in this project was approved by the Institutional Review Boards for all participating hospitals. A waiver of consent was granted given the retrospective nature of the project.

**Study Hospitals.**
This multi-center matched-outcomes study was conducted at one tertiary care center (750 beds) and six community hospitals (range of hospital sizes = 102 to 305 beds; mean 208 beds). Each of the community hospitals were members of the Duke Infection Control Hospital Network (DICON). The structure and function of DICON have been previously described [10,11].

SSIs were prospectively identified by trained infection preventionists using CDC definitions and National Healthcare Surveillance Network (NHSN) criteria [12,13]. Surveillance was identical at all study hospitals and included all operative procedures with only one exception. Surveillance was limited to cardiothoracic, neurosurgical, and orthopedic procedures at DUMC.

**Study Population.**
The study population for this analysis has been described in detail elsewhere [14]. Briefly, three sets of patients were identified from preexisting prospectively collected databases during the time period from January 1, 1998, through April 1, 2003 (the “study period”): patients with SSI due to MRSA, patients with SSI due to MSSA, and uninfected surgical patients. We compared patients with SSI due to MRSA to two sets of controls: uninfected matched controls and patients with SSI due to MSSA. Uninfected surgical patients were frequency matched to patients with SSI due to MRSA by type of operative procedure, hospital, and year of procedure. All patients with SSI due to either MRSA or MSSA at the study hospitals during the study period were included. Thus, no matching was performed between patients with SSI due to MRSA and patients with SSI due to MSSA.

**Study Variables.**

**Independent variables.** Data were abstracted from two sources: prospectively collected surgical surveillance databases and patient records. The following data were prospectively collected and maintained in surgical surveillance databases: patient age, type of procedure, date of surgery, length of procedure, type of procedure, wound classification, American Society of Anesthesiologists (ASA) score, NNIS risk index score, and, if SSI was present, pathogen, anatomic site of infection, and date of culture [15]. Study nurses retrospectively collected gender, race, admission source, insurance, comorbid conditions, preoperative functional status, serum glucose, and antibiotic administration from patient charts.

**Definitions.** Obesity was defined as a body mass index of 30 or more. Peri-operative antimicrobial prophylaxis was considered to be appropriate if an antimicrobial agent recommended by a published guideline was administered 2 hours or less before the surgical incision [16]. The preoperative level of independence as determined by activities of daily living was determined according to the Katz criteria [17]. The overall level of comorbid illness was determined for each study patient by calculating a Charlson score [18]. Acute severity of illness was determined by calculating a McCabe score [19]. Effective antimicrobial therapy was defined as initiation of an antibiotic with in vitro activity against the pathogen within 7 days of diagnosis of SSI.

**Outcome variables.** Outcomes data were obtained from patients chart and the U.S. Social Security Death Index. Four outcome variables were analyzed for the 90-day postoperative period: hospital readmission, mortality (including both in-hospital and outpatient), total hospital days (including readmissions), and hospital charges (including readmissions). All hospital charges were adjusted to reference year 2003 by inflating charges from prior years at a 3% annual rate.

**Statistical Analysis.**
All statistical analyses were performed using SAS software, version 9.1 (SAS). Continuous variables were compared in bivariable analysis using the Wilcoxon rank sum test or Student t-test. Dichotomous and ordinal variables were compared using the Fisher exact or chi-square tests, where appropriate. The Kaplan-Meier method was used to determine differences in 90-day mortality over time.

Each of the four outcomes was analyzed in two ways: 1) patients with SSI due to MRSA were compared to uninfected controls to determine the impact of SSI due to MRSA on outcomes and 2) patients with SSI due to MRSA were compared to patients with SSI due to MSSA to determine the impact of methicillin-resistance on outcomes. Logistic regression was performed to determine the independent effects of SSI due to MRSA and methicillin resistance on 90-day readmission rates and 90-day mortality. Linear regression was used to determine the independent effects of SSI due to MRSA and methicillin-resistance on 90-day duration of hospitalization after surgery and 90-day hospital charges (after log transformation of the outcome variable). In addition, linear regression with the least squares means method was used to determine adjusted mean values attributable to SSI due to MRSA and methicillin-resistance for postoperative total hospital days and 90-day hospital charges.

Variables with a p-value<0.2 in bivariable analysis were included as candidate variables for the multivariable models. Models were derived using backwards selection. Only confounding variables and variables with an adjusted p-value<0.05 were included in the final models. Confounding variables were identified as variables that, once removed, changed β coefficients by more than 10%.

Variables considered for inclusion in the models were assessed for missing data. Missing data for these variables were imputed using unconditional imputation: imputation of the mean for continuous variables or the mode for categorical variables [20]. If >5% of data for a variable were missing, the variable was tested for bias by creating dummy variables for the imputed data. If the imputation dummy variable was significantly associated with the outcome (e.g., 90-day mortality), then it was left in the final model to control for bias generated by imputation [10].

Finally, because inappropriate therapy for MRSA infections leads to worse outcomes [21], a sensitivity analysis was performed that compared patients with SSI due to MRSA who received appropriate therapy to patients with SSI due to MSSA who received appropriate therapy to see if outcomes were worse among patients with SSI due to MRSA, even if therapy was administered appropriately.

**Results.**
A total of 278 patients with SSI due to S. aureus were identified following 141,345 procedures during the study period (overall rate...
of SSI due to \textit{S. aureus} = 0.20/100 procedures); 150 patients were
diagnosed with SSI due to MRSA (54% of SSI due to \textit{S. aureus};
rate of SSI due to MRSA = 0.11/100 procedures) and 128 patients
were diagnosed with SSI due to MSSA (rate of SSI due to
MSSA = 0.09/100 procedures). Table 1 summarizes key demo-
graphic, clinical, and surgical variables.

Orthopedic and cardiothoracic procedures were the two most
common procedure types (Table 1). Approximately 60% of
procedures were performed at the tertiary care center (Table 1).
Among the community hospitals, an average of 9 SSIs due to
MRSA and 9 SSIs due to MSSA were diagnosed. In addition, 23
(15%) of patients with SSI due to MRSA and 17 (13%) patients
with SSI due to MSSA were admitted to the ICU prior to the
diagnosis of their SSI ($p = 0.63$). Finally, 107 (71%) patients with

SSI due to MRSA and 89 (70%) of patients with SSI due to MSSA
received appropriate antimicrobial therapy ($p = 0.73$).

Outcomes – Impact of SSI Due to MRSA

All outcomes were more severe among patients with SSI due to
MRSA compared with matched uninfected controls in unadjusted
analyses (Table 2). Patients with SSI due to MRSA were 30-fold
more likely to be readmitted and 7-fold more likely to die within
90 days compared to uninfected controls. Similarly, patients with
SSI due to MRSA stayed in the hospital 16 more days and accrued
more than $40,000 of additional charges compared to uninfected
controls.

Table 3 summarizes independent predictors for each outcome
of interest for patients with SSI due to MRSA and matched

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**Table 1.** Key characteristics of 150 patients with methicillin-resistant \textit{Staphylococcus aureus} surgical site infections (SSI) compared
with 231 uninfected controls and 128 patients with methicillin-susceptible \textit{S. aureus} SSI.$^a$

<table>
<thead>
<tr>
<th></th>
<th>MRSA SSI N = 150 n(%)</th>
<th>Uninfected Controls N = 231 n(%)</th>
<th>MSSA SSI N = 128 n(%)</th>
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<tr>
<td><strong>Demographics</strong></td>
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<tr>
<td>Age (mean±STD)</td>
<td>62.1±15.4</td>
<td>65.7±15.6</td>
<td>60.4±15.0</td>
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<td>Gender (male)</td>
<td>70 (46.7)</td>
<td>121 (52.4)</td>
<td>64 (50.4)</td>
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<td>Race (Caucasian)</td>
<td>104 (70.3)</td>
<td>184 (80.4)</td>
<td>98 (77.2)</td>
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<td>Admitted from home</td>
<td>103 (67.6)</td>
<td>168 (74.3)</td>
<td>93 (71.6)</td>
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<tr>
<td>Medicaid insurance</td>
<td>16 (11.0)</td>
<td>6 (2.6)$^b$</td>
<td>14 (11.5)</td>
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<td><strong>Selected comorbid conditions</strong></td>
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<tr>
<td>Charlson≥3</td>
<td>35 (23.3)</td>
<td>33 (14.3)$^a$</td>
<td>18 (14.1)$^a$</td>
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<tr>
<td>McCabe score on admission of 1</td>
<td>12 (8.2)</td>
<td>4 (1.8)$^a$</td>
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<td>BMI&gt;30</td>
<td>57 (41.3)</td>
<td>59 (26.9)</td>
<td>57 (48.7)</td>
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<td>Diabetes mellitus</td>
<td>39 (26.0)</td>
<td>58 (25.1)</td>
<td>29 (22.7)</td>
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<tr>
<td>Congestive heart failure</td>
<td>44 (29.3)</td>
<td>37 (16.0)$^b$</td>
<td>23 (18.0)$^b$</td>
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<td>Cerebrovascular disease</td>
<td>15 (10.0)</td>
<td>18 (7.8)</td>
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<td>Chronic obstructive pulmonary disease</td>
<td>26 (17.3)</td>
<td>20 (8.7)</td>
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<td>Renal disease</td>
<td>15 (10.0)</td>
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<td>Use of immunosuppressive medications</td>
<td>17 (12.0)</td>
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<td><strong>Preoperative functional status</strong></td>
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<tr>
<td>No limitations</td>
<td>74 (49.3)</td>
<td>166 (71.9)$^b$</td>
<td>84 (65.6)$^b$</td>
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<td>Need assistance with 3 or more ADLs</td>
<td>46 (30.7)</td>
<td>12 (9.4)$^b$</td>
<td>25 (19.8)$^b$</td>
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<td><strong>Surgical Characteristics</strong></td>
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<td>Orthopedic procedure</td>
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<td>43 (28.7)</td>
<td>84 (36.4)</td>
<td>44 (34.4)</td>
</tr>
<tr>
<td>Procedure performed at tertiary care hospital</td>
<td>94 (62.7)</td>
<td>150 (64.9)</td>
<td>75 (58.6)</td>
</tr>
<tr>
<td>Repeat procedure at same operative site</td>
<td>17 (11.6)</td>
<td>24 (10.8)</td>
<td>18 (14.4)</td>
</tr>
<tr>
<td>Operative procedure &gt;75th percentile</td>
<td>36 (24.2)</td>
<td>49 (20.7)$^b$</td>
<td>16 (25.0)$^b$</td>
</tr>
<tr>
<td>Wound class &gt;2</td>
<td>16 (10.7)</td>
<td>7 (3.0)$^c$</td>
<td>0$^c$</td>
</tr>
<tr>
<td>ASA score ≥3</td>
<td>109 (73.2)</td>
<td>156 (69.6)$^c$</td>
<td>94 (75.8)</td>
</tr>
<tr>
<td>Serum glucose &gt;200 mg/dL</td>
<td>42 (27.2)</td>
<td>65 (28.6)</td>
<td>30 (33.7)</td>
</tr>
<tr>
<td>Antimicrobial prophylaxis administered appropriately</td>
<td>108 (75.5)</td>
<td>176 (77.9)</td>
<td>91 (79.1)</td>
</tr>
<tr>
<td>Surgery on same day as hospital admission</td>
<td>74 (49.3)</td>
<td>131 (57.0)$^f$</td>
<td>79 (61.7)$^f$</td>
</tr>
</tbody>
</table>

$^A$ - All percentages were calculated using denominators that excluded missing data. Data were missing for the following variables: McCabe score (4 MRSA SSI, 5
uninfected controls, 10 MSSA SSI, BMI (12 MRSA SSI, 12 uninfected controls, 10 MSSA SSI), repeat procedure (3 MRSA SSI, 8 uninfected controls, 3 MSSA SSI), operative procedure >75th percentile (65 MRSA SSI, 66 uninfected controls, 64 MSSA SSI), ASA score (1 MRSA SSI, 7 uninfected controls, 4 MSSA SSI), serum glucose (37 MRSA SSI, 67 uninfected controls, 39 MSSA SSI), antimicrobial prophylaxis (7 MRSA SSI, 6 uninfected controls, 3 MSSA SSI), same day procedure (1 uninfected control).

$^B$ - $p<0.001$ compared to patients with SSI due to MRSA.

$^C$ - $p<0.05$ compared to patients with SSI due to MRSA.

**Table 2.** Outcomes - Impact of SSI Due to MRSA

All outcomes were more severe among patients with SSI due to
MRSA compared with matched uninfected controls in unadjusted
analyses (Table 2). Patients with SSI due to MRSA were 30-fold
more likely to be readmitted and 7-fold more likely to die within
90 days compared to uninfected controls. Similarly, patients with
SSI due to MRSA stayed in the hospital 16 more days and accrued
more than $40,000 of additional charges compared to uninfected
controls.

Table 3 summarizes independent predictors for each outcome
of interest for patients with SSI due to MRSA and matched

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**Exhibit 3 - Duke Study Cont.**
uninfected controls. Similar to unadjusted analyses, all outcomes were worse among patients with SSI due to MRSA. SSI due to MRSA was independently predictive of readmission within 90 days (OR = 3.50, 95% CI 1.73–7.07), death within 90 days (OR = 7.27, 95% CI 2.85–18.7), longer hospitalization (OR = 4.36, 95% CI 3.31–5.75), and higher hospital charges (OR = 4.44, 95% CI 2.68–7.34) compared to uninfected controls. Of note, need for assistance with ≥3 ADLs was also independently predictive of readmission within 90 days, 90-day mortality, and increased length of hospitalization, but not increased hospital charges.

The mean length of stay independently and directly attributable to SSI due to MRSA was 23 days (95% CI 19.7–26.3) compared to uninfected controls (Table 4). The mean hospital charge independently and directly attributable to SSI due to MRSA was $61,681 (95% CI 23,352–100,011). In total, the charge attributable to SSI due to MRSA was approximately $19 million for the 7 hospitals.

Outcomes – Impact of Methicillin-Resistance

In unadjusted analyses, most outcomes were worse among patients with SSI due to MRSA compared with patients with SSI due to MSSA (Table 2). Patients with SSI due to MRSA were 2.6-fold more likely to die within 90 days following surgery than patients with SSI due to MSSA. Similarly, patients with SSI due to MRSA stayed in the hospital 6 more days and accrued more than $23,000 of additional charges compared to patients with SSI due to MSSA. The one exception to this trend was readmission within 90 days of procedure. Patients with SSI due to MRSA were one-half as likely to require readmission within 90 days of procedure as patients with SSI due to MSSA. Ninety-day survival curves for each of the three groups are presented in Figure 1.

Table 5 summarizes independent predictors for each outcome of interest for patients with SSI due to MRSA compared to patients with SSI due to MSSA. Methicillin-resistance was independently predictive of increased length of hospitalization (OR = 1.27, 95% CI 1.22–1.33) and increased hospital charges (OR = 1.20, 95% CI 1.16–1.25) but was not independently associated with increased mortality (OR = 1.72, 95% CI 0.70–4.20). Interestingly, patients with SSI due to MRSA were less likely to be readmitted within 90 days than patients with SSI due to MSSA (OR = 0.43, 95% CI 0.21–0.89). Need for assistance with ≥3 ADLs was associated with increased risk of 90-day mortality while patients who received appropriate administration of perioperative antimicrobial prophylaxis had lower risk of death than patients who did not.

The mean length of stay independently and directly attributable to methicillin-resistance was 5.5 days (95% CI 1.97–9.11) (Table 6). The mean hospital charge independently and directly attributable to methicillin-resistance was $24,113 (95% CI 4,521–48,704).

Sensitivity analyses were performed to determine the impact of appropriate antimicrobial treatment on differences in outcomes among patients with SSI due to MRSA and patients with SSI due to MSSA. Each outcome model was rerun using only the subset of patients who received appropriate therapy. Overall, no differences were noted compared to the results from the full models (data not shown). Specifically, no difference was detected in 90-day mortality for patients with SSI due to MRSA who received appropriate antimicrobial therapy compared with patients with SSI due to MSSA who received appropriate antimicrobial therapy.

Discussion

Our study represents the largest study to date of outcomes due to SSI due to MRSA. Our findings confirm that SSIs due to MRSA lead to significant patient suffering and provide quantitative estimates of the staggering costs of these infections. SSI due to MRSA led to a 7-fold increased risk of death, a 33-fold increased risk of hospital readmission, more than 3 weeks of additional hospitalization, and more than $60,000 of additional charges compared to uninfected controls.

Numerous studies have evaluated the impact of methicillin-resistance in patients with bloodstream infection (BSIs), yet many...
Table 3. Independent Predictors of Post-Operative Adverse Outcomes: Analysis of 150 patients with methicillin-resistant *Staphylococcus aureus* (MRSA) surgical site infections (SSI) compared with 231 uninfected controls to determine the independent effect of SSI due to MRSA on outcomes of surgical patients.

<table>
<thead>
<tr>
<th>Independent Predictor</th>
<th>Odds Ratio [95% Confidence Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Readmission within 90 days of surgical procedure</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>SSI due to MRSA</td>
<td>35.0 [17.3-70.7]</td>
</tr>
<tr>
<td>Need assistance with ≥3 ADLs</td>
<td>4.28 [1.52-12.0]</td>
</tr>
<tr>
<td><strong>Death within 90 days of surgical procedure</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>SSI due to MRSA</td>
<td>7.27 [2.83-18.7]</td>
</tr>
<tr>
<td>Need assistance with ≥3 ADLs</td>
<td>6.73 [2.80-16.2]</td>
</tr>
<tr>
<td>Age≥65</td>
<td>4.45 [1.41-14.6]</td>
</tr>
<tr>
<td>Orthopedic procedure</td>
<td>0.27 [0.10-0.71]</td>
</tr>
<tr>
<td><strong>Increased length of hospitalization during 90 days following surgical procedure</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>SSI due to MRSA</td>
<td>4.36 [3.31-5.75]</td>
</tr>
<tr>
<td>Procedure at tertiary care hospital</td>
<td>1.41 [1.30-1.54]</td>
</tr>
<tr>
<td>Need assistance with ≥3 ADLs</td>
<td>1.35 [1.25-1.46]</td>
</tr>
<tr>
<td>Post-operative serum glucose &gt;200 mg/dL</td>
<td>1.18 [1.15-1.22]</td>
</tr>
<tr>
<td>Orthopedic procedure</td>
<td>0.68 [0.62-0.75]</td>
</tr>
<tr>
<td><strong>Hospital charges during 90 days following surgical procedure</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>SSI due to MRSA</td>
<td>4.44 [2.68-7.34]</td>
</tr>
<tr>
<td>Procedure at tertiary care hospital</td>
<td>2.97 [2.23-3.95]</td>
</tr>
<tr>
<td>Coronary artery bypass graft procedure</td>
<td>1.34 [1.26-1.43]</td>
</tr>
<tr>
<td>Surgical duration &gt;75&lt;sup&gt;th&lt;/sup&gt; NNIS percentile</td>
<td>1.27 [1.22-1.32]</td>
</tr>
<tr>
<td>Procedure on same day as admission</td>
<td>0.75 [0.72-0.79]</td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients who died during the index admission (n=23) were excluded from this analysis. Final model controlled for confounding effect of ASA score and contained term for interaction between SSI due to MRSA and Need assistance with ≥3 ADLs. Reference model also included the following variables: sex, history of congestive heart failure, history of cerebrovascular accident, McCabe score=1, and surgery on same day as admission.

<sup>b</sup>Reference model also included the following variables: admitted from home, Charlson score=2, McCabe score=1, wound class≥2, ASA score≥3, surgery on same day as admission, serum glucose>200 mg/dL, and repeat procedure at same operative site.

<sup>c</sup>Final model controlled for confounding effects of Caucasian race, McCabe score=1, male sex, coronary artery bypass graft procedures, and surgical duration>75<sup>th</sup> NNIS percentile and contained a term for the interaction of MRSA 551 and need assistance with 3 or more ADLs. Reference model also contained the following variables: BMI≥30, age≥65 years, admission from home, Charlson score≥3, ASA score≥3, and repeat procedure at same operative site.

<sup>d</sup>Final model controlled for confounding effects of ASA score≥3 and contained an interaction term for the interaction between MRSA SSI and need assistance with 3 or more ADLs and an interaction term for the interaction between MRSA SSI and procedure at a tertiary care hospital. Reference model also contained the following variables: need assistance with 3 or more ADLs, receipt of immunosuppressive medications, McCabe score=1, post-operative serum glucose>200 mg/dL, and orthopedic procedure.

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Table 4. Length of stay and hospital charges<sup>e</sup> within 90 days of surgery attributable to surgical site infection (SSI) due to methicillin resistant *Staphylococcus aureus* (MRSA): SSI due to MRSA compared to uninfected controls.

<table>
<thead>
<tr>
<th>Length of Stay Least Squares Mean (IQR)</th>
<th>Charges Least Squares Mean (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td><strong>Adjusted</strong></td>
</tr>
<tr>
<td><strong>Unadjusted</strong></td>
<td><strong>Adjusted</strong></td>
</tr>
</tbody>
</table>

| Cases | 23.8 (21.7-25.5) | 28.3 (23.7-30.8) | 105,214 (91,458-118,971) | 112,144 (85,850-138,438) |
| Control | 6.2 (3.7-6.7) | 5.2 (3.5-7.0) | 47,099 (35,465-58,714) | 50,463 (39,351-66,375) |
| Attributable difference | 18.4 (16.0-20.8) | 23.0 (19.7-26.3) | 58,115 (40,111-76,119) | 61,681 (23,352-100,011) |

<sup>e</sup>Charges were normalized to year 2003 by adjusting for inflation at a rate of 0.03% per year.

<sup>f</sup>Adjusted for procedure at tertiary care hospital, need assistance with ≥3 ADLs, post-operative serum glucose>200 mg/dL, orthopedic procedure, caucasian race, McCabe score=1, male sex, coronary artery bypass graft procedures, surgical duration>75<sup>th</sup> NNIS percentile, and contained a term for the interaction between MRSA SSI and need assistance with 3 or more ADLs.

<sup>g</sup>Adjusted for procedure at tertiary care hospital, need assistance with ≥3 ADLs, post-operative serum glucose>200 mg/dL, orthopedic procedure, caucasian race, McCabe score=1, male sex, coronary artery bypass graft procedures, surgical duration>75<sup>th</sup> NNIS percentile, procedure on same day as admission, ASA score≥3, the interaction between MRSA SSI and need assistance with 3 or more ADLs and the interaction between MRSA SSI and procedure at a tertiary care hospital.

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doi:10.1371/journal.pone.0008305.t004
of these studies have come to conflicting results [22,23,24,25,26,27]. An array of confounding factors have been cited as potential causes for these conflicting conclusions, including patient mix and co-morbid conditions, treatment, severity of illness, and even methods for analysis [28,29]. The authors of two meta-analyses analyzed data from many of the studies cited above; both concluded that, on the whole, available data suggested that methicillin-resistance is associated with higher mortality among patients with S. aureus BSI [7,30].

The issue is less clear regarding the impact of methicillin-resistance among patients with S. aureus SSI. To our knowledge, only three other studies directly compared patients with SSI due to MRSA to patients with SSI due to MSSA in an attempt to determine the attributable impact of methicillin-resistance on outcomes among patients with S. aureus [7,8,9].

The first study compared 15 patients with mediastinitis due to MRSA to 26 patients with mediastinitis due to MSSA at a single center in France [9]. Patient follow-up was continued for four years. Using multivariable analytic statistical techniques, the authors of this small study concluded that mediastinitis due to MRSA led to a 4.6-fold increase in risk of mortality compared to mediastinitis due to MSSA. No other outcomes were analyzed.

The second study compared 73 patients with mediastinitis due to MRSA to 145 patients with mediastinitis due to MSSA in a single center in France [8]. Outcomes of patients admitted to the ICU with S. aureus mediastinitis were analyzed. Methicillin resistance was not an independent predictor of ICU mortality using multivariable analyses. However, mediastinitis due to MRSA was a predictor of a longer duration of mechanical ventilation and ICU stay compared to mediastinitis due to MSSA in an unadjusted statistical analysis.

The third study compared 127 patients with SSI due to MRSA to 173 patients with SSI due to MSSA in two centers (one tertiary care and one community hospital) in North Carolina, USA [7]. Several different types of surgical procedures were included in the analysis, though the majority of procedures were cardiothoracic. In multivariable analyses, methicillin resistance was associated with a 3-fold increase in 90-day mortality, 3 additional days of hospitalization, and $14,000 of additional charges per SSI.

Our multi-center study demonstrated that methicillin-resistance led to longer hospitalization and higher charges among patients with S. aureus SSI. Of note, patients with SSI due to MRSA had higher baseline proportions of co-morbid illness than both uninfected controls and patients with SSI due to MSSA. Our outcomes analyses controlled for these differences. Although methicillin resistance led to higher risk of mortality among patients with S. aureus SSI in unadjusted analyses, SSI due to MRSA was no longer an independent predictor for risk of mortality compared to SSI due to MSSA after controlling for variables for co-morbid illness, severity of infection, and appropriateness of treatment. These results did not change in our sensitivity analysis limited to patients who received appropriate therapy. However, our Kaplan-Meier analysis suggests that differences may have existed if other time points had been selected, as the mortality curves for patients with SSI due to MRSA and patients with SSI due to MSSA quickly diverged. Nevertheless, the impact of methicillin resistance on outcome of patients who survived was substantial. Our adjusted analyses also demonstrated that methicillin-resistance among patients with S. aureus SSI led to approximately 6 additional days of hospitalization and more than $24,000 of additional charges.

Our estimates of the financial burden of SSI due to MRSA are unique. On the whole, SSI due to MRSA led to charges in excess of $19 million for the group of study hospitals. We believe our estimate for the attributable impact of a single SSI due to MRSA of more than $61,000 can be used by administrators and infection control personnel to design and evaluate specific preventative interventions. For example, if an intervention (e.g., decolonization, screening, hiring of one FTE) costs less than $61,000 and leads to the prevention of only one SSI due to MRSA, then this intervention will likely be cost effective for the institution.
Our study has limitations. First, our study included only deep incisional and organ/space SSIs, however, are more severe and clinically important than superficial SSI. In fact, cost estimates would have been even higher had we included superficial incisional and organ/space SSIs, however, are more severe and clinically important than superficial SSI.

Table 6. Length of stay and hospital charges a within 90 days of surgery attributable to surgical site infection (SSI) due to methicillin resistant Staphylococcus aureus (MRSA): SSI due to MRSA compared to SSI due to MSSA.

<table>
<thead>
<tr>
<th></th>
<th>Length of Stay Least Squares Mean (IQR)</th>
<th>Charges Least Squares Mean (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>SSI due to MRSA</td>
<td>24.3 (21.7–26.8)</td>
<td>23.7 (21.3–26.0)</td>
</tr>
<tr>
<td>SSI due to MSSA</td>
<td>17.4 (14.5–20.2)</td>
<td>18.1 (15.5–20.7)</td>
</tr>
<tr>
<td>Attributable difference</td>
<td>6.86 (3.07–10.4)</td>
<td>5.5 (1.97–9.11)</td>
</tr>
</tbody>
</table>

aCharges were normalized to year 2003 by adjusting for inflation at a rate of 0.03% per year.

bAdjusted for surgical duration >75th NNIS percentile, ASA score ≥3, procedure at tertiary care hospital, Charlson score ≥3, and surgery on same day as admission.

cAdjusted for surgical duration >75th NNIS percentile, ASA score ≥3, procedure at tertiary care hospital, Charlson score ≥3, surgery on same day as admission, and coronary artery bypass graft surgery.

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doi:10.1371/journal.pone.0008305.t001
incidental infections in our analysis. Second, our charge estimates only included indirect in-hospital costs. As a result, our charge estimates are likely underestimations of the true financial impact of these devastating infections. Third, this study included procedures that were performed prior to 2003. Since this time, greater emphasis has been placed on appropriate peri-operative antibiotic administration; thus, rates of SSI due to MRSA or MSSA may have changed since 2003. Finally, most of the surgical procedures we examined were cardiothoracic and orthopedic procedures. Thus, our results may be more reflective of the outcomes of SSI due to MRSA in these types of procedures. In fact, patients with orthopedic procedures were less likely to have adverse outcomes than patients that underwent other types of procedures. Thus, inclusion of a high number of orthopedic procedures may have biased our results towards the null and led to an underestimation of the impact of SSI due to MRSA on adverse clinical outcomes.

In summary, our study provides novel and interesting data regarding the clinical and financial impact of SSI due to MRSA and the impact of methicillin resistance among patients with SSI due to S. aureus. Not surprisingly, SSI due to MRSA led to incredibly poor outcomes compared to uninfected controls. Of particular interest, methicillin-resistance led to a longer duration of hospitalization and increased healthcare costs but did not increase the risk of mortality among patients with SSI due to S. aureus. Our estimates for the financial impact of SSI due to MRSA can be used to determine the cost-effectiveness of preventative strategies.

Author Contributions
Conceived and designed the experiments: DJA KK DS. Performed the experiments: DJA LC YC. Analyzed the data: DJA KK LC KS RS. Contributed reagents/materials/analysis tools: KS RS. Wrote the paper: DJA LC KS YC RS DS.

References
Exhibit 4 - Univ S FL Silver Dressings Colon Rectal Surgery
The Use of Silver Nylon in Preventing Surgical Site Infections Following Colon and Rectal Surgery

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Department of Surgery, Division of Colon and Rectal Surgery, University of South Florida, Tampa, Florida

BACKGROUND: Patients who undergo colorectal surgery have up to a 30% chance of developing a surgical site infection postoperatively. Silverlon is a silver nylon dressing designed to prevent surgical site infections, but only anecdotal evidence has previously supported its efficacy.

OBJECTIVE: The aim of this study was to evaluate the effect of silver nylon dressings in patients undergoing colorectal surgery.

DESIGN: We performed a prospective, randomized, controlled trial comparing a silver nylon dressing with gauze dressings in patients undergoing elective colorectal surgery.

SETTING: The study was performed at a university-based, tertiary referral center.

PATIENTS: We studied patients undergoing elective colorectal surgery with an abdominal skin incision of at least 3 cm.

INTervention: Patients were randomly assigned to receive either a silver nylon or a gauze dressing.

MAIN OUTCOME MEASURES: The primary end point was surgical site infection occurring within 30 days of surgery.

RESULTS: One hundred ten patients were enrolled in the study and were randomly assigned to 1 of 2 treatment groups. After a 30-day follow-up period, the incidence of surgical site infection was lower in the silver nylon group compared with the control group (13% vs 33%, P = .011). Twenty-five patients in the study developed superficial surgical site infections, 5 in the silver nylon group and 14 in the control group (P = .021). Two patients in the study group developed deep wound infections compared with 4 in the control group (P = .438). Multivariate analysis revealed that patients in the control group had a 3-fold increase in risk of infection compared with patients in the silver nylon group (P = .013).

LIMITATIONS: A limitation of this study is that the members of the surgical team were not blinded to the treatment groups.

CONCLUSION: Silver nylon is safe and effective in preventing surgical site infection following colorectal surgery.

KEY WORDS: Colon and rectal surgery; Silver; Surgical site infection.

Surgical site infections (SSIs) are the third most common cause of hospital-acquired infection and are the leading cause of hospital-acquired infection in surgical patients.1,2 A SSI is defined as an infection that occurs within 30 days of a surgical procedure and affects the incision or deep tissue at the operative site.1 These infections increase the average length of hospitalization from 6 to 11 days and cost an estimated $11,000 to $35,000 per infection to treat.3

Colorectal surgery, because of its contaminated nature, is associated with rates of infection as high as 30%.4,5
The colon is colonized by over 500 different species of bacteria in concentrations of $10^{11}$ to $10^{12}$ cells per g. These bacteria are normal colonic flora, but when they are seeded into other tissues, they can result in infection.

Silver has long been known to have antimicrobial properties. In the 1800s silver nitrate was used in the treatment of venereal infections, acne, and leg ulcers. Silver has broad antimicrobial activities against gram-positive and gram-negative bacteria including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and has antifungal activity against mold and yeast. Silver, as a metal, is relatively inert and poorly absorbed by cells. When it is exposed to a wound or other body fluids, it ionizes and becomes highly reactive to proteins and cell membranes. It has been shown to interact with structural proteins and DNA, inhibiting bacterial replication and causing fatal structural changes within bacterial cell walls. In addition, unlike antibiotics, microbial resistance to silver has rarely been reported.

The application of silver in surgery dates back to when William Halsted used silver foil on his surgical wounds to reduce the incidence of postoperative infections. Technology has since evolved, and there are now a variety of commercially available silver surgical dressings. Silverlon (Cura Surgical, Geneva, IL) is a silver-coated, nylon dressing designed to prevent postoperative SSIs. Its efficacy has been documented in case review studies, but definitive data on its true antimicrobial properties is lacking. The aim of this study was to evaluate the efficacy of this dressing in preventing SSI. We conducted a prospective, randomized, controlled trial directly comparing silver nylon with standard gauze dressings in patients undergoing elective colorectal operations.

**METHODS**

This clinical study was designed as a prospective, randomized, controlled trial at a university-based, tertiary referral center. Institutional review board approval from the University of South Florida was obtained before starting the study. All procedures were performed by a board-certified colorectal surgeon. Patients undergoing elective surgery from July 2009 to April 2010 with an anticipated abdominal incision of at least 3 cm were considered for enrollment. Patients were excluded if they had incisions less than 3 cm, a known allergy to silver, signs of abdominal wall infection, conditions that would prevent full closure of the skin at the primary operation, or prior abdominal mesh that was not planned to be fully removed at the time of operation. Women who were pregnant or lactating and patients who had received antibiotics within 1 week of surgery were also excluded. Enrollment was not limited by any other preexisting medical condition or pathology (Fig. 1).

**Perioperative Protocol**

Participating patients underwent a standardized perioperative protocol. All patients were instructed to restrict their diet to clear liquids 24 hours before surgery. As is our practice, mechanical bowel preparations were not used, with the exception of patients undergoing left colon or rectal surgery who were given an enema the morning of their operation. All patients received preoperative antibiotics 30 to 60 minutes before surgery. Standard perioperative coverage for bowel surgery at our institution is ertapenem; patients with penicillin allergies are given alternative prophylaxis with ciprofloxacin and flagyl or gentamicin and clindamycin. All perioperative antibiotics were discontinued within 24 hours in accordance with the Surgical Care Improvement Project guidelines.

**Study Treatment and Randomization**

Patients were randomly assigned in a 1:1 fashion to receive either a silver nylon dressing in the treatment group or a gauze dressing in the control group. Randomization was completed with nQuery software by a blinded statistician using sealed envelopes. The surgical team was blinded to the surgical dressing until the time of skin closure at the end of the operation.

The initial dressing was placed by the surgical team in the operating room. Patients randomly assigned to the treatment group had their silver nylon dressing hydrated in sterile water before application. The control group had their incisions dressed only with sterile gauze and paper tape.

The particular silver dressing used in this study is designed to last for 7 days. Product instructions specify hydrating the dressing daily and then replacing it with a new dressing after 7 days. On discharge, patients have a new dressing applied that remains for an additional 7 days.

First examination of the surgical wounds was performed at 48 hours. If the silver dressing dried out or the gauze dressing became saturated sooner than this time period, then hydration of the silver dressing or changing of the gauze dressings was done earlier. All dressing changes were performed by a member of the surgical team. On discharge from the hospital, patients with gauze dressings were instructed to change their dressings as needed, whereas the patients with silver nylon dressings were instructed to leave their dressings intact until their follow-up appointment. Although it is not routine practice to continue postoperative dressings after 48 hours, the efficacy of the silver product is based on a longer duration of use and we continued the gauze dressings to keep with a standardized protocol.

Follow-up appointments were scheduled for 7 to 10 days from hospital discharge. At this time, the dressings were discontinued, and the wounds were assessed and treated as needed. If dressing changes were still needed because of drainage or infection, standard dressings were applied per standard medical practice (including dry
gauze, wet to dry dressings, etc). Patients had additional follow-up by telephone at 30 days at which time they completed a standardized survey. Additional appointments were dictated by the patient’s condition and any medical needs.

Determination of whether a wound was infected was made by an unblinded physician member of the surgical team. SSIs were classified by the Centers for Disease Control and Prevention (CDC) guidelines (Table 1). Superficial incisional SSI included infection of the skin or subcutaneous tissue of the incision and either purulent drainage, isolated organisms from culture, wound opened because of signs of infection, or diagnosis of SSI by the surgeon. We modified this definition to include all patients who were placed on antibiotics specifically for these signs or symptoms. The CDC definition of deep incisional SSI and organ space SSI were used to further classify more significant infections.

Statistical Analysis
The primary end point of this study was the development of a SSI. Other prospectively collected data included sex, past medical history, indication for operation, type of operation, length of hospital stay, and complications.

Previous studies have demonstrated a SSI rate of 6% to 30% in patients undergoing colorectal surgery. Because the incidence at our institution is approximately 25%, we chose this as our baseline infection rate. Based on the published Silverlon literature, we estimated that this dressing would reduce the incidence of SSI to 5% in our population. It was calculated that a sample size of 110 patients would be required to have 80% power to detect the difference between a group 1 proportion, \( p_1 \), of 0.25 and a group 2 proportion, \( p_2 \), of 0.05 using Fisher exact probability test with a 0.05 2-sided significance level. Descriptive statistics are reported as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables.

A multivariable logistic regression model using forward likelihood ratio methods was used to evaluate the independent contribution of various factors to infection status.

RESULTS
From July 2009 to April 2010, 110 patients were enrolled in the study. Fifty-five patients were randomly assigned to each of the 2 study groups. One patient assigned to the
TABLE 1. Definition of surgical site infections

<table>
<thead>
<tr>
<th>Type of SSI</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial SSI</td>
<td>Infection occurs within 30 days of the operation and infection involves only skin or subcutaneous tissue and at least one of the following: Purulent drainage, with or without laboratory confirmation. Organism isolated from an aseptically obtained culture of fluid or tissue. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and incision is deliberately opened by surgeon, unless incision is culture negative. Diagnosis of superficial incisional SSI by the surgeon.</td>
</tr>
<tr>
<td>Deep SSI</td>
<td>Infection occurs within 30 days of the operation and infection involves deep soft tissue and at least one of the following: Purulent drainage from the deep incision, but not from the organ space. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever &gt;38°C, localized pain, or tenderness, unless site is culture negative. An abscess or other evidence of infection involving the deep incision found on direct examination, reoperation, or histopathologic or radiologic examination. Diagnosis of deep incisional SSI by the surgeon.</td>
</tr>
<tr>
<td>Organ/space SSI</td>
<td>Infection occurs within 30 days of the operation and infection involves any part of the anatomy, other than the incision, which was opened or manipulated during an operation and at least one of the following: Purulent drainage from a drain that is placed through a stab wound into the organ space. Organism isolated from an aseptically obtained culture of fluid or tissue in the organ space. An abscess or other evidence of infection involving the organ space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination. Diagnosis of an organ/space SSI by the surgeon.</td>
</tr>
</tbody>
</table>

SSI = surgical site infection.

The control group was treated off study protocol and was therefore not included in the final statistical analysis. The median age in the silver nylon group was 62 (range, 24–85), and in the control group, it was 58 (range, 26–76). There was a similar distribution of patient demographics between the 2 treatment groups (Table 2).

There was an equal division between patients undergoing open and laparoscopic surgery. Preoperative enemas were performed in 37 patients in the silver nylon group and 35 in the control group. Seven patients in the study group required intraoperative blood transfusions; no patients in the control group received transfusions.

The total incidence of SSI in the silver nylon group was 13%, which was significantly lower than the 33% in the control group (P = .01). Most SSIs in our cohort were superficial. However, 4 (7.4%) patients in the control group and 2 (3.6%) patients in the treatment group developed a deep SSI (Table 3).

Patients in the silver nylon group had an in-hospital SSI rate of 11% (n = 6), whereas patients in the control group had a rate of 22% (n = 12, P = .11). All patients who developed a SSI were treated with antibiotics. Two patients in the control group required additional treatment with surgical debridement or negative pressure therapy. During their hospitalization, 2 patients in the silver nylon group and 8 patients in the control group received antibiotics for conditions not related to their wound. Reasons for antibiotic use included urinary tract infection, sinus infection, and anastomotic leak. Length of hospitalization was similar between the 2 groups (6 days vs 6.5 days, P = .21).

In the immediate 7- to 10-day postoperative follow-up period, one additional patient in the silver nylon group developed a SSI compared with 6 in the standard of care group. Only one patient (silver nylon group) required readmission for a SSI. No new SSIs were diagnosed at the 30-day follow-up or in the interim.

Multivariate logistic regression revealed that use of the silver nylon dressing was the only independent predictor for infection status. Patients in the control group had an approximately 3-fold increase in risk of infection compared with the silver nylon group (P = .013) (Table 4).

One patient had an adverse reaction to the silver nylon dressing; the patient developed a rash at the site of the dressing that quickly resolved after the dressing was discontinued.

DISCUSSION

In this prospective, randomized, controlled trial, there was a significant reduction in the incidence of SSI in patients treated with the silver nylon dressing following elective colorectal surgery. Patients treated with the gauze dressings were 3 times more likely to develop a SSI than those treated with the silver nylon. The overall incidence of postoperative SSIs in our standard of care group was 33% which is similar to our previously reported rate. Although this rate may appear high in comparison with other published reports of similar operations, and although there is likely a degree of underreporting of this complication, we believe our rate of infection is due to our adherence to the CDC's definition of infection. In addition, in an attempt to capture even very early SSIs, our alteration of the CDC criteria may have also increased our...
TABLE 2. Study group demographics

<table>
<thead>
<tr>
<th></th>
<th>Silver nylon (n = 55)</th>
<th>Control (n = 54)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>62</td>
<td>58</td>
<td>.049*</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (51)</td>
<td>26 (48)</td>
<td>.773b</td>
</tr>
<tr>
<td>Female</td>
<td>27 (49)</td>
<td>28 (52)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>27.5</td>
<td>27.3</td>
<td>.868*</td>
</tr>
<tr>
<td>Tobacco, n (%)</td>
<td>8 (15)</td>
<td>14 (26)</td>
<td>.139b</td>
</tr>
<tr>
<td>Immunosupression, n (%)</td>
<td>4 (7)</td>
<td>6 (11)</td>
<td>.527c</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>5 (9)</td>
<td>4 (7)</td>
<td>1.00c</td>
</tr>
<tr>
<td>pRBC transfusion, n (%)</td>
<td>7 (13)</td>
<td>0</td>
<td>.013c</td>
</tr>
<tr>
<td>Type of operation, n (%)</td>
<td></td>
<td></td>
<td>.778b</td>
</tr>
<tr>
<td>Laparoscopic-assisted</td>
<td>30 (55)</td>
<td>28 (52)</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>25 (45)</td>
<td>26 (48)</td>
<td></td>
</tr>
<tr>
<td>Operation, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small-bowel resection</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Ileocecectomy</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Right colectomy</td>
<td>9 (16)</td>
<td>9 (17)</td>
<td></td>
</tr>
<tr>
<td>Left colectomy</td>
<td>3 (5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sigmoid resection</td>
<td>9 (16)</td>
<td>11 (20)</td>
<td></td>
</tr>
<tr>
<td>Hartmann procedure</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Subtotal colectomy</td>
<td>3 (5)</td>
<td>7 (13)</td>
<td></td>
</tr>
<tr>
<td>Proctocolectomy</td>
<td>3 (5)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Proctectomy</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>LAR</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>APR</td>
<td>2 (4)</td>
<td>5 (9)</td>
<td></td>
</tr>
<tr>
<td>Enterostomy creation</td>
<td>3 (5)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Enterostomy reversal</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Colovesicle fistula repair</td>
<td>1 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Surgical indication, n (%)</td>
<td></td>
<td></td>
<td>.353b</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>36 (65)</td>
<td>34 (63)</td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>5 (9)</td>
<td>10 (19)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14 (25)</td>
<td>11 (19)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization, days</td>
<td>6</td>
<td>6.5</td>
<td>.210b</td>
</tr>
<tr>
<td>Median</td>
<td>3-21</td>
<td>2-17</td>
<td></td>
</tr>
</tbody>
</table>

pRBC = packed red blood cells; LAR = low anterior resection; APR = abdominoperineal resection.

*Student t test.

bFisher exact probability test.

cMann-Whitney U test.

doing developed evidence of mediastinitis compared with 13 patients (1%) in the control group. Epstein performed a similar study in patients undergoing lumbar laminectomy; no patients treated with the silver nylon developed a SSI compared with 11% of patients treated with standard dressings. 15

Several limitations to our study design are worthy of mention. As with any unblinded study, the possibility of bias must always be acknowledged. This is no less so in our trial, because the diagnosis of a SSI was determined by unblinded members of the surgical team. However, we attempted to standardize the definition by use of previously established CDC criteria. In addition, we included for analysis any questionable SSI that was being treated with antibiotics. This aggressive treatment of possibly early SSIs may also explain the low incidence of deep incisional infections. And whereas a minimum incision length was an inclusion criterion, we did not routinely measure the exact length in every patient in the study. Incision length could definitely factor into the development of a SSI, and these data are missing from our study.

Many prior studies have identified various risk factors associated with the risk of development of SSIs. Some of these risk factors include diabetes, smoking, systemic steroid use, extremes of age, malnutrition, obesity, coincident remote site infections, and perioperative blood transfusions. 4,5 Although a substantial portion of our study population had one or more of these risk factors, on multivariate analysis these factors fell out and the only independent predictor for risk of infection was the surgical dressing.

TABLE 4. Multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.805</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>.775</td>
</tr>
<tr>
<td>Tobacco</td>
<td>.696</td>
</tr>
<tr>
<td>Diabetes</td>
<td>.078</td>
</tr>
<tr>
<td>pRBC transfusion</td>
<td>.895</td>
</tr>
</tbody>
</table>

pRBC = packed red blood cells.
SSIs are a considerable health care problem in the United States that costs up to 1.8 billion dollars a year to treat. Although a formal cost analysis of SSI prevention and treatment was not performed, it appears that there was a considerable monetary savings with the silver nylon group. The cost of the dressing is based on its size but ranges from $12 to 46. Because only 2 dressings are used on average per patient, the typical maximum cost for this treatment is less than $100. This compares favorably to the additional cost of antibiotics, surgical debridement, and negative pressure therapy that was needed to treat the infections in the control group.

CONCLUSION

SSIs are a source of significant morbidity following any surgical procedure, and they directly contribute to the increasing cost of health care in the United States. We have demonstrated a significant reduction of SSI with the use of a silver nylon dressing in patients undergoing elective colorectal surgery. Future efforts should be directed toward evaluating specific patient populations that would most benefit from its use.

ACKNOWLEDGMENTS

The authors thank Kathryne Downes for her help in the statistical analysis of this paper.

REFERENCES


Exhibit 5 - Fort Sam Houston LC-SMM-56-A; Silverlon in Military Evacuation
The Use of a Silver–Nylon Dressing During Evacuation of Military Burn Casualties

Amit Aurora, D.Eng.,* Alexander Beasy, BA,* Julie A. Rizzo, MD,*† and Kevin K. Chung, MD†,‡

The military has used silver–nylon dressings as a topical antimicrobial on combat-related burns for the past 15 years. However, their clinical efficacy and associated risks have not been evaluated. Herein, the authors document our experience with the use of a specific silver–nylon dressing (Silverlon®) during global evacuation of casualties from combat zones to the United States Army Institute of Surgical Research Burn Center. A 10-year retrospective analysis was performed. Variables included patient demographics, total body surface area, length of stay, Injury Severity Score, incidence of urinary tract and burn infections, pneumonia, patient status at the time of discharge, and a composite endpoint. The patient cohort was stratified into two groups: Silverlon® (Group 1) and topical antimicrobial agents (Group 2). Data were analyzed using appropriate statistical tests (P ≤ .05). Nine hundred eighty-eight patients (26 ± 6 years) were identified with 184 patients (Group 1) and 804 patients (Group 2). Silver–nylon dressings trended toward decreased wound infection rate (5.4 vs 9.5%) even when applied to full-thickness burn injuries. When compared with topical antimicrobial agents, the silver–nylon dressing was not associated with significant differences in burn-related complication. The authors demonstrate the antimicrobial efficacy of the silver–nylon dressing during global evacuation of burn casualties from combat zones to the burn center. Compared with topical antimicrobials, the silver–nylon dressing is lightweight and easy to apply and requires minimal wound management which makes it desirable as a burn dressing for combat applications as well as mass casualty situations.

Burns sustained during military operations constitute approximately 8% of all combat-related injuries. Typically, combat burn casualties undergo immediate medical stabilization in the deployed environment followed by evacuation through multiple echelons of care to the United States Army Institute of Surgical Research (USAISR) Burn Center in San Antonio, Texas. Key priorities of care of combat burn casualties during global evacuation include burn resuscitation, wound care, organ support, and damage control surgery, if necessary. On average, combat burn casualties arrive at the burn center approximately 4 days after injury for definitive surgery, which includes excision and grafting1,2.

Wound management immediately following combat-related burns includes debridement of devitalized tissue and application of topical antimicrobials as prophylaxis against infection during evacuation until surgical excision can be performed3. At USAISR, topical antimicrobials have included alternation of silver sulfadiazine (SSD) and 12% mafenide acetate cream or soaks with 5% mafenide acetate solution. Alternating creams require application of a one-sixteenth inch thick layer with dressing changes twice a day with complete removal of the cream, wound debridement, and reapplication4. On the other hand, 5% mafenide acetate solution applied to dry gauze covering burn wounds needs to be soaked every 6 hours to maintain appropriate antimicrobial levels in the wound bed. In general, mafenide acetate has been prone to cause pain on application5, 6. Silver-containing dressings such as Silverlon® (Argentum Medical, Geneva, IL) which
are comprised of nylon fibers coated with metallic silver, have also been used for wound care during global evacuation\(^7\text{-}^9\). The sustained release of silver ions from the dressing on application of water every 6 hours has a theoretical benefit of providing broad spectrum antimicrobial coverage, which obviates the need for frequent dressing changes\(^{7,10}\). Over the past decade, the aforementioned strategies have been used during evacuation of combat burn casualties\(^8\), \(^9\), \(^11\).

A variety of commercial silver-containing dressings that differ in their silver content and dressing formulations are available for clinical use in the military as well as civilian populations\(^{10,12,13}\). The silver-containing dressings are a simple and shelf-stable alternative to cream and solution-based topical antimicrobials for civilian disaster preparations. Based on a cost-benefit-convenience decision by the US Army, Silverlon\textsuperscript{®} is currently being used during aeromedical evacuation of military burn casualties and is being supplied to Combat and Support Hospitals including Tactical Forward Surgical Teams \(^8\), \(^9\). Despite the on-going use of the silver–nylon dressing in military medicine, there is lack of information on its clinical efficacy and associated risks, if any. The objective of the study was to document our experience with the use of the silver–nylon dressing as an antimicrobial burn dressing on combat-related burns injuries during global evacuation from combat operations in Iraq and Afghanistan to the USAISR Burn Center in San Antonio, Texas.

MATERIALS AND METHODS

After Institutional Review Board approval, we conducted a retrospective study of consecutive service members burned during combat operations admitted to the USAISR Burn Center from March 2003 to December 2013. The data were collected from two sources, namely, query of electronic medical record and paper flight documentation. The variables included patient demographics (race, age, and gender), length of stay (LOS, days) in the hospital and burn intensive care unit, Injury Severity Score, total body surface area burned, and status of patients at the time of discharge. Laboratory records were reviewed to extract information on the incidence of urinary tract infection, pneumonia, bacteremia, and wound infection during the hospital stay. The cohort of patients was stratified into two groups: patients with combat-related burn injuries covered with the silver–nylon dressing (Group 1) and other topical antimicrobials (SSD, 12% mafenide acetate cream, and 5% mafenide acetate solution; Group 2). All burn dressings were applied before transport from the Role IV hospital in Landstuhl Germany to USAISR (estimated travel time of 8–12 hours). We also evaluated a composite endpoint that combines bacteremia, wound infection, and/or mortality as an outcome measure.

The USAISR Burn Center serves as the sole referral center for all combat burn injuries. The burn center is a 40-bed facility of which 16 beds are designated as intensive care unit beds. All definitive care for burned military personnel, including rehabilitation and reconstruction, takes place at USAISR. USAISR also functions as the civilian regional burn center for 49 counties in South Texas.

Statistical Analysis

As appropriate, the chi-squares test was used for categorical variables, a two-tailed student \(t\)-test or nonparametric Mann–Whitney test for continuous variables. Statistical significance was set at \(P \leq .05\). Results are expressed as mean ± standard deviation (SD) or median ± interquartile range (IQR).

RESULTS

A total of 987 combat burn casualties (mean age: 26 ± 6 years) were identified with 184 patients (male: 178 [97%]; female: 6 [3%]) treated with the silver–nylon dressing (Group 1) and 803 patients (male: 780 [97%]; female: 23 [3%]) with topical agents (Group 2). The cohort included 484 (~49%) patients with third-degree burns. The median percent of full thickness burns in Group 1 (74 patients) was 10% (IQR: 3–33) and Group 2 (414 patients) was 10% (IQR: 3–30). Median total body surface area in Group 1 was 8.5% (IQR: 0–22) and 7% (IQR: 0–18.5) in Group 2 \((P = .767)\). Median Injury Severity Score in Group 1 was 9 (IQR: 0–16) and 8 (IQR: 0–18) in Group 2 \((P = .803)\). In Group 1, the median hospital LOS (11 days; IQR: 0–27) and ICU LOS (0 day; IQR: 0–12) were not significantly different from Group 2 (hospital LOS: 12 days [IQR: 0–31]; ICU LOS: 0 day [IQR: 0–10]; \(P \geq .5\)). The mean incidence of urinary tract infection was not significantly different between the groups (Group 1: \(n = 5 \) [2.7%]; Group 2: \(n = 16 \) [2%]; \(P = .57\)). Likewise, mean incidence of pneumonia (Group 1: \(n = 22 \) [12%]; Group 2: \(n = 98 \) [12.2%]; \(P = 1.0\)), bacteremia (Group 1: \(n = 8 \) [4.3%]; Group 2: \(n = 44 \) [5.5%]; \(P = 1.0\)), and wound infection (Group 1: \(n = 10 \) [5.4%]; Group 2: \(n = 76 \) [9.5%]; \(P = .08\)) were not significantly different between the groups. Overall, there was no difference in the mortality rate (Group 1: \(n = 14 \) [8%];
DISCUSSION

The objective of the study was to document our experience with the use a silver–nylon dressing as an antimicrobial dressing on combat-related burns injuries during global evacuation from combat operations in Iraq and Afghanistan to the USAISR Burn Center. The primary finding is that when compared with topical antimicrobials, the silver–nylon dressing was not associated with a significant difference in pertinent burn-related complications. The silver–nylon dressing trends to reduce wound infection rates (5.4 vs 9.5%) even when applied to full-thickness burn injuries.

The silver–nylon dressing trending towards reduced incidence of wound infection may be due to a number of factors. The silver–nylon dressing is an elastic bandage that can be immediately applied over burn injuries in the deployed environment. The immediate application of the dressing prevents further exposure of the wound to the environment. Upon moistening, the silver–nylon dressing releases positively charged silver ions in a sustained manner into the wound bed allowing the dressing to remain in place for 5–7 days\(^7,14\). Compared with topical antimicrobials, the need for fewer dressing changes with the silver–nylon dressing reduces wound exposure to external pathogens. Unlike topical antimicrobial creams, the silver–nylon dressing may prevent maceration of the wound bed and formation of loose edges, which together may impede bacterial proliferation and ingress in the devitalized tissue\(^15-17\). The silver–nylon dressing has been shown to reduce infection in other applications, which corroborates the finding of this study\(^18-20\).

The silver–nylon dressing used in this study has been approved by the U.S. Food and Drug Administration for local burn wound management of partial and deep partial thickness burns. The use of the dressing on full-thickness burns provides evidence of the efficacy of the dressing for severe burn injuries as well. Regular assessment of wound healing and burn depth is critical for burn wound management. SSD creams adhere to burn wounds giving it a whitish appearance, have poor penetration in the burn eschar, and form a pseudo-eschar\(^21,22\). The film formed over the burn makes the wound appear deeper, thereby complicating burn wound assessment. From a clinical standpoint, the silver–nylon dressing is beneficial as it allows for regular and unbiased burn wound assessment with minimal patient discomfort.

Compared with solution and cream-based topical antimicrobial agents, the silver–nylon dressing has several advantages. Unlike mafenide acetate cream (12%) that causes pain on contact with intact free nerve endings and forms a neceschar often requiring

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Table 1. Demographic data and clinical outcomes of combat burn casualties admitted to the Burn Intensive Care Unit (BICU) at the United States Army Institute of Surgical Research (USAISR)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Silver-nylon</th>
<th>Topical agents</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients, n (%)</td>
<td>184 (18.6)</td>
<td>803 (81.4)</td>
<td></td>
</tr>
<tr>
<td>Age, yr (median [IQR])</td>
<td>25.5 (8)</td>
<td>24 (7)</td>
<td>.536</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>178 (97)</td>
<td>780 (97)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>6 (3)</td>
<td>23 (3)</td>
<td></td>
</tr>
<tr>
<td>Third degree burns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients, n (%)</td>
<td>74 (60)</td>
<td>414 (48)</td>
<td></td>
</tr>
<tr>
<td>% (median [IQR])</td>
<td>10 (31)</td>
<td>10 (30)</td>
<td>.810</td>
</tr>
<tr>
<td>TBSA, % (median [IQR])</td>
<td>8.5 (22)</td>
<td>7 (18.5)</td>
<td>.767</td>
</tr>
<tr>
<td>ISS (median [IQR])</td>
<td>9 (16)</td>
<td>8 (18)</td>
<td>.803</td>
</tr>
<tr>
<td>Hospital LOS, days (median [IQR])</td>
<td>11 (27)</td>
<td>12 (31)</td>
<td>.503</td>
</tr>
<tr>
<td>Burn ICU LOS, days (median [IQR])</td>
<td>0 (12)</td>
<td>0 (10)</td>
<td>.540</td>
</tr>
<tr>
<td>UTI, n (%)</td>
<td>5 (2.7)</td>
<td>16 (2)</td>
<td>.57</td>
</tr>
<tr>
<td>Pneumonia, n (%)</td>
<td>22 (12)</td>
<td>98 (12)</td>
<td>1.0</td>
</tr>
<tr>
<td>Bacteremia, n (%)</td>
<td>8 (4.3)</td>
<td>44 (5.5)</td>
<td>.71</td>
</tr>
<tr>
<td>Wound infection, n (%)</td>
<td>10 (5.4)</td>
<td>76 (9.5)</td>
<td>.08</td>
</tr>
<tr>
<td>Composite endpoint, n (%)</td>
<td>26 (14)</td>
<td>146 (18)</td>
<td>.19</td>
</tr>
<tr>
<td>Discharge condition, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full recovery</td>
<td>136 (74)</td>
<td>649 (81)</td>
<td>.156</td>
</tr>
<tr>
<td>Moderate recovery</td>
<td>26 (14)</td>
<td>76 (9.5)</td>
<td>.179</td>
</tr>
<tr>
<td>Death</td>
<td>14 (8)</td>
<td>55 (7)</td>
<td>.152</td>
</tr>
</tbody>
</table>

Group 2: n = 55 [7%]; P = .152 or the composite endpoint (P = .19) (Table 1).
hydrotherapy to remove\textsuperscript{5, 23}, the application and dressing changes of the silver–nylon dressing are relatively pain-free. Silver particles when absorbed systematically do not result in metabolic acidosis often observed with mafenide acetate solution (5\%) application, especially in patients with pulmonary dysfunction\textsuperscript{24–27}. As opposed to mafenide acetate that lacks antifungal properties\textsuperscript{28, 29}, the silver–nylon dressing provides a broad spectrum fungicidal activity that may possibly mitigate burn-related fungal infection\textsuperscript{30, 31}. Unlike hydrochlorous acid and sodium hypochlorite solutions that are cytotoxic to human cells and detrimental to macrophage survival and function, the silver–nylon dressing does not present any deleterious effect to human cells\textsuperscript{32, 33}. The silver–nylon dressing when applied to burn wounds does not stain tissues as observed with silver nitrate solution that turns black on contact with tissue and also causes electrolyte disturbances\textsuperscript{34, 35}. The silver–nylon dressing is hypoallergenic and neither presents cytotoxicity nor impairs re-epithelialization as reported with SSD cream\textsuperscript{36}.

SSD cream contains 1\% SSD by weight and 30\% of that compound contains silver, which suggests that SSD cream releases ~3 mg of silver for each gram of cream. Thus, a 16 in.\textsuperscript{2} burn wound would need 17 g of SSD to release the same amount of silver as that of the silver–nylon dressing (52 mg/l). Unlike the silver–nylon dressing that can be left untouched on the burn wound for 7 days, SSD needs to be changed twice daily. This implies that in 1 week, a 16 in.\textsuperscript{2} burn wound would need ~300–400 g (one tube) of SSD cream. The acquisition cost of one tube of the SSD cream is twice as much as that of a single 4" × 4" silver–nylon dressing. Additionally, the twice daily changes needed with SSD cream increase indirect costs of nursing resources and medical supplies. Collectively, from cost as well convenience standpoint, the silver–nylon may be a cost-effective option compared with topical antimicrobial agents.

Immediate global evacuation of burn casualties from combat zones though desirable may be prolonged due to operational requirements. Additionally, the threat of nuclear and chemical terrorism has made it necessary to develop disaster plans for mass casualty incidents. Under such scenarios, an antimicrobial dressing that can easily be applied over burn wounds with minimal wound management is highly desirable. The silver–nylon dressing has ~550 mg of silver in each 4" × 4" dressing. Within 24 hours, the dressing releases 9–10\% (52 mg/l) of its silver, which is higher than that needed for an effective and rapid bacterial kill. The residual silver in the dressing provides a sustained release of silver ions, thereby allowing for fewer dressing changes\textsuperscript{7, 37}. The fewer dressing changes per patient facilitate optimal management of medical inventory and nursing resources that are critical during planning of combat medical operations\textsuperscript{38}. The elastic nature of the silver–nylon dressing allows for ease in application over burn wounds in austere situations by responders that may not be formally trained in burn wound management. Although the use of the dressing by nonmedical personnel may increase the risk of excessive compression, we are of the opinion that this risk can be mitigated by imparting minimal education and training as the dressing is user friendly. Unlike topical antimicrobial agents, the silver–nylon dressing comes in different configurations (gloves, rolls), it is light-weight (~3 g) making it easy to store and transport, can endure extreme temperatures without compromising its antimicrobial properties, and has a stable shelf life of 5 years. Together, the aforementioned properties recommend the use of the silver–nylon dressing as a viable burn dressing for combat operations and mass casualty situations.

The retrospective design is a limitation of the study. The lack of a prospectively selected cohort or control group limits the ability to validate the efficacy of the silver–nylon dressing in comparison to other commercially available burn dressings. Although the study only examined combat-related burn injuries, the findings can be extended to civilian burn injuries as well.

**CONCLUSION**

The study demonstrates the efficacy of the silver–nylon dressing as an antimicrobial dressing during global evacuation of burn casualties from combat zones to the military burn center for definitive care. Compared with topical antimicrobial agents, the silver–nylon dressing is lightweight and easy to apply and requires minimal wound management that makes it a viable burn dressing for combat operations and mass casualty situations. The study underscores the need to develop prospective clinical trials to establish the clinical efficacy of the silver–nylon dressing compared with other commercially available burn wound dressings.

**REFERENCES**


Exhibit 6 - Wound Healing & Cost Saving Benefits of NPWT+Silver
ABSTRACT
A 20-patient case series is presented, demonstrating the incorporation of a silver antimicrobial negative-pressure dressing and a negative-pressure wound therapy device for improved healing outcomes, decreased nursing time expenditure, and decreased cost expenditure.

KEYWORDS: negative pressure wound therapy, wound healing and silver, cost savings

INTRODUCTION
The vacuum-assisted closure (V.A.C.) negative-pressure wound therapy (NPWT) system (Kinetic Concepts, San Antonio, Texas) is approved for the management of chronic wounds, acute wounds, traumatic wounds, subacute and dehisced wounds, partial-thickness burns, ulcers (such as diabetic or pressure), and flaps and grafts in multiple settings. Negative-pressure wound therapy is intended to create an environment that promotes wound healing by preparing the wound bed for closure, reducing edema, promoting granulation tissue formation and perfusion, and by removing exudate and infectious material.

The V.A.C. is composed of 3 components that work together to help promote wound healing through granulation tissue formation. It provides intermittent or continuous therapy and promotes wound healing under the negative pressure created. The V.A.C. GranuFoam dressing applies mechanical forces to the wound, which are known as macrostrain and microstrain force. Macrostrain force is the visible stretch that occurs when negative pressure contracts the foam and draws the wound edges together, provides direct and complete wound bed contact, evenly distributes negative pressure, and removes exudate and infectious materials. Microstrain force is also the microdeformation at the cellular level, which leads to cell stretch. Microstrain force also reduces edema, promotes perfusion, and promotes granulation tissue formation by facilitating cell migration and proliferation.

Silver is used in numerous medical products and has broad antimicrobial properties against gram-positive and gram-negative bacteria. In a 30-patient prospective study, Silverlon (Argentum Medical, Geneva, Illinois) antimicrobial negative-pressure dressing (NPD), in combination with a dermal-engineered substitute, appeared to be efficacious in healing diabetic, ischemic, and lower-extremity chronic wounds. The Silverlon NPD is designed to intimately make contact with the wound as a primary dressing and permits the passage of fluids (Figure 1). The Silverlon NPD is indicated for the local management of superficial to partial-thickness burns, partial- to full-thickness wounds, donor and graft sites, acute wounds, lacerations, abrasions, traumatic wounds, surgical wounds, dehisced wounds, Stage I-IV dermal ulcers, pressure ulcers, diabetic ulcers, and venous ulcers. The presence of silver in this dressing when used in combination with NPWT provides an effective protection against microbial contamination and may add to the macrostrain and microstrain force benefits of the promotion of granulation material and decreasing infectious materials, even...
though the Silverlon NPD is between the wound and the NPWT device. This continuation of the benefits of the NPWT in the presence of the Silverlon NPD is because of the thinness and fenestration of the Silverlon NPD. This silver dressing provides broad-spectrum coverage, allowing dressing changes every 5 to 7 days.\textsuperscript{5-9}

**METHODS**

Group 1 consisted of 10 patients with 10 wounds, which were located on the foot (7), leg (1), knee (1), and the back (1). Group 1 had weekly surgical excisional wound debridement with dressing changes consisting of application of NPWT and the Silverlon NPD dressing every 5 days with 4 patients and every 7 days with 6 patients. The combination-dressing changes were decreased from 7 days to every 5 days, based on clinical evaluation and discretion of the treating physician. The sequence of applying the Silverlon NPD with NPWT is illustrated in Figure 2 A-D. The Silverlon NPD is cut to overlap the wound margins by 1 cm and then applied to the wound and held in place as NPWT is applied per standard technique. Group 2 also consisted of 10 patients with 10 wounds, which were located on the foot (7), ankle (1), leg (1), and the knee (1). Group 2 patients experienced weekly surgical excisional wound debridement at dressing changes and application of NPWT every 2 days. For both groups, the time measured in days that the wound was open and the time to closure, patient age, patient A\textsubscript{1c} when applicable, cost of wound care per patient, and the nursing time expended for wound care were recorded.

**RESULTS**

In group 1, the average patient age was 65 years, and 7 of the patients had diabetes, with an average A\textsubscript{1c} of 9.41\%. The wounds were open an average of 70.6 days before initiation of NPWT in combination of the Silverlon NPD. The wounds obtained closure...
on an average of 50.5 days. The average cost associated with wound care for this group was $826 per patient, and the nursing time expenditure per patient for wound dressing changes was 4.3 hours. This information is summarized in Table 1. Patient 2 received this therapy in conjunction with hyperbaric oxygen therapy, demonstrating safety for Silverlon NPD in a hyperbaric oxygen chamber (Figure 2).

In group 2, the average patient age was 64 years, and 8 of the patients had diabetes, with an average A1c of 10.3%. The wounds were open an average of 75 days before initiation of NPWT. Following this therapy, the wounds obtained closure an average of 61.7 days. The average cost associated with wound care in this group was $5181 per patient, and the nursing time expenditure per patient for wound dressing changes was 15.4 hours. Table 1 illustrates these data.

The following were found when comparing group 1 with group 2:
• wounds showing improved healing—70.6 versus 75 days
• fewer NPWT kit changes—on average 1.16 vs 3.5 kits per week
• overall total cost $8260 ($826 per patient) versus $51,814 ($5184 per patient)
• less nursing time—43.46 hours (4.3 hours per patient) versus 154.5 hours (15.4 hours per patient) of NPWT in combination of the Silverlon NPD versus NPWT alone

These statistics are presented in Table 1.

**DISCUSSION**

The protocol for the NPWT at this hospital-based wound care center is application and change every 2 days. When the Silverlon NPD was used in conjunction with the NPWT dressing, the changes decreased to every 5 or 7 days, based on clinical evaluation and discretion of the treating physician. In a 2-week period when the Silverlon NPD with NPWT dressing was changed every 5 days instead of every 2 days for the NPWT alone, there was a decreased frequency of dressing changes of 2.5 from 7. When the Silverlon NPD and NPWT dressing was changed every 7 days at the physician’s office or wound care center, this allowed home healthcare visits for wound care to be suspended. Regardless if the dressing was changed every 5 or 7 days, there were no issues with maintaining the seal and no incidence of significant maceration around the wound bed. In the case presentation that follows, because of these decreased visits in 2 weeks, the patient required 12 home healthcare visits from an estimated 35 nurse visits if NPWT was used alone if the dressing changes were being done every 7 days. This reflects a 66% reduction in home healthcare visits by adding a silver antimicrobial NPD. The total cost expenditure of NPWT in combination with Silverlon NPD compared with NPWT alone demonstrated an 84% reduction in total cost and a 72% decrease in total time expenditure.

In groups 1 and 2, there was no incidence of infection during the treatment. Changing the NPWT dressing every 5 to 7 days did not have any additional noticeable odor than would be expected. Pain was not assessed as 15 of the 20 patients had diabetes, and all had a significant neuropathy and some differing degree of pain sensation loss. Using the Silverlon NPD with NPWT in conjunction with hyperbaric oxygen therapy did not increase the time
needed to dive the patient, as no additional steps were required to place the patient in the hyperbaric chamber.

CASE PRESENTATION
A 91-year-old woman (group 1, patient 10), who did not have diabetes, presented with a painful, chronic infected knee prosthesis with 2 ulcers to deep facial tissue, episodically open for 3 years' duration, and now open for 97 days (Figure 3). To date, the patient had undergone multiple incision and drainage procedures, as well as debridements. The patient was not a candidate to return to the operating room for revision surgery.

Long-term osteomyelitis management had included oral doxycycline, rifampin, and fluconazole. Cultures revealed yeast and Enterococcus faecium. Wound management was initiated with ulcer surgical excisional debridement and application of the NPWT device in combination with the Silverlon NPD, which was placed in apposition to the wounds covered by the NPWT. The addition of the Silverlon NPD decreased NPWT dressing changes from 3 times a week to once a week. This decrease in dressing changes significantly decreased the patient's pain and cost of the wound care.

This patient progressed very well. The 2 ulcers were healed at 70 days after initiation of wound treatment. This patient has had no recurrence of the osteomyelitis or wounds in 2 years (Figure 4). She is functioning well and bearing weight without restrictions.

CONCLUSIONS
This retrospective case series presentation demonstrates the successful management, ease of application, decreased nursing time, and cost savings utilizing NPWT in combination with the Silverlon NPD versus NPWT alone. The Silverlon NPD was easy to apply and well tolerated by the patient. The Silverlon NPD was safe and effective when used with NPWT in the management of diabetic foot ulcers, venous stasis ulcers, ulcers in the presence of osteomyelitis, and upper torso ulcers. In addition, NPWT combined with Silverlon NPD may be used safely with hyperbaric oxygen therapy.

REFERENCES
Exhibit 7 - 2013 Siegel Study Univ. Alabama NPD Study
Silver Negative Pressure Dressing With Vacuum-assisted Closure of Massive Pelvic and Extremity Wounds

Herrick J. Siegel MD, Diego F. Herrera MD, Jason Gay CRNFA

Abstract

Background Massive soft tissue loss involving the pelvis and extremities from trauma, infections, and tumors remains a challenging and debilitating problem. Although vacuum-assisted closure (VAC) technology is effective in the management of soft tissue loss, the adjunct of a silver dressing in the setting of massive wounds has not been as well tested.

Questions/purposes Does a silver negative pressure dressing used in conjunction with a wound VAC decrease (1) the length of acute hospital stay and overall length of treatment; (2) the number of surgical débridements the patients underwent as part of their care; and (3) the likelihood of wound closure without soft tissue transposition?

Methods We evaluated 42 patients with massive (>200 cm²) pelvic and extremity wounds from trauma, infection, or tumor who were treated with the wound VAC alone, and in the final 16 consecutively treated patients, the silver dressing was added to the regimen. We reviewed medical records to determine length of treatment as well as the number and type of surgical interventions these patients underwent. We compared the group treated with the wound VAC alone with those patients treated with the wound VAC and silver negative pressure dressing.

Results Hospital stay averaged 19 days in the VAC only group and 7.5 days in the VAC with silver dressing group (p < 0.041), length of overall treatment averaged 33 days in the VAC only group and 14.3 days in the VAC with silver dressing group (p < 0.022), number of operative débridements averaged 7.9 in the VAC alone group and 4.1 in the VAC with silver dressing group (p < 0.001), and success of wound closure without soft tissue transposition was 16 of 26 patients in the VAC alone group and three of 16 patients in the VAC with silver dressing group (p < 0.033).

Conclusions Based on the reduced length of care and the number of surgical procedures these patients with massive wounds of the pelvis and extremities underwent, we now use the silver negative pressure dressing in combination with the wound VAC as part of routine care of such patients. These results may be used as hypothesis-generating data for future randomized studies.

Each author certifies that he or she, or a member of his or her immediate family, has no funding or commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

Clinical Orthopaedics and Related Research neither advocates nor endorses the use of any treatment, drug, or device. Readers are encouraged to always seek additional information, including FDA-approval status, of any drug or device prior to clinical use.

Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Please note that this study may involve findings that exceed the claims currently cleared by the FDA for the product. The various cleared uses for Silverlon® Dressings can be found in the “Cleared Indications Sheet” found in this information packet. Full prescribing information can be found at: www.silverlon.com/indications or call 1 888-581-0188
Introduction

Massive pelvic and extremity soft tissue loss remains a complex and cumbersome problem. Infection, trauma, and tumors are common etiologies and may result in a prolonged course of treatment resulting from delayed healing, persistent drainage, pain, and other complications [1, 4, 16, 17, 20]. Dressing changes and the need for repeat surgical débridement often result in extensive hospital costs, increased pain, and deconditioning of patients. Soft tissue rotational and free flaps may be used; however, there is often harvest site morbidity, extensive operative time, and prolonged hospitalization [6, 19].

Vacuum-assisted closure (VAC) technology has been shown to be effective in the management of soft tissue loss from infections, vascular insufficiency, radiation-induced soft tissue necrosis, and traumatic disorders [1, 28, 29, 32]. Additionally, the advent of a portable VAC unit allows patients to mobilize earlier and expedites the return to maximal function. It has been shown that bacterial colonization can increase with wound VAC therapy, possibly resulting in delayed or impaired healing [25, 26, 33]. The use of a silver negative pressure dressing in conjunction with the VAC may inhibit the colonization of drug-resistant organisms and sustain early granulation leading to expedited healing [27, 29–31]. There is little evidence that bacteria develop resistance from continuous exposure to silver concentrate [18, 20–24]. Silver has been associated with reduced inflammation and modulation of matrix metalloproteinases in studies regarding the effects on burn patients [10, 15].

SilverlonTM (Cura, Chicago, IL, USA) is a highly concentrated negative pressure dressing that is a knitted fabric material that has been silver-plated by means of a proprietary autocatalytic chemical (reduction-oxidation) plating technique. This technique coats the entire surface of each individual fiber from which the dressing is made, resulting in a very large surface area for the release of ionic silver. Silverlon has been shown to reduce surgical site infection [8, 11]. This technology avoids the deposition of silver crystals in the wound and has not been shown to be cytotoxic or to cause skin discoloration. We are not aware of any prior studies comparing the wound VAC with and without a silver negative pressure dressing in the treatment of massive wounds of the pelvis and extremities. Accordingly, we sought to determine whether a silver negative pressure dressing used in conjunction with a wound VAC decreases (1) the length of acute hospital stay and overall length of treatment; (2) the number of surgical débridements the patients underwent as part of their care; and (3) the likelihood of wound closure without soft tissue transposition.

Importantly, we have studied the use of the VAC before [29]; five patients from that report are included in this report, with additional clinical followup, as part of the control group (the group treated with the wound VAC but without the silver negative pressure dressing).

Patients and Methods

Between January 2003 and January 2010, 42 patients were treated for massive pelvic and/or extremity wounds and were managed with the VAC device (KCI, San Antonio, TX, USA) by one surgeon (HJS). All patients with soft tissue defects > 200 cm² involving the pelvis and/or the extremity that were treated with wound VAC therapy were included. The study group included 28 males and 14 females with an age range of 20 to 72 years (mean, 50 years). In this series, the first 26 patients were treated using the wound VAC alone, and in the last 16 consecutive patients, a SilverlonTM negative pressure dressing was used (Fig. 1).

The most common etiologies of soft tissue loss were infection (22), tumor (14), and trauma (six). Soft tissue infections were associated with a metal implant or prosthesis in 18 of 42 (43%) patients. All metal implants and/or prostheses were removed at the initial débridement. Antibiotic-impregnated spacers were placed during the wound management period. To date, six of the 18 patients with metal implants have undergone a second-stage reimplantation.

Fig. 1 Basic wound VAC and silver negative pressure dressing setup is shown. The silver fabric dressing is placed between the VAC sponge and the wound. It is then sealed with an impervious sticky dressing.
procedure. Twelve of 18 continue to have an antibiotic spacer in place. Eleven patients had a history of local radiation and 12 had a history of immunosuppression from either chemotherapy or organ transplantation. Twenty-two had surgical débridements before referral and 26 patients were on antibiotics before referral. The most common organisms cultured were sensitive Staphylococcus aureus (11), methicillin-resistant S aureus (nine), Enterococcus faecalis (eight), and Staphylococcus epidermidis (seven). Infectious disease consultation was obtained after the initial débridement once initial cultures were obtained.

Before initiation of VAC therapy, débridement of necrotic and/or infected tissue was performed in the operating room (OR) when indicated. In some instances, patients returned to the OR for serial débridements with VAC replacement. The VAC was changed at regular 2- to 3-day intervals for the wound VAC only group and every 7 days in the silver negative pressure dressing subgroup. The current recommendation for wound VAC management is to change the sponge no more than 72 hours because it can be difficult to remove as a result of overgrowth of exuberant granulation tissue. This is particularly important if the VAC dressing is to be performed as an outpatient, because removal after 72 hours may cause bleeding, pain, or retention of a portion of the sponge. A foul smell is also frequently appreciated with the VAC dressing, particularly if it is changed at intervals > 48 hours. The silver negative pressure dressing substantially slows the granulation ingrowth into the sponge and may be left on up to 7 days. The VAC dressings were either changed in the inpatient setting by a physician or as an outpatient by skilled nursing. The VAC change was performed under sterile technique in the OR if débridement was required. Otherwise it was changed in a clean but nonsterile environment either at the bedside or at the patient’s home. Patients were allowed to ambulate with a portable VAC unit and encouraged to do so. Wound measurements were recorded at each VAC change by either a physician or skilled nurse.

Treatment (whether with the wound VAC alone or with the wound VAC plus silver negative pressure dressing) continued until wound healing was accomplished by either primary or secondary intention, skin grafting, or soft tissue transposition. The minimum followup was 12 months (average, 35.3 months; range, 12–96 months).

The surgical technique for the silver dressing application is variable depending on the location and size of the wound. The dressing is a fabric material and easily cut into shapes to fit all wound geometries. It is recommended that the entire open wound be covered by the silver dressing as well as a portion of the surrounding skin. By overlaying the skin, it will protect it from the overlying VAC sponge. This will reduce skin irritation, breakdown, and maceration. The silver fabric dressing does not require fixation to the skin. The sponge is applied over the silver dressing and the application is completed by covering the sponge with an impervious sticky dressing. The wound VAC is then set to 125 mmHg on continuous mode. When removed the suction should be turned off or occluded and the dressing removed as one unit. Complex areas including the perineum, sacrum, and buttock were managed with VAC sponges secured in position with widely spaced circumferential staples and the impervious dressing was adhered to the skin with stoma paste (Convatec, Princeton, NJ, USA [29] (Fig. 2). Minor complications were reported in both VAC alone and silver dressing with VAC groups. As mentioned earlier, five patients were included in this study whose earlier results were published previously [29]. In this report, we extend followup on these five patients by a mean of 32 months (range, 16–45 months). All of these patients were treated in the wound VAC group without silver negative pressure dressings.

Institutional review board approval was obtained and patients gave consent for the use of their medical

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Fig. 2A–B  (A) Photograph of a large fungating mass involving the adductor compartment. The patient was treated with neoadjuvant chemotherapy and radiation followed by wide resection. A wound VAC with silver negative pressure dressing was applied for 3 weeks followed by primary closure. (B) Postoperative photograph showing primarily closed wound after 3 weeks of wound VAC treatment. The incision healed without further intervention.
information for purposes of this study. The parameters evaluated included size of the soft tissue defect, duration of treatment, and patient compliance. Compliance was determined as per home nursing records and patient interview. Student’s t-test and log rank were used to determine statistical significance. Tests were considered significant if the p value was < 0.05.

**Results**

The VAC with silver dressing group had shorter hospitalizations than the VAC only group (Table 1). The hospitalization for the VAC alone group was 19 days (range, 1–31 days) and for the VAC with silver negative pressure dressing 7.5 days (range, 2–22 days; p = 0.022). The average length of hospitalization for all patients was 8.1 days (range, 1–31 days).

The VAC with silver dressing group underwent fewer surgical débridements. The group treated with the VAC alone had 7.9 (range, 3–12) and the group with the VAC with silver negative pressure dressing had 4.1 (range, 2–9; p < 0.001). The average number of surgical débridements for all patients was 5.1 (range, 1–12).

Patients treated with the VAC plus silver underwent fewer soft tissue flaps for coverage (16 of 26 [61.5%] versus three of 16 [19%]; p = 0.024). Skin grafts were used in 11 of 26 (42.3%) patients in the VAC only group; nine of 11 (82%) healed without complication and nine of 16 (56.3%) patients in the silver group had skin grafts; all healed without complication. Twenty-two of 46 (47.8%) patients healed by secondary intention without the need for skin grafting (Fig. 3). Home health records indicated excellent compliance with only two of the 42 (4.7%) patients requesting discontinuation.

Since our previous publication [29], the five patients who were included in that earlier article have had a mean of 32 months additional followup (range, 16–45 months). These patients continue to have close followup for soft tissue sarcoma surveillance. None has been readmitted for wound complications and none has undergone further surgical procedures associated with wound complications.

**Discussion**

The use of silver dressings has gained popularity in recent years [3, 5, 7, 9, 10]. There are several theoretical advantages including an antimicrobial inhibition and enhancement of soft tissue granulation [2, 12–14]. The prevalence of antibiotic-resistant organisms continues to rise; the antimicrobial effect of the local environment may be essential. Silver-resistant organisms have been reported but are extremely rare [27–29]. However, microbial resistance to silver remains somewhat controversial. It appears that silver negative pressure may be successfully used with a reduction of the frequency of dressing changes and reduction of a malodorous smell often reported with the use of wound VACs. The use of silver dressings has been substantiated as an adjunct in complex wounds [18, 20, 22], although it has not been studied in the setting of massive wounds such as those we evaluated. In this report we compared the use of the wound VAC with and without a silver negative pressure dressing in terms of length of care and the frequency with which surgical procedures were needed as part of that care.

This study had a number of limitations. First, because it was not a randomized controlled study, it is possible that some selection bias (among other kinds of bias) affected the decision to use the treatments under study. However, the fact that this was a sequential series should have offset some of the selection bias. It is important to note also that the patients had large soft tissue defects from different etiologies. However, they were comparably sized and all in compromised patients, and the etiologies did not vary over
the course of the study. Related to that, wound characteristics (such as shape), adjuvant therapies, and host factors were not specifically evaluated or controlled; however, the study groups showed no significant differences in terms of immunosuppression, history of radiation, wound location, and size. Additionally, the study groups are relatively small; however, they were sufficiently large to allow us to detect significant differences between them. Finally, because this study involved a comparison of patients treated in two sequential series, the comparisons necessarily were historical. It is possible, if not likely, that other changes to treatments would have come into play during the time period in question, and it is possible, if not likely, that those cotreatments would have tended to inflate the apparent beneficial effects of silver dressings. Changes in hospital and outpatient care patterns likely also influenced issues such as duration of hospitalization over the period of time considered in this study.

To our knowledge, this is the only report of the use of the VAC in conjunction with a silver negative pressure dressing. The addition of a silver negative pressure dressing reduced the length of hospitalization compared with the VAC alone. The frequency in which the wound VAC would have come into play during the time period in question, and it is possible, if not likely, that those cotreatments would have tended to inflate the apparent beneficial effects of silver dressings. Changes in hospital and outpatient care patterns likely also influenced issues such as duration of hospitalization over the period of time considered in this study.

The use of wound VAC technology in conjunction with soft tissue transposition has been previously reported [16, 19, 29]. However, to our knowledge, there have not been prior reports specifically addressing this; however, the inhibition of bacterial colonization by the silver may be a contributing factor [2, 23, 27]. Surgical débridement of necrotic tissue remains an essential component of treatment. Reducing the frequency of VAC dressing changes to weekly in the VAC with silver dressing group may have protected the surgical wound from bacterial colonization during the hospitalization.

Fig. 3A–C  (A) Preoperative photograph of a patient with massive chondrosarcoma recurrence involving the pelvis, perineum, and thigh. Late ischemic/necrotic changes are seen. A hemipelvectomy with perineum/genital resection was performed. (B) Intraoperative photograph after resection. The massive wound was initially managed with a wound VAC with silver negative pressure dressing followed by skin grafting. (C) Postoperative photograph 8 weeks postoperatively from resection. A well-healed skin graft is shown.
cumbrous treatment; however, use of this tool appears to improve wound healing potential. The adjunct use of silver negative pressure appears to reduce the overall duration of care and decrease the likelihood that the patient will have other surgical procedures during treatment.

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References


Exhibit 8 - Epstein study
Infection

Do silver-impregnated dressings limit infections after lumbar laminectomy with instrumented fusion?

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Abstract
Background: Silver has been used to reduce infection for centuries. This study retrospectively analyzed whether the introduction of silver-impregnated dressing (SD; Silverlon, Argentum Medical, LLC, Lakefront, GA) rather than RD (iodine- or alcohol-based swab and dry 4 × 4 gauze) would reduce the risk of superficial or deep infection after lumbar laminectomy with instrumented fusion.

Methods: The first 128 patients had RD applied postoperatively, whereas the second population of 106 patients received SD. These dressings were used for the first 2 weeks after surgery. Other clinical, surgical, and outcome data were comparable for both groups.

Results: Three of 128 patients who underwent multilevel laminectomies with instrumented fusions receiving RD developed deep postoperative wound infections (culture confirmed). All were successfully managed with 6 weeks of postoperative antibiotics, and none required secondary surgery. In addition, 11 patients who had RD developed superficial infection/irritation; 7 required oral antibiotics (7-10 days) alone, whereas 4 were referred to plastic surgeons for superficial wound revision. Alternatively, there were neither deep nor superficial wound infections/irritation among the 106 patients who received SD. Although the number of cases in each series was small, there appeared to be a positive trend toward a reduction in postoperative wound infection using SD.

Conclusions: Use of SD for application on lumbar wounds after laminectomies with instrumented fusions appeared to limit/reduce the incidence of both postoperative deep and superficial wound infections.

Keywords: Superficial infection; Deep infection; Silver-impregnated dressings; Lumbar laminectomy; Instrumented fusions

1. Introduction

Silver has been used for centuries or even thousands of years to counter infection [8,9]. More recently, silver-impregnated wound dressings containing slow-release silver compounds/ions (ie, Ag+) have been used to limit/treat bacterial, yeast, and viral-induced wound infections associated with surgery, burns, trauma, and ischemia [3,8,9]. Here, the relative infection rates using RD vs SD (both for the first 2 postoperative weeks) were compared in 2 populations of patients undergoing lumbar-instrumented fusions. The first group of patients (n = 128) received routine postoperative dressings (RD) defined by the use of either an iodine or alcohol swab with a dry 4 × 4 gauze. The second group of patients (n = 106) received SD (Silverlon, Argentum, Lakemont, Ga).

2. Materials and methods

2.1. Silver-impregnated dressings

Silver, and in particular silver nitrate (AgNO₃), has long been used to control/treat infection [3,8,9]. At the micro-
cellular level, silver ions overturn the transmembranous energy metabolism of bacteria, resulting in a dose-related bacteriostatic or bactericidal reduction of infection [15]. Silver has been effectively used in the laboratory and clinically used to treat such organisms as MRSA and PA [2,10,11,14]. Silverlon dressings have demonstrated activity against microorganisms with 1 to 2 hours of application, and the same dressings continue to show activity for up to 7 days if appropriately cleaned once daily with sterile/clean water alone (eg, no alcohol, iodine, saline) [7].

2.2. Lumbar laminectomies

Two patient populations underwent lumbar laminectomies with posterolateral instrumented fusions (Table 1). The first group, consisting of 128 patients, received RD postoperatively (2 weeks duration). The second group of 106 patients received SD postoperatively (2 weeks duration). Of note, most other clinical and surgical factors were comparable for both groups: average age, neurologic deficits, number of laminectomy/fusion levels, average operative time, average hospital stay, rate of pseudarthrosis/reoperation, average time to fusion, and outcome (Table 1). All patients were fused with the same pedicle/screw instrumentation system (3D, Medtronic).

3. Results

Three of the 128 patients who underwent multilevel laminectomies with instrumented fusions receiving RD dressings developed deep postoperative wound infections with SA. All infections were confirmed based on wound cultures and were corroborated with enhanced MR scans. Major comorbidities for these 3 patients included severe diabetes (1 patient required an insulin pump), hypertension (2 patients), morbid obesity (2 patients), and prior surgery (1 patient). All 3 infections were successfully managed with 6 weeks of postoperative antibiotics, and none required secondary surgery. Enhanced MR studies continued to demonstrate progressive resolution of infection up to 6 months after antibiotic administration. In addition, 11 patients developed superficial wound infection/irritation; 7 were successfully managed with 7- to 10-day courses of oral antibiotics, whereas 4 required superficial plastic surgical wound revisions. Alternatively, none of the 106 patients managed with SD developed deep or superficial wound infections.

4. Discussion

The value of silver in limiting/controlling infection has been known for centuries [3,8,9]. The antimicrobial activity of the silver ion (Ag+) is attributed to its ability to reversibly or irreversibly block (depending on concentration) transmembranous energy metabolism in bacteria [8]. In 1968, silver sulfadiazine (Silvadene, Marion Kansas City, Miss) was introduced as a topical agent to treat wounds and burns [3,8]. Since then, several slow-release silver sulfadiazine–impregnated dressings have become available to treat postsurgical, traumatic, ischemic, and/or burn-related wounds. Three commonly used dressings include the Silverlon (Argentum, Lakemont Ga) used in this series, Acticoat (Smith and Nephew, Largo, Fl), and the Silvasorb (Medline Industries Inc, Mundelein, Ill) [3]. When Heggers et al [3] performed a laboratory study using a Sprague-Dawley rat model for assessing the treatment of burns, they documented that the 3 SD noted earlier equally countered infection, especially those attributed to PA and SA. All infections were confirmed based on wound dressings developed deep postoperative wound infections.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Laminectomy and fusion with RD (128 patients)</th>
<th>Laminectomy and fusion with SD (106 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range)</td>
<td>49.14 (29-75)</td>
<td>49.6 (23-77)</td>
</tr>
<tr>
<td>Men, n</td>
<td>74</td>
<td>51</td>
</tr>
<tr>
<td>Women, n</td>
<td>54</td>
<td>55</td>
</tr>
<tr>
<td>Average laminectomy (range)</td>
<td>3.9 levels (3-6 levels)</td>
<td>3.75 levels (3-6 levels)</td>
</tr>
<tr>
<td>Average levels fused</td>
<td>1.3</td>
<td>1.27</td>
</tr>
<tr>
<td>One level fusion</td>
<td>88</td>
<td>77</td>
</tr>
<tr>
<td>Two level fusions</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Types of fusion</td>
<td>Pedicle/screw*</td>
<td>Pedicle/screw*</td>
</tr>
<tr>
<td>Incidence of deep infections</td>
<td>3 deep wound infections</td>
<td>0</td>
</tr>
<tr>
<td>Treated antibiotics alone</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Treated surgical removal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Incidence of superficial infections</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Treated with antibiotics</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Required plastic surgery</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Fused/fibrous union</td>
<td>124</td>
<td>103</td>
</tr>
<tr>
<td>Average time to fusion, mo</td>
<td>4.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Pseudarthrosis/reoperation</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Obesity</td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>DVT</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Depression</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Outcomes: Odom’s criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent/good</td>
<td>116</td>
<td>97</td>
</tr>
<tr>
<td>Fair/poor</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Average operative time, h</td>
<td>5.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Average hospital stay, d</td>
<td>4.8</td>
<td>4.5</td>
</tr>
<tr>
<td>Average follow-up, y (range)</td>
<td>4.0 (2.25-16)</td>
<td>1.45 (1-2.5)</td>
</tr>
</tbody>
</table>

* Pedicle/Screw (3D; Medtronic, Memphis, Tenn).
healing, reduced pain, and limited the frequency of dressing changes [2-4,8,10,11,13-15]. Silverlon dressings created an effective antibacterial barrier within 1 to 2 hours of application that could be maintained by using the same dressing for up to 7 days (ideally cleaned once a day with sterile water/clean water) [7,5]. Used in a clinical series of burn patients, the Acticoat dressing effectively reduced the incidence of burn wound cellulites and antibiotic use, and was less expensive than Silvazine [1]. One of the rare negative factors observed when using Acticoat in burn patients was an increase in scar formation at skin graft donor sites [6]. Although the numbers of patients presented in the 2 surgical series using RD (128 patients) or SD (106 patients) were small, there appeared to be a “trend” toward a reduction in both deep and superficial wound infections when SD were used. A larger series of patients undergoing multilevel lumbar laminectomies with instrumented fusions should be prospectively analyzed to better determine whether SD significantly reduce the risk of postoperative deep and superficial wound infections.

Acknowledgment

I would like to thank the Joseph A. Epstein Neurosurgical Education Foundation for its support of this work and Ms. Sherry Grimm, administrator of Long Island Neurosurgical Associates for her editorial assistance.

References


Commentary

When I was in training in Neurosurgery the 1960s, my mentor was Eric Oldberg, who was Harvey Cushing’s last single resident. Eric used to recount the tale that Cushing insisted on covering the surgical wound with a thin layer of silver foil in order to prevent infection. He (Cushing) based this concept on finding out from his laboratory technicians that bacteria could not grow on silver doorknobs, which were plentiful at the time and consistently handled so that they were inundated with plenty of bacteria. Oldberg insisted that the technique be assiduously carried out in all cases performed at our department, the Neuropsychiatric Institute. Although the rest of the surgery units in the then Research and Educational Hospitals at the University of Illinois had long since dropped that particular dressing technique, Neurosurgery continued to use the silver foil dressings until Oldberg retired in 1973. No one conducted a study to compare the infection rates between our service and that of the others, but anecdotally, our infection rate was low, consistent with the findings in the current study. As Dr Epstein points out, a prospective study is clearly indicated.

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Exhibit 9 - Mediastinitis Study
A Clinical Trial to Investigate the Effect of Silver Nylon Dressings on Mediastinitis Rates in Postoperative Cardiac Sternotomy Incisions

Roger Huckfeldt, MD, FACS, Clyde Redmond, MD, Debbie Mikkelsen, BSN, Phillip J. Finley, MS, Cindy Lowe, BS, CCRP, and Jennifer Robertson, RN

OSTOMY WOUND MANAGEMENT 2008;54(10):36–41
Exhibit 9- Silver Nylon Dressings on Postoperative Incisions Study
A Clinical Trial to Investigate the Effect of Silver Nylon Dressings on Mediastinitis Rates in Postoperative Cardiac Sternotomy Incisions

Roger Huckfeldt, MD, FACS; Clyde Redmond, MD; Debbie Mikkelsen, BSN; Phillip J. Finley, MS; Cindy Lowe, BS, CCRP; and Jennifer Robertson, RN

Mediastinitis is a rare but serious postoperative complication of cardiac surgery that increases mortality rates, hospital length of stay, and medical costs. A clinical trial was conducted to investigate whether the type of postoperative surgical dressing (silver nylon or standard gauze) affects the rate of mediastinal infections. The sample consisted of 1,600 surgical cardiac patients. Infection rates in the standard gauze group (control, n = 1,235) were collected retrospectively from 24 months of infection control records. In the prospective treatment arm of the study, the wounds of all consecutive surgical patients (n = 365) were covered with a silver nylon dressing and patients were assessed during the 3-week postoperative visit. Thirteen (13) patients in the control group (1%) and none of the patients in the treatment group developed mediastinitis ($\chi^2 \{1, N = 1,600\} = 3.88, P <0.05$). Study findings support the need for a large, prospective, controlled clinical study to confirm the effects of these dressings on mediastinitis, resultant morbidity, and costs of care.

KEYWORDS: silver nylon fabric, mediastinitis, mediastinum infections

Ostomy Wound Management 2008;54(10)36–41

Although uncommon, mediastinitis is a serious postoperative complication associated with many negative outcomes. Methicillin-susceptible *Staphylococcus aureus*, Gram-negative bacilli, and methicillin-resistant *S. aureus* are three strains of bacteria most commonly associated with mediastinitis.1,2 The occurrence of mediastinal infections varies but has been reported to be between .04% and 5.0%.3 Heart transplant patients have the greatest risk for developing mediastinitis when compared to other cardiac procedures, with rates ranging between 2.5% and 6.0%.4 Mortality rates, hospital stays, and medical costs increase considerably for patients who develop this infection.5,6 Mortality rates for patients who develop mediastinitis after undergoing any cardiac procedure increase by an average of 10% to

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Dr. Huckfeldt is Medical Director; Dr. Redmond is a cardiovascular and thoracic surgeon, Ms. Mikkelsen is the Burn Unit Nursing Director, Mr. Finley is a Clinical Research Coordinator, and Ms. Lowe and Ms. Robertson are Clinical Research Associates, St. John's Regional Health Center, Springfield, Mo. Please address correspondence to: Roger Huckfeldt, MD, St. John's Regional Health Center, 1900 S. National, Suite 1950, Springfield, MO 65804; email: rhuckfeldt@sprg.mercy.net.
20% and can be as high as 47%.9 Milano et al,10 after conducting a study involving 6,459 patients undergoing coronary bypass grafting (CABG), report that early debridement and delayed closure can decrease mortality rates to less than 20%. Medical costs and hospital stays have been found to increase with the development of mediastinitis, on average, by $20,00011 and 12.2 days,12 respectively.

Many studies have identified preoperative risk factors that increase the risk of developing mediastinitis. These factors include smoking, obesity, vascular disease, longer stays in the intensive care unit, infections at other sites, diabetes, and hypertension.13-16 Additional studies17'18 have shown the benefits of using different postoperative care techniques to reduce mediastinitis, including incision closure with rigid fixation and the application of topical bacitracin ointment. Song et al18 showed a significant reduction in the incidence of mediastinitis when rigid plate fixation rather than wire-circlage was utilized for sternotomy closure. None of the patients in the prospective rigid plate fixation study group (n = 45) developed mediastinitis compared to 28 cases reported in the retrospective, wire-closed control group. In 2006, MacIver et al17 investigated the impact of topical bacitracin ointment on mediastinitis development in patients who underwent sternotomy incisions for valvar and ischemic heart disease. They compared patients who underwent surgery before 1999 (n = 1,036) who did not receive topical bacitracin to patients treated after 1999 (n = 1,419) who had bacitracin ointment applied to their incisions. The results showed 12 patients in the untreated group and three patients in the treated group developed mediastinitis. These findings suggest topical antimicrobial agents may be an effective method to lower the incidence of mediastinitis.

Silver’s antimicrobial properties have been well documented throughout history. Silver was used by the Roman Empire, American settlers, and the National Aeronautics and Space Administration (NASA) as a method to preserve water purity.19,20 Medical practitioners have utilized silver in advanced wound care for more than 40 years.21 Clinical and laboratory research19-21 has shown silver to be an effective antimicrobial agent against bacteria, viruses, yeast, and fungi. In the 1970s, in vitro studies20'27 demonstrated that silver ions had a broad-spectrum bactericidal profile with favorable outcomes compared to synthetic antibiotics. Wound histology is also different in silver-treated wounds compared to controls. Reporting on the results of porcine wound study, Warriner and Burrell22 noted that wounds treated with silver had active fibroblasts, thicker granulation beds, limited inflammation, and no signs of contracture as compared to control wounds that showed raised edges, edema, and full contracture, which are signs of inflammation. They also found wounds treated with silver healed an average of 10 days faster than control wounds. Wright et al,28 after conducting a porcine study, had similar histology findings, reporting silver-treated wounds displayed more apoptosis and higher levels of fibroblasts, monocytes, and neutrophils compared to controls.

In the early 1980s, silver was plated on nylon fabrics and shown in vitro studies to contain antimicrobial properties.23 Since the initial studies, the antimicrobial benefits of silver-plated nylon dressings have been well recognized in both in vitro and in vivo studies24-32 that demonstrate that silver nylon
fabric inhibits common wound pathogens including *Pseudomonas aeruginosa* and *S. aureus*. A major advantage of silver nylon fabric is its reported ability to continuously release silver ions, providing constant antimicrobial protection.

Silver-containing fabrics are now available for use in the care of partial- and full-thickness burns and acute and chronic wounds. Postsurgical dressings constructed with the same silver nylon fabric are available but data to support outcomes that would justify the associated costs are limited.

The purpose of this study was to compare the incidence of mediastinitis in cardiac surgery patients whose wounds dressed with standard gauze dressings (SGD) (historical control) to the incidence of infection in wounds covered with silver nylon dressings (SND).

**Methods**

**Participants and variables.**

*Silver nylon dressing (study) group.* All consecutive patients receiving CABG or valve replacement procedures (VR) at a southern Missouri tertiary care hospital were considered for enrollment in the study group. Exclusion criteria included patients younger than 18 years of age and patients who were pregnant, incarcerated, and/or enrolled in another clinical study within the past 30 days.

Variables collected included demographics, history of procedure and study compliance, and infection rates. All were recorded with anonymous identifiers, ensuring anonymity and confidentiality.

*Standard gauze dressing (control) group.* Patients who underwent a CABG or VR procedure in previous years and received a SGD were included in the control group. The only variables collected from the 24-month period retrospective review were the number of patients undergoing surgery and whether mediastinitis developed as recorded by the treating physician based on infection control records.

**Materials and design.** The hospital’s Institutional Review Board approved both the retrospective and prospective components of this study. Because all CABG and VR procedures were conducted at the same hospital, each patient received similar pre-operative care. Sternotomy incisions were performed in a similar method and closed with staples and/or vicryl suture. The incisions then were covered with a SND or a SGD. All data for both retrospective and prospective arms of this study were maintained under control of study coordinator in a secure office.

**Dressing application and management in the SND group.** The SND used in this study was Silverlon® Island Dressing (Argentum Medical, LLC, Willowbrook, Ill). This dressing is comprised of fabric with a polymeric substrate surface, silver-plated via a proprietary autocatalytic electroless chemical (reduction-oxidation) plating technique. The dressing releases silver in the ionic (Ag⁺) form and has electrical conductivity of 0.10 ohms/cm². According to the manufacturer, during the first 24 hours, 42.615 ppm or 10% of the total amount of silver is released into the wound. The remaining silver continues to be released until the dressing is removed.

All dressings in this group were left in place for 7 days after surgery unless they became loose or saturated with drainage. Patients discharged before the seventh postoperative day received a new SND and were instructed to leave the new dressing on for 5 days after discharge. After removal, the patients were instructed to use standard postoperative wound care. The incisions were examined by the study coordinator and treating surgeon for signs of infection at the patients’ 3-week follow-up visits.

**Dressing application and management for the SGD group.** Standard procedures in the control group consisted of the application of gauze and abdominal dressing secured with tape. Dressings remained in place for the initial 24 hours after the surgery unless they became saturated. After 24 hours, dressings were changed daily or more frequently as needed depending on drainage.

**Identification of mediastinal infection.** To confirm the diagnosis of a mediastinal infections, all incisions with signs or symptoms of an infection were cultured and evaluated by a surgeon following standard procedure — ie, cultures were collected using standard wound culture protocols and sent to the hospital’s microbiology laboratory for evaluation. A surgeon made the final diagnosis based on culture results and wound appearance in both the retrospective and prospective arms of the study.
A chi-square test for independence was conducted by using a 2 x 2 contingency table analysis. A contingency table representing the distributions of the two nominal variables is presented in Table 1. The type of dressing applied to the wound and the development of mediastinitis were found to be significantly related, Pearson chi² (1, N = 1600) = 3.88, P < 0.05, phi = 0.049. The mediastinal infection rate was 0.0% in the SND and 1.1% in the SGD group.

### Discussion

The cumulative evidence from *in vitro* and *in vivo* research strongly supports an empirical association between silver dressings and antimicrobial benefits. The current study investigated the association of SND and mediastinal infection rates. Although causal inference cannot be made, the actual infection rate was significantly lower than the expected infection rate in the SND treatment arm of this study and a significant relationship between surgical dressing type and the rate of mediastinitis was observed. The rate of mediastinitis in the retrospective control group was within the range of 0.04% to 5.0% reported in the literature, but underreporting in this arm of the study may have occurred. Although many postsurgical dressing are commercially available (some with silver antimicrobial properties), gauze dressings were the standard of care at this institution and continue to be widely used. While no institutional infection control changes were implemented during the study period, the possibility of outside confounds affecting the final results always remains. These study findings support the need for a large, prospective, controlled clinical study to confirm the effects of dressing types on mediastinitis and resultant morbidity.

### Limitations

The study design, including the absence of demographic patient information and the potential of underreporting in the retrospective control group, limits the ability to draw conclusions about the relationship between dressing type and infection rates. A prospective, randomized, multicenter study would...
more accurately be able to identify a causal relationship between dressing type and the rate of mediastinitis, mortality, morbidity and costs of care.

Conclusion

This clinical trial examined whether silver nylon or standard gauze dressings affected the rate of mediastinitis in cardiac surgery patients. Silver nylon dressings were statistically related to lower mediastinitis rates. Conclusions should be drawn with caution because these results support the need for a multicenter, prospective, randomized clinical trial to completely delineate the effects of silver nylon dressings on mediastinal infections.

Acknowledgments

The silver nylon dressings were provided free to the patients and institution by Argentum Medical LLC.

References

20. Lansdown AB. Silver 2: Toxicity in mammals and


Exhibit A -Studies Bibliography
Independent, peer-reviewed, and published clinical studies suggest Silverlon® Dressings can be an important element in wound care, and control of wound bacteria within the dressing may help reduce the risk of infection.

Please note that these studies may involve findings that exceed the claims currently cleared by the FDA for the product. Argentum Medical, LLC is not intending to make performance claims about its product. The intent is to disseminate the scientific literature on these products. We encourage you to read these studies to understand the strengths and limitations of the data. For some claims, Argentum is seeking to broaden the indications with the FDA in the future using data, such as these studies, to provide the substantiation.

Studies are available for download at Silverlon.com/clinical-studies
Surgical

• Use of a Silver Nylon Dressing Following Total Hip and Knee Arthroplasty Decreases the Postoperative Infection Rate
  Authors: Ashley J. Tiosky MD1, Otadade Iyoha-Bello BSc1, Nicholas Demosthenes BA1, Giovanni Quimbayo MD1, Tara Coreanu BSc1, Ayse A. Abeen MD FRCSC1
  1 Department of Orthopaedic Surgery, Harvard Combined Orthopaedic Residency Program, Massachusetts General Hospital, Boston, MA, USA
  2 Department of Orthopaedic Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA
  3 Department of Health Care Quality, Beth Israel Deaconess Medical Center, Boston, MA, USA
  4 Faculty of Health Sciences, Clinical Research Center, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheba, ISRAEL
  5 Department of Orthopaedic Surgery, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA
  Publication: JAACS - journal of the American Academy of Orthopaedic Surgeons

• The Use of Silver Nylon in Preventing Surgical Site Infections Following Colon and Rectal Surgery
  Authors: Beth Krieger MD, Donald M. Davis MD, Jaime E. Sanchez MD, James J. Mateka, Valentine N. Nfonsam MD, Jared C. Frattini MD, Jorge E. Marcet MD
  • Department of Surgery, Division of Colon and Rectal Surgery, University of South Florida, Tampa, FL, USA
  Publication: Diseases Of The Colon & Rectum

• A Clinical Trial to Investigate the Effect of Silver Dressings on Mediastinitis Rates in Postoperative Cardiac Sternotomy Incisions
  Authors: Roger Hussfeld MD FACS, Clyde Redmond MD, Debbie Mikkelson BSM, Philip J. Finley MS, Cindy Lowe BS CCRP, Jennifer Robertson RN
  • St John’s Regional Health Center, Springfield, MD, USA
  Publication: Ostomy Wound Management

• Do Silver-impregnated Dressings Limit Infections After Lumbar Laminectomy with Instrumented Fusion?
  Author: Nancy E. Epstein MD
  • Albert Einstein College of Medicine, Bronx, NY, USA
  Publication: Surgical Neurology

• Left Ventricular Assist Devices: An Innovative Approach to Decrease Infections Using a Silver Contact Dressing
  Author: Joan Lerner Selekof BSN RN CWOCN
  • University of Maryland Medical Center, Baltimore, MD, USA
  • Presented at: Mid Atlantic Region Wound Ostomy and Continence Nurses Annual Conference, 2010

• Healing Chronic, Ischemic, Infected Saphenous Vein Harvest Sites in the Legs with Silver Plated Cloth and Allograft Dermal Regenerative Matrix
  Authors: Stanley Carson MD FACS, Eric Travis DPM, Carol Ajifu PT, Diana To MPT

• Silver-Based Dressings for the Reduction of Surgical Site Infection: Review of Current Experience and Recommendation for Future Studies
  Authors: Elia Charbel Abboud MD, Judson C. Settle MD, Timothy B. Legare MD, Jorge E. Marcet MD, David J. Barillo MD, Jaime E. Sanchez MD
  • University of South Florida, Tampa, FL, USA
  Publication: BURNS: The Journal of the International Society of Burn Injuries

Silver In Medicine

• Silver In Medicine: A Brief History BC 335 to Present
  Authors: David J Barillo MD FACS FACC1, Jorge E. Marcet MD FACS FASCRS1
  1 Department of Surgery, University of South Florida, Morsani College of Medicine, Tampa General Hospital, Tampa, FL, USA
  Publication: Journal of Intensive Care Medicine 1-6

• Silver Negative Pressure Dressing With Vacuum-assisted Closure of Massive Pelvic and Extremity Wounds
  Authors: Herrick J. Siegel MD, Diego F. Herrera MD, Jason Gay CRNP
  • University of Alabama at Birmingham (UAB), Birmingham, AL, USA
  Publication: Clinical Orthopaedics and Related Research

• Wound Healing and Cost-Saving Benefits of Combining Negative-Pressure Wound Therapy with Silver
  Authors: Jeffrey C. Karr DPM, Fernando Loret de Mola MD, Tri Pham MD, Leslie Tooke RN
  • The Wound Care Center at Lakeland Regional Medical Center, Lakeland, FL, USA
  Publication: Advances in Skin & Wound Care

Negative Pressure Wound Therapy

• Reduction in Central Line-Associated Bloodstream Infections Correlated With the Introduction of a Novel Silver-Plated Dressing for Central Venous Catheters and Maintained for 6 Years
  Authors: Rachel Karinozi PKD1, Elia Charbel Abboud MD1, Peggy Thompson BSN CIC FAIPC1, Asa Z. Oxner MD1, John T. Sinnott, MD FACP2, Jorge E. Marcet MD FACS FASCRS3
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  3 Department of Internal Medicine, University of South Florida, Morsani College of Medicine, Tampa, FL, USA
  Publication: Journal of Intensive Care Medicine 1-6

Central Line Catheter

• Non-Inferiority of a Novel Silver-Plated Dressing for Central Venous Catheters: A Retrospective Cohort Evaluating Rates of Central Line-Associated Bloodstream Infections in Adult Intensive Care Patients
  Authors: Aa Donyer MD, Andrew Myers MD, John Sinnott MD, Jorge Marcet MD, Jillian Sajdak, Peggy Thompson BSN CIC, Charles Myers
  • U. of South Florida College of Medicine, Tampa General Hospital, Tampa, FL, USA
  • Presented at: Infectious Disease Society of America Annual Conference, 2011