# EFFICACY OF MEPILEX® AG VERSUS XEROFORM® AS A SPLIT-THICKNESS SKIN GRAFT DONOR SITE DRESSING: BAD HABITS DIE HARD

## *COMPARAISON DE MEPILEX AG® ET XÉROFORM® POUR LE PANSEMENT DES SITES DONNEURS DE GREFFE: DIFFICILE DE SE DÉPARTIR DES MAUVAISES HABITUDES*

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**SUMMARY**. Autografting with split-thickness skin grafts (STSG) remains an essential procedure in burn and reconstructive surgery. The process of harvesting STSG, however, leaves behind a donor site, an exposed area of partial-thickness dermis left to heal by secondary intention. There has yet to be a consensus amongst surgeons regarding optimal management of the donor site. The ideal donor site dressing is one that allows for expeditious healing while minimizing pain and infection. Despite numerous studies demonstrating the superiority of moist wound healing, many surgeons continue to treat STSG donor sites dry, with petroleum-based gauze. In this study, two burn centers performed a retrospective review of burn patients whose STSG donor sites were treated with either Xeroform® or Mepilex® Ag dressings. Infections were documented and in a subgroup analysis of patients, postoperative pain scores were noted and total opiate usage during hospitalization was calculated. Analysis revealed an overall infection rate of 1.2% in the Mepilex® Ag group and 11.4% in the Xeroform® group ($p<0.0001$). Patients with Xeroform® donor site dressings had increased odds of donor site infection (OR=10.8, $p=0.002$). In subgroup analysis, there were no significant differences in maximum pain scores between Mepilex® Ag and Xeroform® groups, nor were there differences in opiate usage. STSG donor sites dressed with silver foam dressings have a lower rate of donor site infection relative to those dressed with petroleum-based gauze. Moist donor site dressings such as foam dressings (including Mepilex® Ag) should be the standard of care in STSG donor site wound care.

**Keywords**: split-thickness skin graft, autograft, burn, donor site, donor site infection, donor site dressing

***RÉSUMÉ.*** *La greffes de peau mince (GPM) demeure une procédure essentielle dans la chirurgie de brûlure et de reconstruction. La zone donneuse de greffe (ZDG) représente une perte de substance cutanée superficielle, cicatrisant spontanément. Il n'y a pas de consensus concernant la prise en charge optimale de la ZDG. Le pansement idéal de la ZDG doit promouvoir la cicatrisation et réduire la douleur ainsi que le risque infectieux. Malgré les nombreuses publications montrant l'intérêt d'un environnement humide pour la cicatrisation, de nombreux chirurgiens réalisent des pansements secs vaselinés. Cette étude rétrospective effectuée dans 2 CTB compare les pansements de ZDG réalisés au Xéroform® ou au Mepilex Ag®. Les infections ont été documentées et, dans un sous-groupe, les scores de douleur et la consommation d'opiacés au long de l'hospitalisation ont été notés. Les taux d'infection sont de 1,2% dans le groupe Mepilex Ag® et 11,4% avec Xéroform® ($p<0,0001$). Le risque d'infection de la ZDG est augmenté (OR 10,8 ; $p = 0,002$) en cas d'utilisation de Xéroform®. Il n'y avait pas de différence de douleur et de consommation d'opiacés entre les 2 groupes. Les ZDG recouvertes d'un pansement hydrocellulaire imprégné d'argent s'infectent moins que celles traitées avec une gaze imprégnée de vaseline. L'utilisation sur les ZDG d'un pansement humide comme une mousse hydrocellulaire (par exemple Mepilex Ag®) devrait devenir la norme.*

***Mots-clés:*** *greffe de peau mince, autogreffe, brûlure, site donneur, pansement, infection*

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Manuscript: submitted 12/02/2022, accepted 01/03/2022

## Introduction

Autografting with split-thickness skin grafts (STSG) remains a core and essential procedure in burn and reconstructive surgery. The process of harvesting STSG, however, leaves behind a donor site, an exposed area of partial-thickness dermis left to heal by secondary intention. The STSG donor site is a standardized, sterile, partial-thickness wound that provides an abundance of information as it serves as a good model for the healing of any partial-thickness wound. The management of this donor site varies between surgeons, and there has yet to be a consensus regarding optimal management of the site. Early dressing methods used gauze but were noted to be inferior to vapor permeable clear adhesive dressings with respect to rate of healing, donor site pain, and infection rate.[1-3] Gauze dressings were found to be more painful and often sheared off new epithelium upon removal.[4] Unfortunately, clear adhesives are impractical in the setting of large donor sites, as uncontrolled leakage and little room for adhesion around the borders of the wounds makes them fail as effective dressings.

Dressings for STSG donor sites are broadly categorized as "dry" and "moist," though the degree of moisture in reality must be maintained at an appropriate level to avoid maceration. Dry dressings include saline-moistened gauze, petroleum gauze, and Xeroform® petroleum-based gauze (Covidien, Dublin, Republic of Ireland). Moist dressings include clear adhesive drapes and a variety of foams, hydrocolloids, and alginates.[4] While existing research on donor site dressings is highly variable, one general consistency is the superiority of moist dressings over non-moist dressings, especially with regard to healing time and pain control.[4-11] Moist wound dressings have been shown to effectively stimulate re-epithelialization and reduce the formation of scars compared to dry dressings.[12] In 1962, George Winter demonstrated this concept in his experiments that compared epithelialization rates of dry and moist wounds in a porcine model.[13] The provision of a moist wound environment also allows for the delivery of bioactive substances such as antimicrobials, which can, in turn, prevent infection and promote healing.[12] One large systematic review suggested moist dressings are superior to dry ones with respect to infection rate, while another suggested there is no clear difference.[10,11] These systematic reviews are inherently limited because few studies of STSG donor sites record or have an explicit definition of donor site infections. There is the rare study that suggests superiority of dry dressings, which are certainly less expensive than many of the more novel moist dressings.[14] Among moist dressings such as transparent films and foam dressings, the optimal dressing is less clear.[15-18]

To date, there has been limited research focused on antimicrobial dressings versus non-antimicrobial dressings and the rate of infection of the STSG donor site. Silver-containing Aquacel hydrofiber dressing has been compared to paraffin gauze, but no infections were noted in either group.[7] A large study comparing five different dressing types noted the highest rate of infection with Bactigras®, a paraffin gauze dressing with chlorhexidine (Smith & Nephew, London, UK), but did not find significant differences in the infection rate between other antimicrobial and non-antimicrobial dressings.[18]

In 2010, the standard of care for treatment of STSG donor sites at the Massachusetts General Hospital (MGH) Sumner Redstone Burn Center was petroleum-based gauze. This type of dressing proved difficult to remove and resulted in patient-reported pain as well as erythema leading to treatment with antibiotics in many cases. A change in practice was introduced in 2013 in order to address these problems. Xeroform® was replaced with Mepilex® Ag (Molnlycke, Gothenburg, Sweden), an antimicrobial silver foam dressing.

Mepilex® Ag is a medicated foam dressing that contains silver sulfate particles that release silver ions when the foam is exposed to fluid.[19] These silver ions possess antimicrobial properties that can destroy the bacterial cell wall and impede cellular processes such as respiration, nutrient absorption and processing, and cell division, all of which are necessary for bacterial cell survival.[19] Bactericidal activity begins within 30 minutes of dressing placement and the dressing can be worn effectively for up to seven days.[19] While the removal of Xeroform® often proves to be a difficult task involving pain and discomfort for the patient, impregnated dressings such as Mepilex® Ag have been shown to be less painful.[20]

The many studies comparing myriad donor site dressings perhaps underplay some of the other important factors that affect infection rates and healing of STSG donor sites. As always, a patient's health is a crucial aspect of healing any surgical wound. In elderly patients, "back-grafting" the donor site accelerates healing and decreases morbidity associated with this site relative to petrolatum gauze dressings.[21.] Finally, the quality of nursing care, the management and changing of dressings, and the overall attention paid to donor site wounds remain largely subjective and difficult to study with any degree of resolution.

## Materials and methods

*Patient enrollment*

Patients who were treated in the Michigan Medicine Burn Center for burn injuries between January 1 and December 18, 2017 were included in the study under IRB HUM00151530. Two hundred and twelve consecutive patients with burn injuries were treated; we excluded patients with frostbite, Stevens-Johnson syndrome/toxic epidermal necrolysis, necrotizing fasciitis, and staphylococcal scalded skin syndrome. Of these patients, 86 underwent autografting with STSG. STSG donor sites were managed with either Xeroform® or Mepilex® Ag. The choice of donor site dressing was dependent entirely on the attending burn surgeon; of the three burn surgeons, one used Mepilex® Ag for all of his donor sites while the other two used Xeroform® exclusively.

At MGH, an IRB-approved (2016P002014) retrospective review was performed on two groups each consisting of consecutive burn patients who had undergone split thickness skin grafting and whose donor sites were managed with either Xeroform® or Mepilex® Ag. The first group included 135 patients whose donor sites were covered with Xeroform® between 2010 and 2012, and the second group consisted of 135 patients who were treated with Mepilex® Ag between 2014 and 2017. The calendar year 2013 was not included in analysis as it was a time for practice transition at MGH. Patients were matched for burn size of up to 20% total body surface area (TBSA). Peri-operative prophylactic antibiotics were routinely given to all patients. The primary outcome variable was donor site cellulitis. Demographic data such as age and BMI were also assessed to determine if these characteristics were associated with infection rate.

Donor sites were cared for according to standard unit policies. At Michigan Medicine, donor sites dressed with Xeroform® were typically wrapped in dry gauze immediately postoperatively for one day, then left open to air to desiccate. Heating lamps are not used to accelerate the drying of these dressings out of concern for causing iatrogenic burns. Mepilex® Ag on donor sites was changed once on postoperative day 1 due to the degree of leakage from these dressings, then typically left in place until the donor site was healed. Occasionally the dressing was changed again in clinic if it had become soiled. At MGH, Xeroform® dressings were managed in the same manner as those at the Michigan Medicine Burn Center. Donor site Mepilex® Ag dressings were covered with Kerlix™ gauze and ACE™ wrap for the first five to seven days. The dressings were then taken down and replaced for another five to seven days, after which the donor sites were covered with Bacitracin and Adaptic™.

*Clinical incidence of infection*

Infections were noted subjectively, recorded, and treated appropriately. Infections were counted for any patients who had documented cellulitis at the donor site or anyone who was started on antibiotics at the time of the first dressing takedown with reference to donor site cellulitis or infection in the patient record. Subjective findings were augmented with documented fever, leukocytosis, and other data consistent with infection in the absence of another documented reason for such findings. Donor site infections were treated by discontinuing the original donor site dressings, initiating systemic antibiotics, and applying antimicrobial dressings, typically consisting of silver sulfadiazine, to the infected donor site.

*Clinical assessment of postoperative pain*

As donor site pain is another significant factor in choosing the optimal donor site dressing, we examined pain metrics to ensure that the Mepilex® Ag dressing is not more painful than standard Xeroform® dressings. Analysis of the Michigan Medicine

Burn Center patients was performed to assess their degree of pain as a function of donor site dressing. Maximum pain scores on a 10-point scale were recorded by nursing on postoperative days 1, 3 and 5 for the included patients. Pain scores for children under age 7 were recorded using a 10-point FLACC scale. Verbal pain scores and other pain scoring systems were not included out of concern for inconsistency between patients reporting such scores and nurses recording such scores. Total amount of all opiate pain medications administered during hospitalization was obtained from the medical records. These medications and their dosages were converted to their oral morphine milligram equivalent (MME) dose and each of these values for all medications were added together for all patients.

*Statistical analysis*

The incidence of donor site infection in the petroleum-based gauze and silver foam dressing groups was compared using unadjusted chi-square analyses. Pain scores, opiate use totals, and demographic covariates were compared using t-tests. Multivariate logistic regression analysis was performed for odds of donor site infection as a function of donor site dressing, age, and percent TBSA using JASP (JASP Team [2019]. JASP [Version 0.9.2]. Amsterdam, Netherlands).

*Microbiological studies*

Quantitative bacterial cultures were collected from one of the patients at Michigan Medicine Burn Center who sustained a donor site infection. The bacteria grown from the cultures were plated on agar at concentrations of $1x10^8$, $1x10^6$, and $1x10^4$ organisms/mL. Pieces of either Mepilex® Ag or Xeroform® were placed on the agar, and zones of inhibition were documented. The agar from directly under the dressing materials was then itself cultured using a culture swab, which was plated on agar for growth.

## Results

*Clinical results*

Of all of the patients treated with STSG autografting at the Michigan Medicine Burn Center, 37 patients (43%) had donor sites dressed with Mepilex® Ag and 49 patients (57%) had donor sites dressed with Xeroform®. The mean age of the Mepilex® Ag group was not significantly different from that of the Xeroform® group (34.6 years vs. 34.4 years, p=0.98). Gender was not different between the groups as well, with 35% of the Mepilex® Ag group and 33% of the Xeroform® group being female (p=0.8). The percent TBSA was somewhat less in the Mepilex® Ag group than in the Xeroform® group (6.8% vs. 10.4%, p=0.03). Of the patients whose donor sites were dressed with Mepilex® Ag, none (0%) had donor site infections. Of those patients whose donor sites were dressed with Xeroform®, five patients (10%) had donor site infections. The difference was statistically significant (p=0.03). Results are summarized in *Table I*.

**Table I** - Incidence of donor site infection, percent total body surface area burned, hospital length of stay, age, and percent female gender between Mepilex® Ag and Xeroform® groups at Michigan Medicine Burn Center.

| | Infections | % TBSA | Hospital LOS (days) | Age (years) | % Female |
|---|---|---|---|---|---|
| **Mepilex Ag** | 0/37 | 6.8 | 11.4 | 34.6 | 35.1% |
| **Xeroform** | 5/49 | 10.4 | 13.3 | 34.4 | 32.7% |
| **p-value** | 0.03 | 0.03 | 0.37 | 0.98 | 0.81 |

%TBSA = Percent of total body surface area; LOS = Hospital length of stay in days; % Female = Percent female gender

The study conducted at MGH reviewed 135 patients whose STSG donor sites were treated with Xeroform® and 135 patients whose STSG donor sites were treated with Mepilex® Ag. There was no association between infection rate and age, burn size, or comorbidities. Sixteen of the patients (11.9%) in the Xeroform® arm had a donor site infection and two patients (1.5%) in the Mepilex Ag® arm had a donor site infection. The difference was statistically significant ($p < 0.001$). Of note, the Xeroform® and Mepilex® Ag groups were similar in age (47.7 vs. 48.2 years, P=0.83), mean BMI (28.8 vs. 28.4, p=0.65), and mean percent TBSA (9.8% vs 9.3%, p=0.33). Results are summarized in *Table II*.

In our combined analysis, two of the 173

**Table II -** Incidence of donor site infection, mean age, mean BMI, and percent total body surface area burned for Mepilex® Ag and Xeroform® groups at Massachusetts General Hospital

| | Infections | Age (years) | BMI | % TBSA |
|---|---|---|---|---|
| **Mepilex Ag** | 2/135 | 48.2 | 28.4 | 9.3 |
| **Xeroform** | 16/135 | 47.7 | 28.8 | 9.8 |
| **p-value** | 0.0006 | 0.83 | 0.65 | 0.33 |

BMI = Body mass index; %TBSA = Percent of total body surface area

Mepilex® Ag patients experienced infections while 21 of the 184 Xeroform® patients did (1.2% vs 11.4%, p<0.0001). Patients in the two groups were similar in age (44.2 years in the Xeroform® group vs. 45.3 years in the Mepilex® Ag group, p=0.61), but the Mepilex® Ag patients had a somewhat lower mean percent TBSA compared to the Xeroform® group (8.8% vs 10.0%, p=0.03). Results are summarized in *Table III*.

**Table III -** Incidence of donor site infection, mean age, and percent total body surface area for Mepilex® Ag and Xeroform® groups in combined analysis including Michigan Medicine and Massachusetts General Hospital patients

| | Infections | Age (years) | % TBSA |
|---|---|---|---|
| **Mepilex Ag** | 2/172 | 45.3 | 8.8 |
| **Xeroform** | 21/184 | 44.2 | 10.0 |
| **p-value** | 8.45E-05 | 0.61 | 0.03 |

BMI = Body mass index; %TBSA = Percent of total body surface area

Multivariate logistic regression was performed for donor site infection as a dependent variable as a function of donor site dressing, increasing age in years, and increasing percent TBSA. Xeroform® donor site dressing was found to be associated with increased odds of donor site infection (OR=10.8, p=0.002). Age and percent TBSA were not found to be associated with increased odds of donor site infection (OR=1.0, p=0.61 and OR=0.98, p=0.63, respectively).

*Subgroup pain analysis*

In the subgroup analysis of pain scores, the mean recorded pain scores on postoperative days 1, 3 and 5 were not significantly different between the Mepilex® Ag and Xeroform® groups. Mean pain scores were 7.0 vs 6.8 (p=0.7) on postoperative day 1; 6.3 vs 6.2 (p=0.8) on postoperative day 3; and 5.7 vs. 5.8 (p=0.9) on postoperative day 5 (*Fig. 1*). Pain scores were not significantly different between those patients who sustained infection and those who did not.

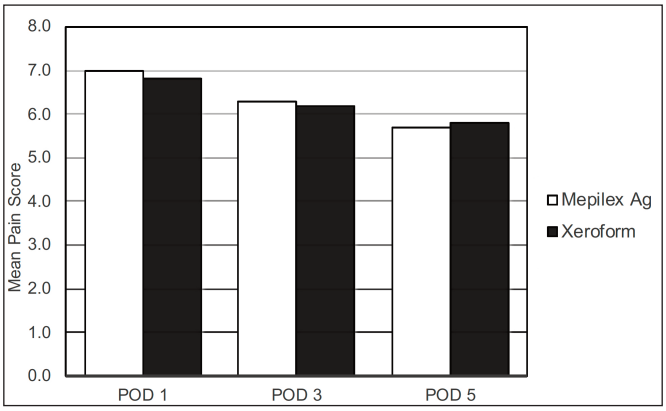


**Fig. 1 -** Mean postoperative pain scores on postoperative days (POD) 1, 3 and 5 on a patient-reported 0-10 scale. Differences between groups did not achieve statistical significance (p>0.05)

In the subgroup analysis, total in-hospital opiate usage did not differ between the Mepilex® Ag and Xeroform® groups (1283 MME vs. 883 MME, p=0.2). Opiate usage per day trended higher in the Mepilex® Ag group compared to the Xeroform® group, but this did not achieve statistical significance (128.45 MME/day vs. 73.34 MME/day, p=0.07, *Fig. 2*). Opiate usage trended higher in the Xeroform® patients who sustained infection versus those who did not, but this difference fell short of statistical significance (1461 MME vs. 817 MME, p=0.07).

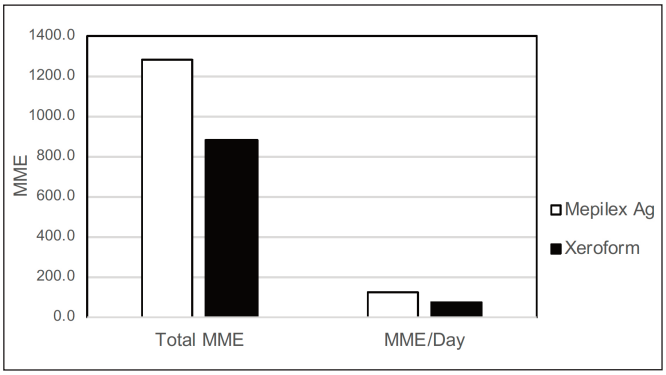


**Fig. 2 -** Mean total hospital opiate use (total morphine milligram equivalent, or Total MME) and mean opiate use per day (MME/day) in Mepilex® Ag vs. Xeroform® groups. Differences between groups did not achieve statistical significance (p>0.05)

This difference was found to decrease when MME per day was examined (103.52 MME/day vs. 69.91 MME/day, p=0.4).

*Microbiological results*

At all three concentrations of $1x10^4$, 1x106, and $1x10^8$ organisms/mL, we observed inhibition of growth beneath the piece of Mepilex Ag® placed on the culture plate, but no clear zone of inhibition beneath the Xeroform®.

Culture swabs from beneath the pieces of Xeroform®, plated on agar, demonstrated full growth of the previously isolated *Staphylococcus* and Gram-negative rod species at all concentrations of initial culture. The swabs from beneath the Mepilex Ag®, however, demonstrated no growth of the Gram-negative rod. There was no growth of the *Staphylococcus* species from beneath the Mepilex Ag® placed on the $1x10^6$ dilution, and only a few colonies of *Staphylococcus* developed from the swab beneath Mepilex Ag® placed on the $1x10^8$ dilution plate.

## Discussion

In patients undergoing STSG autografting for burn management or reconstruction, donor sites dressed with silver-based foam dressings are associated with fewer donor site infections than those dressed with petroleum-based gauze dressings. This may be due to the inherent antimicrobial activity of ionic silver compared to the lack of *in vivo* antimicrobial activity of plain petrolatum or Xeroform® (petrolatum with bismuth tribromophenate). It may also be due to the faster epithelialization of moist versus dry dressings, though we did not measure the rate of re-epithelialization in this study and are thus left to speculate about this. In addition, the difference in infection rate could be due to differences in how nursing and overall wound care are applied in these two dressing regimens. While hospital length of stay was not significantly different between groups, it trended toward longer stays with Xeroform patients®. In specific instances, a donor site infection did prolong patients' hospitalizations and expose them to additional antibiotics and dressing changes.

In addition to possessing antimicrobial properties, the ideal dressing for treating wounds is one that provides a moist wound environment. In comparison with dry conditions, a moist wound environment has been shown to decrease the duration of dermal repair in both the inflammatory and proliferative phases in a porcine model.[12] Moist healing conditions have also demonstrated a greater rate of revascularization and more organized angiogenesis compared to dry environments.[22] In 1962, George Winter utilized a porcine model to examine the rates at which dry and moist wounds underwent epidermal regeneration. Winter's experiments revealed a significantly faster rate of epithelialization for moist wounds compared to dry wounds.[13] In dry wounds, a scab can form and incorporate into the original surface of the wound, above the new epidermis that forms. This can impede wound closure and cause some of the dermis to become part of the scab.[13] The prevention of scab formation, as seen in a moist wound environment, can allow for an increased rate of epithelialization and for the new epidermis to form above the original wound surface.[13] The faster regeneration of epidermis can also aid in earlier formation of new connective tissue underneath.[13]

We recognize that there are limitations to this retrospective study. The decision to use petroleum-based or silver foam dressings was not truly randomized. In the Michigan Medicine group, this limitation was due to the fact that Michigan Medicine burn surgeons rotate through a schedule with roughly even numbers of weeks on call, and the decision regarding donor site dressing is based entirely on the burn surgeon on call in a given week. In the MGH group, the lack of randomization was due to the shift in practice between the 2009-2012 cohort and the 2014-2017 cohort.

The documentation of infection is somewhat subjective, though the infections noted were quite clinically clear and unambiguous. Our analysis of pain in these patient groups, which was a secondary endpoint of interest, was not with a large enough cohort to ascribe superiority to one dressing over the other, but we did not show that pain was appreciably worse in the Mepilex® Ag group than in the Xeroform® group.

The effect of nursing care in maintaining a clean donor site without excessive leakage or moisture is difficult to quantify in a study setting and may in fact play a significant role in preventing donor site infection.

Finally, we did not include rate of re-epithelialization in this study because it was not explicitly and consistently recorded in the chart and thus available for retrospective analysis. There are already numerous studies that have demonstrated improved rates of re-epithelialization using moist wound care versus dry wound care.[1-13] Furthermore, our primary endpoint of infection status is relevant to wound healing because infection can lead to a donor site progressing to a full-thickness wound.

With respect to the antimicrobial activity of the different dressing materials, there is likely a difference in efficacy between Xeroform® and ionic silver compounds such as those found in Mepilex® Ag and other silver foam dressings. Xeroform® gauze has remained the standard of care for open STSG donor site management for decades. The dressing is composed of petroleum-based gauze with 3% bismuth tribromophenate. While Xeroform® has been commonly presumed to have antimicrobial activity in a wound site, a recent study shows that it does not have antimicrobial activity against common burn pathogens *in vitro* on culture plates, which aligns with our research findings.[23] The same study showed better antimicrobial activity of other bismuth preparations, including bismuth subsalicylate and bismuth tribromophenate not bound to Xeroform® gauze.[23] Each material was tested against 15 common pathogens found in burns; while bismuth subsalicylate and bismuth tribromophenate both possessed some antimicrobial efficacy, the experiment performed with Xeroform® showed no antimicrobial activity.[23] In one large study comparing multiple silver-containing wound dressings against common burn pathogens, all of the silver-containing dressings effected bactericidal activity against common burn pathogens, albeit with different spectra of activities.[24] The differences in infection observed in our study may reflect the superiority of silver compounds over Xeroform®-bound bismuth tribromophenate, and may also illustrate the efficacy of silver foam dressings against the specific bacteria commonly encountered in our respective burn units.

## Conclusion

Our research described here strongly suggests the superiority of Mepilex® Ag over Xeroform® in mitigating donor site infection, a dreaded complication. Our study stands among many others, cited in this paper, that strongly suggest the superiority of moist wound dressings over dry ones. The standard practice of dry donor site dressings such as Xeroform® should be abandoned. Moist donor site dressings such as foam dressings (including Mepilex® Ag) should be the standard of care in STSG donor site wound care.

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*Ethics approval and consent to participate.* The study protocol was approved by the Institutional Review Board of Michigan Medicine (IRB No. HUM00151530. 212) and the Institutional Review Board of Massachusetts General Hospital (IRB No. 2016P002014). Patients received information during their hospital stay that data abstracted from their medical charts could be used for research purposes.
*Availability of data and materials.* The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
*Competing interests.* All authors declare no competing interest for this work.
*Funding.* This study was not supported by any funding or grant.