

An Inexpensive Bismuth-Petrolatum Dressing for Treatment of Burns

Arhana Chattopadhyay, BA*†
 Kathleen Chang*†
 Khoa Nguyen*†
 Michael G. Galvez, MD*†
 Anais Legrand, MD*†
 Christopher Davis, MD*†
 Rory McGoldrick, MBBS,
 MBA*†
 Chao Long, BA*†
 Hung Pham, BS*†
 James Chang, MD*†

Background: Xeroform remains the current standard for treating superficial partial-thickness burns but can be prohibitively expensive in developing countries with prevalent burn injuries. This study (1) describes the production of an alternative low-cost dressing and (2) compares the alternative dressing and Xeroform using the metrics of cost-effectiveness, antimicrobial activity, and biocompatibility in vitro, and wound healing in vivo.

Methods: To produce the alternative dressing, 3% bismuth tribromophenate powder was combined with petroleum jelly by hand and applied to Kerlix gauze. To assess cost-effectiveness, the unit costs of Xeroform and components of the alternative dressing were compared. To assess antimicrobial properties, the dressings were placed on agar plated with *Escherichia coli* and the Kirby-Bauer assay performed. To assess biocompatibility, the dressings were incubated with human dermal fibroblasts and cells stained with methylene blue. To assess in vivo wound healing, dressings were applied to excisional wounds on rats and the rate of re-epithelialization calculated.

Results: The alternative dressing costs 34% of the least expensive brand of Xeroform. Antimicrobial assays showed that both dressings had similar bacteriostatic effects. Biocompatibility assays showed that there was no statistical difference ($P < 0.05$) in the cytotoxicity of Xeroform, alternative dressing, and Kerlix gauze. Finally, the in vivo healing model showed no statistical difference ($P < 0.05$) in mean re-epithelialization time between Xeroform (13.0 ± 1.6 days) and alternative dressing (13.5 ± 1.0 days).

Conclusions: Xeroform is biocompatible, reduces infection, and enhances healing of burn wounds by preventing desiccation and mechanical trauma. Handmade petrolatum gauze may be a low-cost replacement for Xeroform. Future studies will focus on clinical trials in burn units. (*Plast Reconstr Surg Glob Open* 2016;4:e737; doi: 10.1097/GOX.0000000000000741; Published online 13 June 2016.)

Burn injuries worldwide are a significant cause of both mortality and morbidity, with 265,000 deaths and 11,271 lost disability-adjusted life

years seen in 2004.¹ Moreover, 90% of burn injuries occur in low- and middle-income countries (LMICs), with at least half in Southeast Asia alone, due to overcrowding, the use of traditional cooking practices, flammable clothing, and domestic combustibles. Children under 5 years are most vulnerable to burn injuries, and millions of burns survivors must cope with lifelong disabilities and contracture deformities due to lack of adequate and timely wound care resources.² In LMICs, access to adequate burn care is limited by both lack of healthcare infrastructure and prohibitive costs of available treatment.³⁻⁵ A

From the *Division of Plastic and Reconstructive Surgery, Stanford Health Care, Stanford, Calif.; and †Division of Plastic and Reconstructive Surgery, Veterans Affairs Palo Alto Health Care System, Palo Alto, Calif.

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cost analysis of a hospital in Turkey revealed that the mean cost for treating victims of flame burn was US \$368 per 1% burn surface area; furthermore, although intensive care unit care was the most significant cost driver (27%), dressings constituted 15% of the cost of care.⁶

Specifically, partial-thickness burns require frequent and expensive changes of moisture-retaining antimicrobial dressings.³ Without dressings, burns are more susceptible to infections, desiccation, trauma, and delayed epithelialization, thereby causing progression to deep partial- or full-thickness burns.⁷⁻⁹ The treatment of choice for superficial partial-thickness burns, and split-thickness skin graft donor sites, is Xeroform petrolatum gauze.¹⁰⁻¹² Xeroform consists of a mixture of petroleum jelly and bismuth tribromophenate that is processed into a homogenized suspension using a colloid mill and impregnated into fine mesh sterile gauze.¹³ Petroleum jelly creates an occlusive, nonadhesive barrier that enables the wound to retain moisture.¹¹ Bismuth tribromophenate is antimicrobial, possibly mediated by bismuth ions accumulating in and disrupting microbial organelles.¹⁴ Xeroform is preferred over other occlusive dressings such as DuoDERM, Biobrane, Kaltostat, Aquacel, Mepilex, and Jelonet because it is stable, is easily stored at room temperature, facilitates rapid re-epithelialization, and is available at a lower cost than other dressing types.^{10,12,15}

Several studies have explored lower-cost alternatives for use in LMICs, such as topical amniotic membrane, honey, boiled potato peel, and papaya.¹⁶⁻¹⁸ Amniotic membrane is available from cesarean sections at no cost but has a limited shelf life and requires sterile procurement, human immunodeficiency virus and hepatitis testing, and storage with antibiotics in a cold room or freezer.¹⁶ Although honey and papaya, and to a lesser extent potato peel, were shown to confer some antimicrobial benefit on burn wounds, their effect on wound healing is less reproducible than conventional dressings.^{17,18}

We propose an inexpensive method of producing a dressing with comparable properties to Xeroform, made with readily available materials by hand without a colloid mill, for use in low-resource settings. We hypothesize that this alternative dressing would be a viable, economic alternative to Xeroform with comparable antimicrobial efficacy, biocompatibility, and wound healing. The ultimate goal is to optimize an inexpensive, handmade dressing that can be custom-produced at the bedside for use in burn units in low-resource settings.

METHODS

Patent Search

A patent search was performed using the online USPTO Complete Patent Documents Database. Search terms “xeroform,” “bismuth tribromophenate,” and “petrolatum dressing” were entered, and all patents from 1790 to present were queried.

Preparation of Alternative Dressing

Vaseline (Unilever, Rotterdam, Netherlands) was vigorously mixed with 3% bismuth tribromophenate powder by weight (Dudley Corp., Lakewood, N.J.) for 3 minutes in a plastic bowl using a plastic spoon sterilized with 70% ethanol spray. The resulting colloid suspension was spread onto Kerlix gauze (Covidien, Dublin, Republic of Ireland) by hand using sterile gloves. The gauze was pressed to remove excess Vaseline until the dressing macroscopically resembled Xeroform in color and consistency.

Cost Analysis

Costs for dressing materials were obtained through an online search engine (Google Shopping, Mountain View, Calif.). Item names were queried and prices sorted by cost. The lowest possible cost for the appropriate item was used.

Antimicrobial Growth Test

The susceptibility of bacteria to the dressings was tested using the standardized single disk method.¹⁹ Starter colonies of HB101 *Escherichia coli* (Carolina Biological Supply, Burlington, N.C.) were inoculated onto Mueller-Hinton agar plates (Thermo Fisher Scientific, Huntington Beach, Calif.) and grown overnight at 35°C. Five colonies of *E. coli* were transferred from the growth plate into 3 tubes, each containing 4 mL Tryptic Soy Broth (Thermo Fisher Scientific). The bacterial suspensions were incubated in a shaking incubator at 35°C for 2.5 hours, and the turbidities of the suspensions were matched to a 0.5-McFarland standard (Pro-Lab Diagnostics, Richmond Hill, Canada). After incubation at 21°C for 1.5 hours, 100 µL of the bacterial suspensions was inoculated onto Mueller-Hinton agar plates (Thermo Fisher Scientific). Xeroform (Covidien), alternative dressing, and Kerlix gauze measuring 2 cm × 2 cm were gently placed onto the center of the agar plates using forceps (n = 2). Plates were incubated at 21°C for 72 hours and photographed to measure zones of inhibition (areas with no discernible bacterial growth).

Cytotoxicity Assay

Cytotoxicity of dressings was evaluated using a method described previously by Kempf et al.²⁰ In

brief, human NHDF-Ad adult dermal fibroblasts (Lonza, Walkersville, Md.) were seeded at a density of 5000 cell/cm² onto 35-mm diameter tissue culture plates and maintained in an incubator at 37°C and 5% CO₂. Cells were grown to confluence in fetal bovine media supplemented with fetal bovine serum. A circular, 1-cm diameter piece of dressing (Xeroform, alternative dressing, Kerlix gauze, or gauze soaked in commercial bleach, n = 3) was positioned on a Nunc insert membrane (Thermo Fisher Scientific). The Nunc inserts were gently centered on the tissue culture plates. Samples were incubated at 37°C for 24 hours before washing several times to remove nonadherent dead cells and staining with 1% methylene blue (Science Company, Lakewood, Colo.) for 10 minutes. Excess methylene blue was aspirated, and stained cells were visualized and photographed to measure surface area of surviving cells.

Quantification of Wound Healing

The effect of dressings on in vivo wound healing was studied by modifying an animal model described by Galiano et al²¹ for use with rats. In brief, the dorsal skin of Sprague-Dawley rats (n = 4) was shaved and depilated. The dorsa were rinsed 3 times with alcohol and swabbed with Betadine (Purdue Pharma, Stamford, Conn.) in a sterile field. As previously described, 3 uniform 6-mm diameter circular full-thickness wounds were made on the dorsal skin of each rat by outlining the wound with a 6-mm punch biopsy and excising the skin and panniculus carnosus with a No. 15 blade scalpel. Circular silicone discs (10-mm internal diameter; 12-mm external diameter; 0.5-mm thickness) were individually prepared from silicone sheets (Grace Bio-Labs, Bend, Ore.) and stored in 95% ethanol before use. These silicone discs were centered on the wounds and fixed with a small amount of permanent adhesive (Krazy Glue; Elmer's Inc., Columbus, Ohio) before securing to the skin with 8 interrupted 6-0 Ethilon sutures (Ethicon, Edinburgh, United Kingdom). The superior wound was covered with a 10-mm diameter circular piece of Xeroform followed by gauze; the middle wound covered with gauze; and the most inferior wound was covered with an alternative dressing followed by gauze. Dressings and discs were covered with Tegaderm (3M, Two Harbors, Minn.). Wounds were photographed every other day to measure re-epithelialization until wound closure (defined by the presence of new tissue filling the entire wound bed).

Wound Healing Analysis

Wound images were analyzed using ImageJ software (National Institutes of Health, Bethesda, Md.). The wound area was outlined and measured by an

independent researcher blinded to the condition and time point. The area of the inner ring of the circular splint was used to normalize the values so that each data point was represented as a percentage. Time to closure was represented as a mean ± standard deviation and analyzed using an unpaired Student *t* test. Statistical significance was accepted at *P* < 0.05. All animal experiments were undertaken at the Palo Alto VA Veterinary Medical Unit with prior IRB approval.

RESULTS

The Terms of the Xeroform Patent Have Expired

A patent search revealed that the terms of US Patent no. 3592909 for a stable tribromophenate ointment impregnated on gauze had been filed on July 13, 1971. The patent had expired after 20 years, in 1991.

Alternative Dressing Can Be Prepared by Hand

Alternative dressing was prepared by hand without the use of a colloid mill in fewer than 10 minutes (Fig. 1). Vaseline and 3% bismuth tribromophenate were combined by hand mixing to form a stable suspension. Macroscopically, the petrolatum-bismuth suspension mixed by hand was less homogeneous than Xeroform, but large particles of bismuth were eliminated through vigorous mixing. The alternative dressing was also more adhesive than Xeroform even after squeezing off excess petrolatum suspension. Xeroform utilizes finer mesh gauze than the Kerlix that was used to produce the alternative dressing. Notably, it was determined that 8.3 g of bismuth-petrolatum suspension was required to adequately cover Kerlix measuring 12.7 cm × 22.9 cm, the size of a standard Xeroform dressing, and this value was subsequently used in cost analysis calculations.

Alternative Dressing Can Be Produced at a Lower Cost Compared with Xeroform

A cost analysis of Xeroform from various brands compared with alternative dressing was conducted (Table 1). Per surface area unit cost of Xeroform from Covidien (Medtronic, Dublin, Republic of Ireland), Curad (Medline Industries, Mundelein, Ill.), and Kendall (Tyco, Cork, Republic of Ireland) was calculated from online market prices of standard 12.7 cm × 22.9 cm Xeroform. Similarly, per surface area unit cost of alternative dressing composed of Kerlix gauze (Covidien), Vaseline petroleum jelly (Unilever, Rotterdam, Netherlands), and bismuth tribromophenate (City Chemical LLC, West Haven, Conn.) was calculated. Alternative dressing costs 27% of the price of Covidien Xeroform, 34% of the

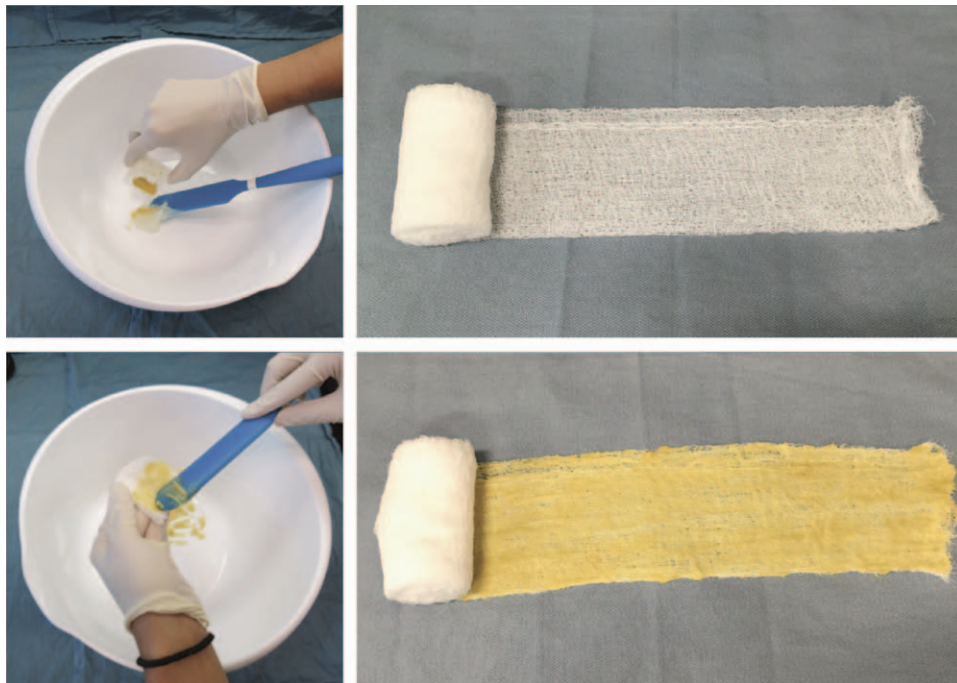


Fig. 1. Production of Xeroform.

Table 1. Cost Analysis of Xeroform and Alternative Dressing

Covidien Xeroform	Curad Xeroform	Kendall Xeroform	Alternative Dressing	
\$0.0068/cm ²	\$0.0055/cm ²	\$0.0062/cm ²	Kerlix	\$0.00036/cm ²
			Petroleum jelly	\$0.00015/cm ²
			Bismuth tribromophenate	\$0.0014/cm ²
				\$0.0019/cm ²

price of Curad Xeroform, and 30% of the price of Kendall Xeroform.

Alternative Dressing and Xeroform Are Bacteriostatic to *E. coli* Growth

The plates with Kerlix gauze dressing showed lawns of bacterial growth similar to the plates with no dressing, whereas the plates with Xeroform and the alternative dressing demonstrated no antimicrobial growth in the areas where the dressing was placed (Fig. 2). The alternative dressing was shown to be at least as bacteriostatic to *E. coli* growth compared with Xeroform.

Alternative Dressing and Xeroform Are Not Cytotoxic to Human Dermal Fibroblasts

There was no significant statistical difference in the cytotoxicity of Xeroform, alternative dressing compared with Kerlix gauze (Fig. 3). The surface area of live cells was 86.2% ± 3.4% for Xeroform, 84.3% ± 2.3% for alternative dressing, and 82.2% ± 1.3% for Kerlix gauze. In contrast, the gauze soaked in bleach (negative control) demonstrated

an 11.9% ± 7.7% surface area of cell growth. Overall, the 3 dressings were biocompatible with dermal fibroblasts, but bleach was significantly more cytotoxic ($P < 0.01$).

In Vivo Wound Healing Assay

Figure 4 summarizes the effect of each dressing type on re-epithelialization of wounds. There was no statistical difference in time to wound closure with Xeroform, alternative dressing, and Kerlix gauze (Fig. 5). Mean time to wound closure was 13.0 ± 1.6 days for Xeroform, 13.5 ± 1.0 days for alternative dressing, and 14.0 ± 1.2 days for Kerlix gauze. In addition, there was no significant difference in rates of wound closure over time between the 3 conditions (Fig. 6).

DISCUSSION

Xeroform is a nonadherent, moisture retaining, and antimicrobial dressing that promotes healing of superficial partial-thickness burns; however, disposable dressings contribute to the high expense of burns treatments in LMICs. We hypothesized that an

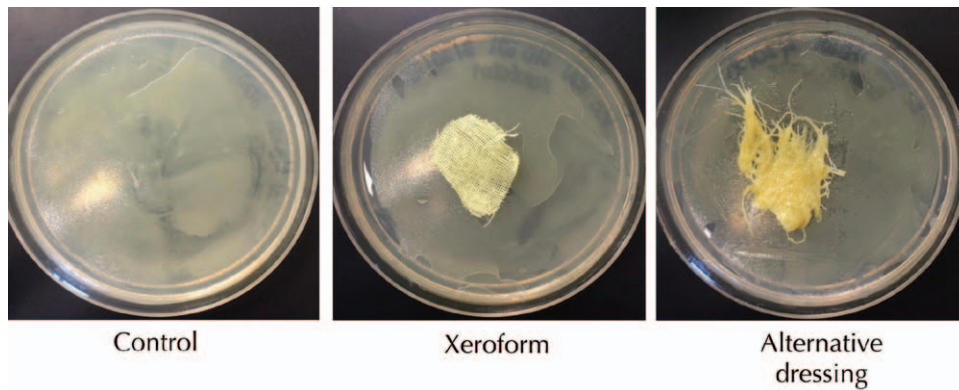


Fig. 2. Xeroform and the alternative dressing are bacteriostatic to *Escherichia coli* after 24 h.

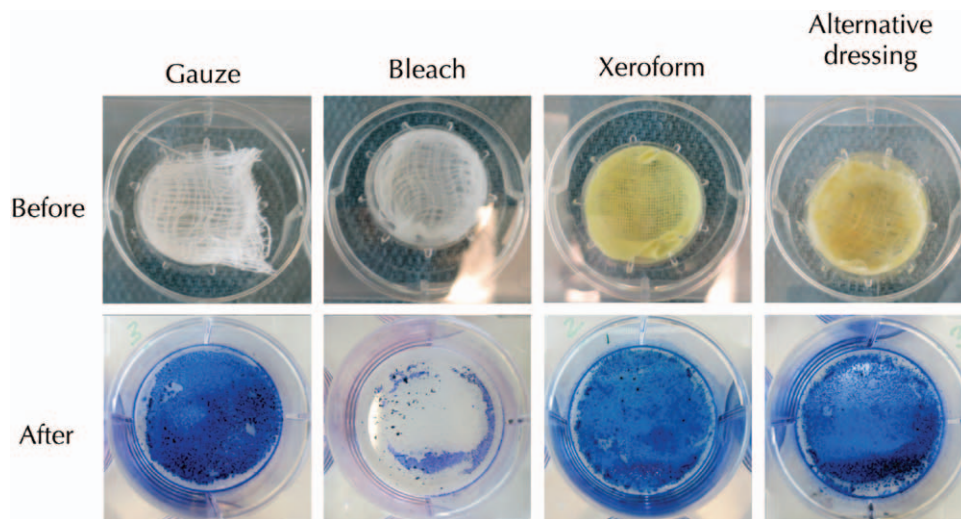


Fig. 3. Gauze, Xeroform, and alternative dressing are biocompatible with human dermal fibroblasts, whereas bleach (negative control) is cytotoxic.

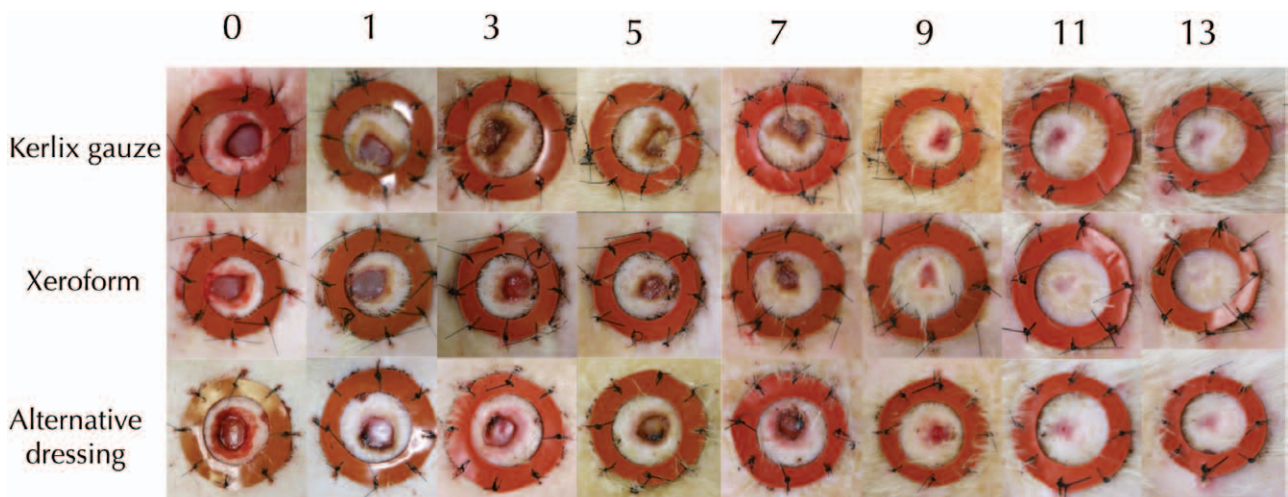


Fig. 4 Re-epithelialization of excisional wounds covered by Kerlix gauze, Xeroform, and alternative dressing.

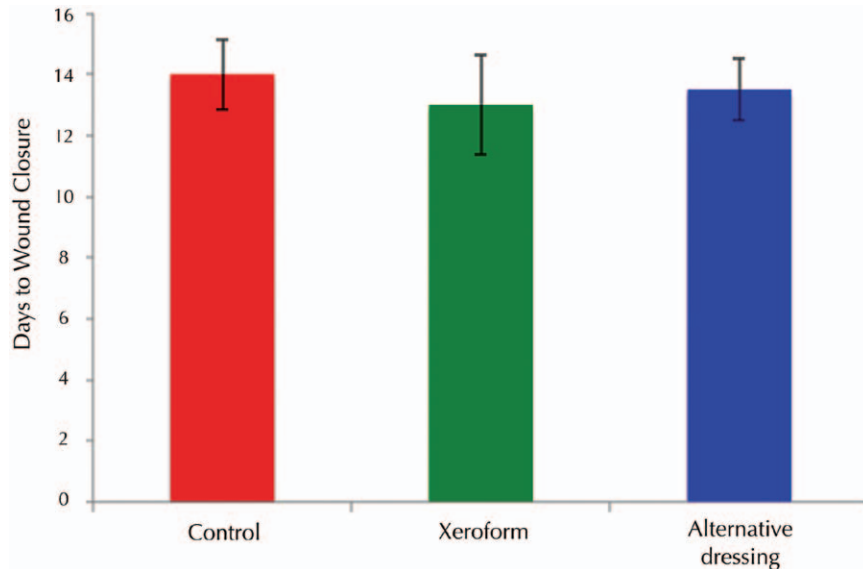


Fig. 5. Gauze, Xeroform, and alternative dressing show no statistical difference in time to wound closure.

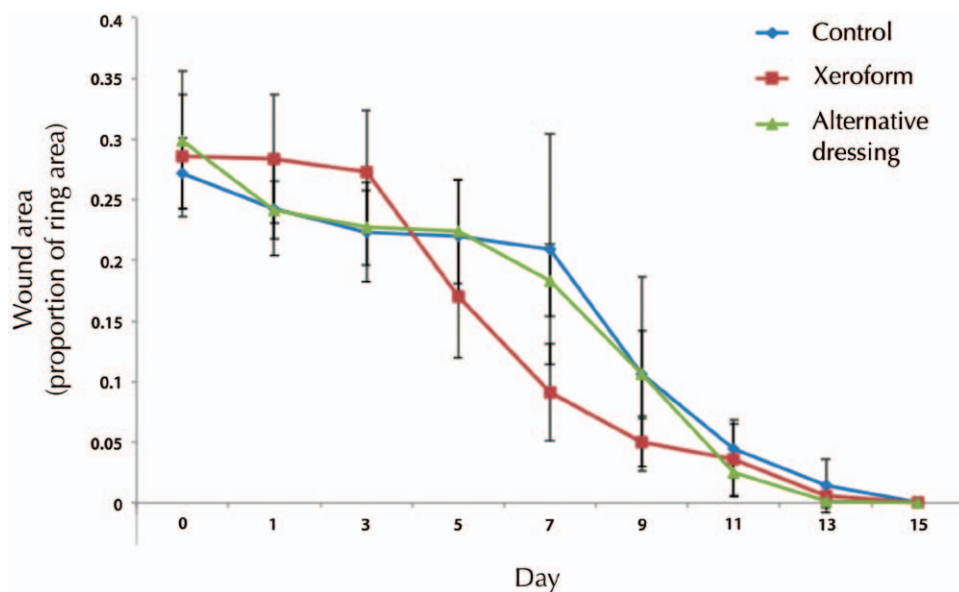


Fig. 6. Gauze, Xeroform, and alternative dressing show no statistical difference in rate of wound re-epithelialization.

alternative dressing produced by hand would reduce costs yet possess comparable antimicrobial efficacy, biocompatibility, and wound re-epithelialization properties.

We found that the alternative dressing can be made by hand from raw materials at 34% of the cost of Kendall Xeroform, the least expensive brand. Given that superficial partial-thickness burn wounds can take several days to heal and frequent dressing changes, this decreased cost would allow for necessary frequent dressing changes. Notably, our

alternative dressing was subjectively more adhesive than Xeroform, less homogeneous, and composed of coarser mesh gauze.

We chose *E. coli* as the model organism to study the antimicrobial properties of the dressings due to the deleterious effects of Gram-negative bacteria on burn wound infections that can lead to bacteremia and sepsis.²² It was observed that the Xeroform and alternative dressing were both bacteriostatic to *E. coli* growth; the dressings inhibited the growth of bacteria on areas occluded by

the dressings, but the antimicrobial effect did not extend beyond the area of the dressing (ie, bactericidal). In contrast, Kerlix gauze alone did not inhibit bacterial growth. It was thus demonstrated that the macroscopic differences between Xeroform and alternative dressing did not affect the ability to prevent bacterial growth. Furthermore, given that the dressing is intrinsically antimicrobial, it is acceptable to prepare it with gloves in a clean setting rather than with strict aseptic technique. Future work should focus on characterizing the antimicrobial efficacy of the dressings on other pathogens that commonly affect burn wounds such as *Pseudomonas*, *Acinetobacter*, *Klebsiella*, and *Staphylococcus aureus*.²³

We next demonstrated that both alternative dressing and Xeroform are as biocompatible with human skin fibroblasts as Kerlix gauze alone. This is consistent with a prior study showing the low cytotoxicity of Xeroform on keratinocytes (1% dead cells).²⁰ This is significant because many burn wounds dressings, particularly those containing ionized silver such as silver sulfadiazine, are highly cytotoxic to keratinocytes (up to 100% dead cells), although silver dressings are typically reserved for deeper burns. Our handmade alternative dressing is thus as safe as Xeroform to use on wounds.

We further demonstrated that there is no significant effect of dressing type on time to complete closure of excisional wounds or rate of wound closure. Both Xeroform and the alternative dressing are equivalent to Kerlix gauze in affecting re-epithelialization. A limitation of this study is that an excisional wound healing model rather than a burn model was utilized for in vivo experiments, and results may not precisely reflect the effect of dressings on burns wounds. An excisional wound model was selected due to the ease and precision of measuring re-epithelialization rates; however, subsequent studies should compare the effect of dressings on both models.²⁴

This study suggests that an inexpensive, effective bismuth-petrolatum dressing can be produced by hand without the need for special equipment and aseptic technique. This dressing is biocompatible and antimicrobial and can protect wounds during re-epithelialization. In addition, the size of the dressing can be customized to the surface area of the wound, which is particularly useful for large burns. The ultimate goal will be to translate our findings so that these dressings could be produced at the bedside in low- and middle-income country burn units with materials that are purchased inexpensively or donated in bulk.

James Chang, MD

Division of Plastic and Reconstructive Surgery
Veterans Affairs Palo Alto Health Care System
770 Welch Road, Suite 400
Palo Alto, California 94304
jameschang@stanford.edu

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