



Wound Bed Preparation

It's About TIME

During the normal process of wound healing, a series of molecular events prepare the wound for repair, deposition of new extracellular matrix, and eventually complete wound closure. This orderly process of cellular control is impaired in chronic wounds, delaying or interrupting the repair process.

Despite best efforts, some wounds do not to heal — the most obvious sign is the failure of the epidermal margin or “edge” to migrate across the wound bed. At a cellular level, the lack of epidermal migration is due to non-responsive wound cells and abnormalities in protease activity that degrade the extracellular matrix while it is formed. If the first three principles of TIME have already been successfully applied (removal of non-viable tissue, restoration of bacterial and moisture balance), patient factors should be reassessed and alternatives, such as using a dermal substitute, considered.

This is the ninth in a series of 12 articles addressing TIME and wound bed preparation.



83 General Warren Boulevard, Suite 100
Malvern, PA 19355
Phone (800) 237-7285 FAX (610) 560-0502
www.hmpcommunications.com

This publication is provided by Smith & Nephew, Inc., as a continuous professional service. For additional reprints or information on Smith & Nephew products, contact your local Smith & Nephew representative or call (800) 876-1261.

The Problem — How to Encourage Epidermal Migration in the Recalcitrant Wound

Diabetic foot ulcers. Many types of wounds are prone to chronicity but diabetic foot ulcers present a significant medical challenge. Of the 18 million patients with diabetes, 2.7 million will develop foot ulcers.^{1,2} More than 80,000 patients with diabetes require amputation¹; 85% of lower extremity amputations are due to complications from unhealed foot ulcers.³⁻⁵ Nationally, the annual cost of ulcer care and lower limb amputations may be as high as \$13 billion.⁶

The reason for the proliferation of diabetic foot ulcers is clear: the diabetic foot is particularly vulnerable to chronic ulceration due to the combination of poor nutritional blood flow, peripheral neuropathy, and impaired vascular responsiveness.⁷ Even after 20 weeks of treatment with standard care, 67% of diabetic foot ulcers fail to heal.⁸ The longer the ulcer persists, the greater the possibility the patient will develop a serious infection that can lead to hospitalization and possible amputation.⁹ If these underlying factors have been addressed and healing has not been restored, treatment may require the application of advanced techniques in order to restart the healing process.

The Solution — Human Fibroblast-derived Dermal Substitutes

Products such as DERMAGRAFT[®] have been approved by the FDA as effective and safe solutions in the healing of diabetic foot ulcers. DERMAGRAFT is a cryopreserved, human fibroblast-derived, dermal substitute composed of human fibroblasts, extracellular matrix proteins, glycosaminoglycans, and a bioabsorbable scaffold. Designed to restart the wound healing process, it replaces the compromised dermal bed typically associated with a diabetic foot ulcer. This allows the patient's own epithelial cells to migrate and close the wound.⁹ When implanted in a diabetic ulcer bed, DERMAGRAFT provides a physical replacement of dermal tissue and has the potential to support multiple secondary functions, including colonization of the wound bed, sustained release of growth factors that promote angiogenesis, fibroblast proliferation, matrix deposition, and provision of a permissive substrate for adhesion, migration, and growth of keratinocytes. These properties, in combination, act in a synergistic manner to convert the chronic wound to an environment closer to acute healing.¹⁰ DERMAGRAFT also stimulates angiogenesis to accelerate wound healing and increases blood flow by an average of 72% at the base of diabetic foot ulcers.⁷

Indications. DERMAGRAFT is indicated for use in the treatment of full-thickness diabetic foot ulcers greater than 6 weeks' duration, which extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure. DERMAGRAFT should be used in conjunction with standard wound care regimens and in patients with adequate blood supply to the involved foot.⁸

Clinical validation.

Accelerated wound healing. In a 50-patient multicenter study,¹¹ patients using DERMAGRAFT experienced a 79% reduction in average time to 50% wound closure compared to the standard treatment group (2.5 weeks in group A ver-

sus >12 weeks in the control group; $P = .0047$). In a multicenter trial involving 38 investigational sites (314 patients), Hanft⁹ reported that after 12 weeks, 71% of ulcers in the DERMAGRAFT group healed versus 14% in the control group. In addition, patients treated with DERMAGRAFT achieved wound closure significantly faster than control patients using conventional therapy.^{9,12} Additional clinical studies of DERMAGRAFT versus conventional therapy show significantly greater wound closure at 12 weeks, as measured by area reduction and consistent healing regardless of ulcer location (heel, forefoot, and toe).¹³

Offloading/ambulation. In a study¹² in which offloading was not required, DERMAGRAFT patients were almost two times more likely to heal versus the control group ($P = .023$). By week 12, the median percent wound closure was 91% among patients in the DERMAGRAFT group versus 78% for patients in the control group ($P = .044$), despite patients being ambulatory an average of 8 hours a day.

Recurrence. DERMAGRAFT sustains healing. In one study,¹¹ the average time to recurrences of healed DERMAGRAFT-treated ulcers was 14 months (range 2 to 22 months). In a long-term study¹³ of six patients treated with DERMAGRAFT, only one patient had a late recurrence and was successfully treated with a re-application of DERMAGRAFT. All other patients maintained complete wound healing at 42 months.

Instructions for use.

1. **Identify viable candidates.** The wound must have an adequate arterial blood supply. Coexisting conditions or drug therapy that may interfere with healing should be addressed before application.
2. **Prepare the wound.** Sharply debride necrotic or hyperkeratinized tissue to create a clean, granulating wound bed suitable for a skin graft.
3. **Control bleeding** without using any topical agents.
4. **Assess the wound for infection.** DERMAGRAFT is contraindicated for use in ulcers that have signs of clinical infection or in ulcers with sinus tracts. Because infection is not always visible, nonsensitizing topical antibacterial products, such as ACTICOAT[®], may be indicated before using DERMAGRAFT.
5. **Apply weekly.** Repeated application of DERMAGRAFT is critically important because of the multiple functions this product performs throughout the healing process.¹¹ Patients receiving DERMAGRAFT once a week were 2.5 times more likely to achieve complete wound closure than patients receiving one piece every 2 weeks.¹¹
6. **Utilize proper offloading and dressing changes.** Patients who complied with offloading during treatment were five times more likely than the control group to achieve complete healing.⁹ Successful offloading requires a reliable patient support system (ie, family member, friend, professional) to improve compliance. Many clinicians also have reported that dressing changes performed by professionals rather than by patients can improve healing rates.
7. **Use-by date.** DERMAGRAFT is delivered to the clinician in its cryopreserved state within 24 hours of ordering. Shipping in specially designed packaging maintains cell viability for up to 60 hours when left unopened and maintained at -75°C ($\pm 10^{\circ}\text{C}$). Metabolic activity is guaranteed. The patented cryopreservation process allows extensive testing before product

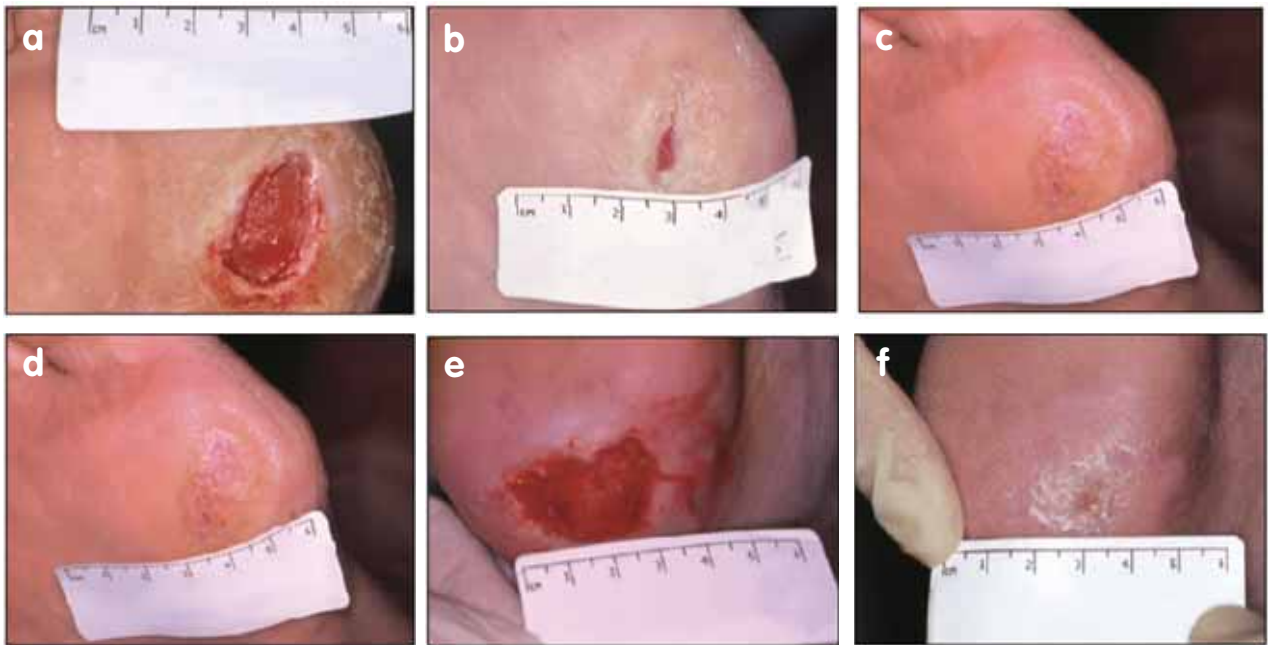


Figure 1. Case 1 wound at weeks 0, 5, and 9 (a-c) and Case 2 wound at weeks 0, 4, and 7 (d-f).

release to protect against pathogenic contamination.

8. *Safety profile.* No rejection was reported in clinical studies. DERMAGRAFT patients experienced significantly fewer ulcer-related adverse events, including local wound infection, osteomyelitis, and/or cellulitis.¹²

9. *Practice management.* Many medical practices coordinate DERMAGRAFT applications on a single day each week to enhance the efficiency of the preparation/application process. Clinical wound evaluations should continue until the ulcer heals or the patient is discharged. Patients should contact their physician if they experience pain or discomfort.

10. *Reimbursement.* DERMAGRAFT is reimbursable through Medicare and many private insurance programs.

Case Studies

Case 1. Mr. D was a 75-year-old Caucasian man with type 2 diabetes. The ulcer on the medial aspect of his right foot had persisted for 12 weeks and did not progress toward healing during the 2-week screening period. Post debridement, the ulcer measured 2.0 cm x 1.5 cm. After 9 weeks of DERMAGRAFT use and comprehensive wound care, the ulcer healed completely (see Figure 1a, b, c).

Case 2. Ms. E was a 54-year-old Caucasian woman with type 1 diabetes. An ulcer of 8 months' duration on the plantar aspect of her left heel did not progress toward healing during the 2-week screening period. Post debridement, the ulcer measured 3.0 cm x 2.3 cm. After 7 weeks of therapy with DERMAGRAFT along with comprehensive wound care, the ulcer healed completely (see Figure 1d, e, f).

Conclusion

The properties of DERMAGRAFT help create a synergy that enables epidermal migration in a wound in which healing has stalled. Attention to edge-of-wound mechanisms is a vital piece of the TIME principle of preparing the wound for healing.

References

- American Diabetes Association. National diabetes fact sheet. Available at: http://www.diabetes.org/utills/printthispage.jsp?PageID=STATISTICS_<http://www.diabetes.org/utills/printthispage.jsp?PageID=STATISTICS_>233193. Accessed February 9, 2005.
- Frykberg RG, Habershaw DG, Giurini J, et al, for the American College of Foot and Ankle Surgeons and the American College of Foot and Ankle Orthopedics and Medicine. Diabetic foot disorders: a clinical practice guideline. *J Foot Ankle Surg.* 2000;39(suppl 2000):S1-S60.
- Pecoraro RE, Reiber E, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. *Diabetes Care.* 1990;13:513-521.
- Larsson J, Agardh C-D, Apelqvist J, Stenström A. Long-term prognosis after healed amputation in patients with diabetes. *Clin Orthop.* 1998;350:149-158.
- Centers for Disease Control and Prevention. Diabetes: Disabling, Deadly, and on the Rise 2004. Atlanta, Ga.: US Department of Health and Human Services; 2004.
- Gordois A, Scuffham P, Shearer A, Oglesby A, Tobin J. The health care costs of diabetic peripheral neuropathy in the U.S. *Diabetes Care.* 2003;26(6):1790-1795.
- Newton DJ, Khan F, Belch JFF, Mitchell MR, Leese GP. Blood flow changes in diabetic foot ulcers treated with dermal replacement therapy. *J Foot Ankle Surg.* 2002;41:233-237.
- Roberts C, Mansbridge J. The scientific basis and differentiating features of Dermagraft. *Can J Plast Surg.* 2002;10(suppl A):6A-13A.
- Hanft JR, Surprenant MS. Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. *J Foot Ankle Surg.* 2002;41:291-299.
- Data on file. Smith & Nephew Wound Management (La Jolla, Calif.).
- Gentzkow GD, Iwasaki SD, Hershon KS, et al. Use of Dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes Care.* 1996;19:350-354.
- Marston WA, Hanft J, Norwood P, Pollak R, for the Dermagraft Diabetic Foot Ulcer Study Group. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers. *Diabetes Care.* 2003;26:1701-1705.
- Hsiang Y. Long term results of the treatment of diabetic foot ulcers with Dermagraft. *Can J Plast Surg.* 2002;10(suppl A):14A-16A.



 **smith&nephew**
DERMAGRAFT[®]
Human Fibroblast-Derived
Dermal Substitute

From active cells comes active healing

Simple, weekly DERMAGRAFT[®] applications help your patients with chronic foot ulcers return to their normal lives more quickly than conventional therapy.*¹

DERMAGRAFT advanced tissue technology can help you lead the way to fast, lasting healing.^{1,2}

Visit www.dermagraft.com or call (800) 876-1261 for more information.

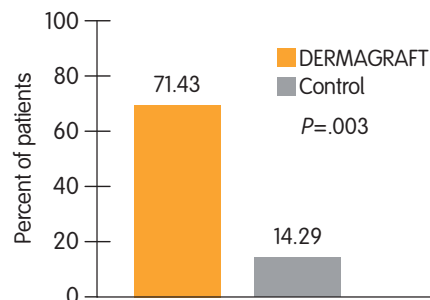
Before using DERMAGRAFT, please read the Directions for Use.

* In the pivotal clinical trial, "chronic" was defined as ulcers greater than 6 weeks in duration. Conventional therapy included sharp debridement, saline-moistened gauze, and pressure-reducing footwear.

1. Gentzkow GD, et al. Use of Dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes Care*. 1996;19:350-354. 2. Hanft JR, Surprenant MS. Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. *J Foot Ankle Surg*. 2002;41:291-299.

©2005 Smith & Nephew [®]Trademark of Smith & Nephew. Certain marks reg. US Pat. & TM Off.

Complete wound closure by Week 12²



****For full Prescribing Information see a copy at www.smith-nephew.com or call 1-800-876-1261 or contact your physician**