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Creating the Ideal Microcosm for Rapid Incorporation of Bioengineered Alternative Tissues Using An Advanced Hydrogel Impregnated Gauze Dressing: A Case Series

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The Foot & Ankle Journal 1 (9): 2

The purpose of this article is to demonstrate the effectiveness of a novel hydrogel impregnated gauze dressing in creating the ideal microcosm around a bioengineered alternative tissue to prevent tissue dehydration and cell death, accelerate angiogenesis, prevent infection and facilitate the interaction of growth factors with the target cells. Using the BRAIN principles along with this hydrogel impregnated gauze dressing in 50 diabetic patients with neuropathic foot ulcerations (including the six cases presented herein) resulted in substantially improved incorporation rates, increased frequency of wound closure, decreased time to achieve wound closure and a reduction in overall costs. Based on a log transformation the typical healing time is 17.8 days with a 95% confidence interval of 15.6 days to 20.2 days.

Key Words: Bioengineered alternative tissue, diabetic wounds, neuropathic wounds, Amerigel®, BRAIN principle

Accepted: August, 2008 **Published:** September, 2008

The efficacy of bioengineered alternative tissue (BAT) for lower extremity ulcers (diabetic and non-diabetic) is well described in the literature. [1-6] As the use of BATs continue to grow world wide, it is important that the wound care specialist consider the principles and tools that will maximize the effectiveness of these tissues to enable wounds to heal faster. Using the BRAIN principles (Table 1) will be fundamental in improving incorporation rates and maximizing the effectiveness of BATs. [7]

Treating wounds in patients with diabetes is more complex than simply choosing what dressing to use. Emerging technologies over the past decade have not only helped improve our understanding of how wounds heal, but more importantly why wounds do not heal. Understanding and addressing the physiological alterations of the wound healing cycle in the diabetic patient is fundamental. As diabetic wounds become stalled in the inflammatory phase of wound repair, chronic wound fluid with elevated levels of matrix metalloproteinases (MMPs) increases proteolytic activity in the wound, which in turn inactivates growth factors.

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ISSN 1941-6806 doi: 10.3827/faoj.2008.0109.0002

	B R A I N
B	Bioburden
R	Reduction of pressure and shear force
A	Adapting to the moisture needs of the wound and the bioengineered tissue
I	Incorporation and Identification
N	Nonadherent dressing

Table 1 The BRAIN principles to maximize BAT incorporation and wound healing.

In addition, with decreased collagen synthesis and impaired cellular activity due to hyperglycemia, there is less nitric oxide available and less endothelial cell proliferation. [8]

With this impaired wound healing physiology, it is vital for the wound care specialist to provide the wound what it lacks (i.e. growth factors, BATs, etc.) and decrease excess chronic wound fluid. Consequently, providing the wound with what it needs at the right time is imperative.

So how can we create the perfect environment for wounds to heal? What is the perfect environment to incorporate BATs into to the wound? Although there is no one right answer, we do know that creating the perfect "microcosm" around the wound will not only actively modify the physiology of the wound environment, but it will also stimulate cellular activity and growth factor release. While no perfect dressing exists for every type of wound, understanding the properties necessary to create the ideal microcosm for the BAT and the periwound area is crucial. [9] (Table 2)

With these characteristics in mind, the AmeriGel® Hydrogel Saturated Gauze Dressing (Amerx Health Care Corp., Clearwater, FL) has, in my experience, been the product of choice in creating the ideal microcosm for both the BAT (cellular or acellular) and the periwound area.

Properties of the ideal wound dressing
Promotes a moist wound environment
Promotes wound healing
Provides mechanical protection
Allows for nonadherence to the wound or to the BAT
Allows for removal without pain or trauma
Capable of absorbing excess exudate
Allows for gaseous exchange
Non-cytotoxic to healthy tissue
Antimicrobial/antifungal
Acceptable to the patient
Easy to use
Cost-effective

Table 2 The properties of the ideal wound dressing to help incorporate BATs into the wound.

This product utilizes a polyethylene glycol base (polyethylene glycol 400 and polyethylene glycol 3350) that has the ability to remain moist without causing maceration. Because the product is still technically a gauze dressing, it will also absorb excess wound fluid into its fibers while keeping the wound moist for up to 5-7 days.

Although there are other hydrogel impregnated gauze products on the market, such as Aquagauze™ (DeRoyal, Powell, TN), Curafil® Hydrogel Impregnated Gauze (Kendall, Mansfield, MA) and Derma Cool® (Afassco, Carson City, NV), none of these products possess the antimicrobial or antifungal properties that are in the AmeriGel® Hydrogel Saturated Gauze Dressing.[10] While most hydrogel impregnated gauze products are capable of absorbing excess fluid, the AmeriGel® Hydrogel Saturated Gauze Dressing (AmeriGel®) can effectively reduce the bioburden through not only its intrinsic antimicrobial and antifungal properties, but also through its absorptive capabilities that trap debris and bacteria in its fibers. AmeriGel® is an easy to apply, non-woven 4-ply, 2x2 inch dressing that is non-cytotoxic, nonadherent, and antimicrobial.

The antimicrobial agent is Oakin®, an oak extract containing tannins. Its mode of antimicrobial action is through its ability to inactivate microbial adhesins, enzymes, and cell envelope transport proteins. [11,12] Tannins are astringent compounds that act locally by precipitating proteins to the wound, decreasing cell membrane permeability, and exerting anti-inflammatory and bactericidal properties.

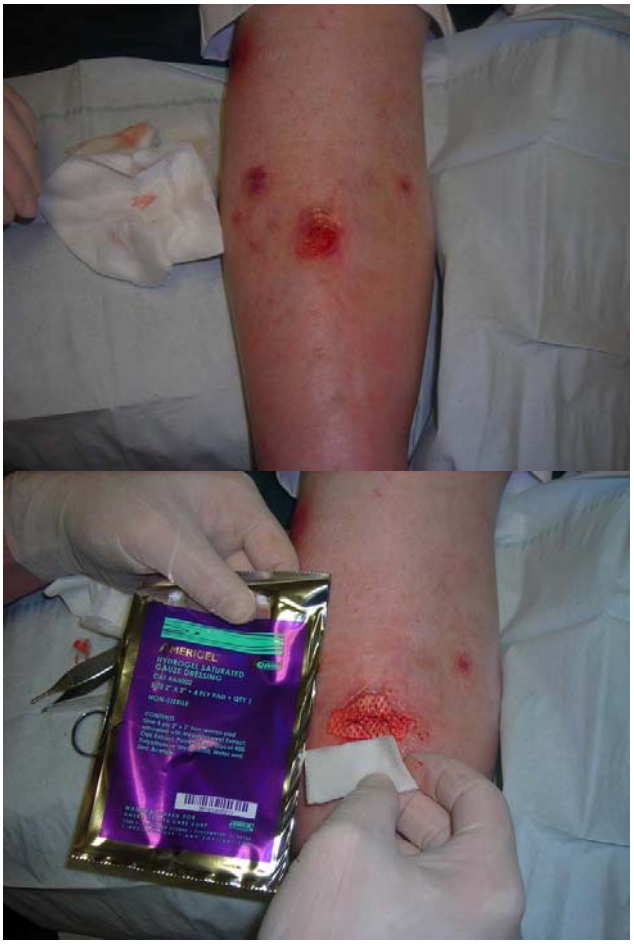
The use of AmeriGel® over the BAT application site will facilitate not only a closer adherence of the living or acellular tissue to the wound bed, it will also have an "anchoring" effect by its adherence to the surrounding tissues thus reducing the incidence of hematoma or seroma formation under the BAT.

Although some controversy exists regarding the use of certain products with or on a living skin equivalent, there is no definitive evidence that demonstrates that hydrogels (especially the one being proposed in this paper) are cytotoxic. The objective of using any adjunctive wound care product (i.e. AmeriGel® Hydrogel Saturated Gauze Dressing) with a BAT (cellular or acellular) is to enhance its incorporation into the wound while maintaining the ideal environment in and around the wound site. Using the right product is key, but putting the right product on the wound in and of itself won't get wounds healed.

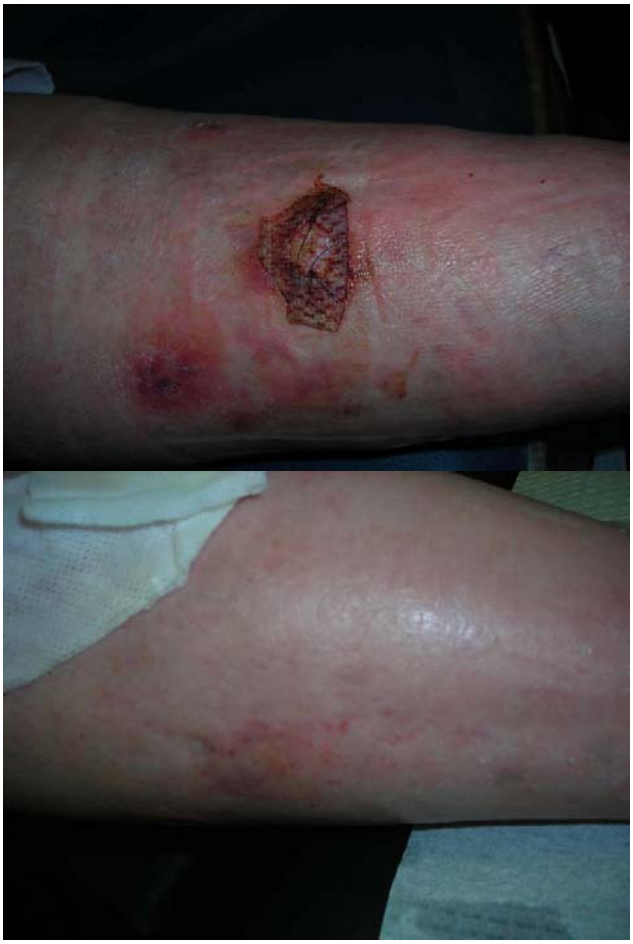
The following is a series of case reports utilizing the BRAIN principles along with the AmeriGel® Hydrogel Saturated Gauze Dressing as the product of choice for local BAT incorporation into the wound.

We utilized a variety of products for a variety of particular wound beds. Strict protocol to maintain the consistency of wound preparation and BAT application was followed. The following protocol was used for every BAT application:

1. Conservative topical wound care was performed in every case (collagen wound care products, enzymatic agents etc.) prior to every BAT application.
2. Sharp debridements were performed regularly to prepare the wound base for the application of the chosen BAT.
3. Care was taken to assure that no active bleeding was occurring prior any BAT application
4. Wound margins were thoroughly debrided to remove any hyperkeratosis and or any undermined tissue.
5. All patients in this series were diabetic, although some wounds treated using this protocol were of venous origin.
6. The BAT was placed on the wound bed such that the entire wound was covered.
7. BATs were not applied to wounds in which tendon or bone was exposed.
8. BATs were not applied in cases of infection or active drainage.
9. BATs were not applied to arterial leg ulcers.
10. AmeriGel® was applied directly over the BAT, followed by a secondary dressing (or some cases a compressive wrap in cases of edema)
11. More than one AmeriGel® Gauze Dressings were used in cases were one did not cover the wound site entirely.
12. All wounds were appropriately offloaded according to the BRAIN principles.
13. In cases where there was lower extremity edema, compression was applied over the BAT site using either an Unna's boot, or a ProFore® Bandage System (Smith & Nephew, Largo, FL)
14. The patient was instructed to leave the dressing intact and dry for one week after application.
15. The patients returned for follow-up no more than 10 days after application, most returned at 7 days.
16. GammaGraft® (Promethean LifeSciences, Inc., Pittsburgh, PA) was chosen in most cases for two reasons; The product has a greater than 2 year shelf life and it is easy to apply and manage.
17. The AmeriGel® Gauze Dressing was used daily until wound closure in every case after BAT application.



Figures 1AB Application of GraftJacket® and AmeriGel® Dressing over this non-healing venous ulceration. Sutures were applied to assure fixation of the BAT under a compressive wrap.



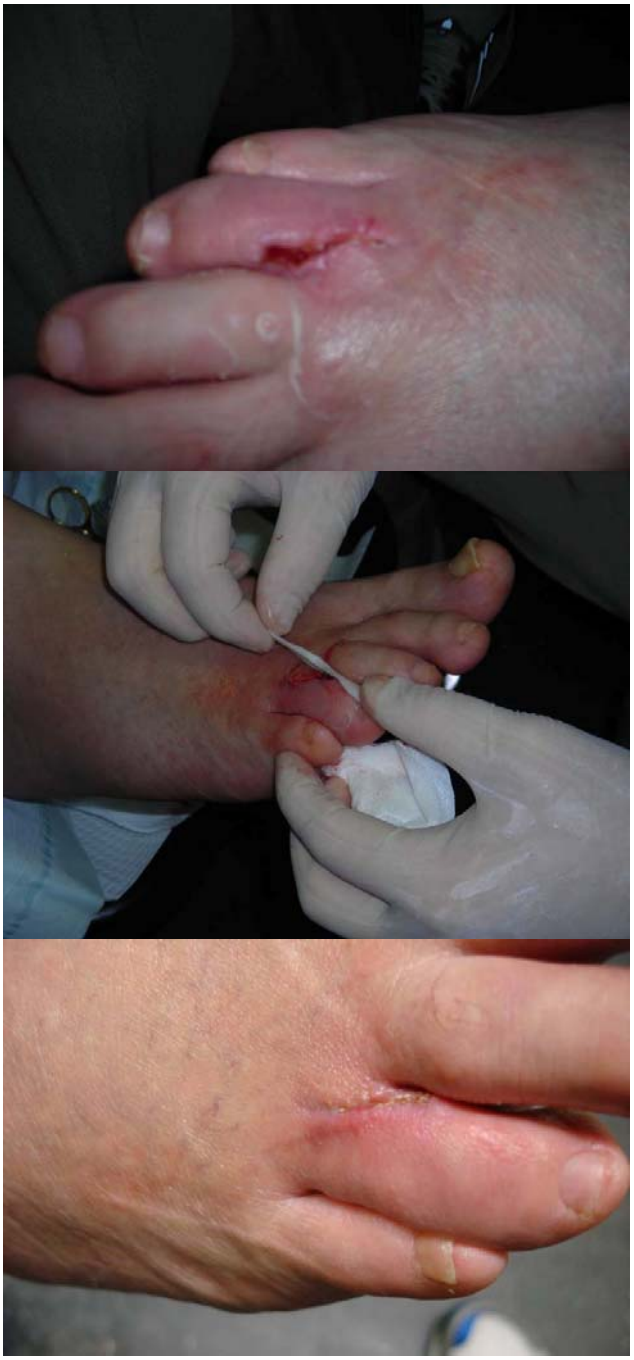
Figures 1CD The wound site 1 week and 4 weeks after application of BAT. Compression and continued use of AmeriGel® played a pivotal role.

Case 1

A 63-year-old female with diabetes and rheumatoid arthritis presented with a chronic venous ulceration (2 cm X 2.6 cm) to the dorsal aspect of the right leg. (Fig. 1A) The wound had been present for over two months despite application of compression therapy and topical agents. The GraftJacket® (Wright Medical Technology, Inc., Arlington, TX) was sutured to the wound site followed by AmeriGel® placed directly over the BAT site. (Fig. 1B) A 4" X 4" fluff and an elastic bandage were applied over the AmeriGel® for moderate compression. After one week, the initial dressing was removed (Fig. 1C) and was changed daily thereafter with AmeriGel® at home by the patient. The secondary dressing was dry sterile gauze. Four weeks after application of the GraftJacket®, the wound site along with all of the surrounding erythema was completely resolved. (Fig. 1D) It was surmised that AmeriGel® facilitated significant reduction of the erythema that had been persistent around the wound.

Learning points: Treating wounds on the leg in the presence of venous insufficiency will require compression in conjunction with proper local wound care. Although care must be taken not to apply too much compression such that the BAT is disrupted, no compression or too little can be equally harmful.

Tip: Size and trim the BAT prior to application to ensure the BAT is capable of covering the deepest portion of the wound without tenting.



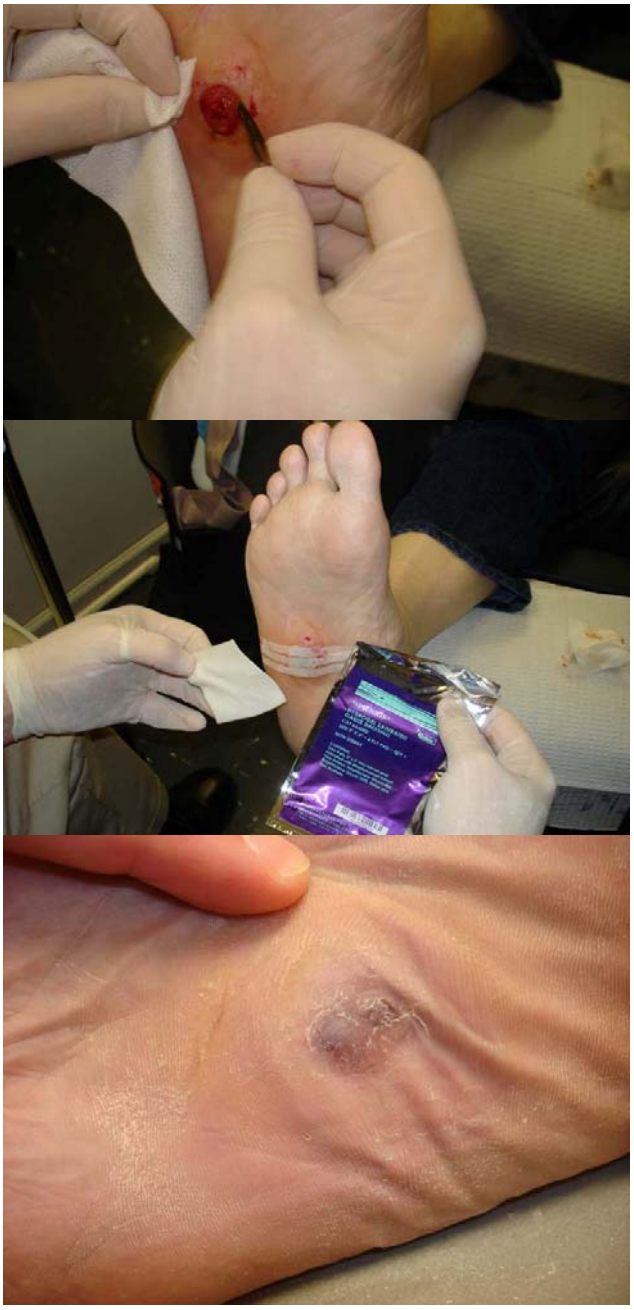
Figures 2ABC In case 2, GammaGraft® was used with AmeriGel® to advance closure of this chronic interdigital ulcer that occurred from a long standing and ignored fungal infection.

Case 2

A 42-year-old poorly controlled diabetic male presented with a chronic interdigital ulceration (1.6 cm X .9 cm) to the right foot. (Fig. 2A) The ulcer started as a result of a severe Tinea pedis infection. After the fungal infection was cleared, the ulceration was recalcitrant to traditional topical wound care agents and regular debridements. Thus, a GammaGraft® was chosen to close the wound. The GammaGraft® was anchored securely to the surrounding tissue followed by the AmeriGel® carefully placed to serve as a spacer interdigitally as well as to cover the BAT to promote more rapid healing. (Fig. 2B) After one week, the initial dressing was removed and the patient was instructed to change the dressing daily by applying AmeriGel® over the wound site followed by dry sterile gauze as a secondary dressing. After 3 weeks and 4 days, the wound site completely closed. (Fig. 2C)

Learning points: Desiccation of the BAT is a major concern when treating distal extremity wounds where there is often autonomic impairment common in patients with diabetes. A dressing like AmeriGel® will supplement moisture to the wound site.

Tip: Because of the previous fungal infection, the antifungal properties of AmeriGel® served well to provide the ideal environment for healing.



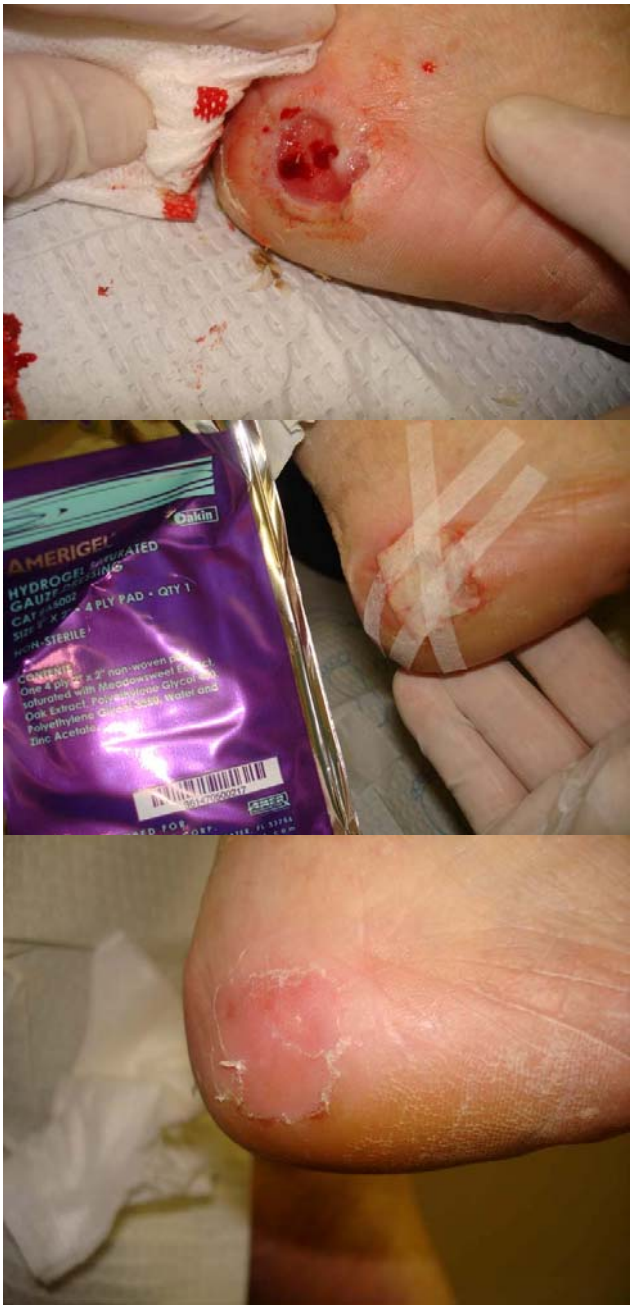
Figures 3ABC In case 3, GammaGraft® was used with AmeriGel® to facilitate healing of this plantar ulcer that occurred due to Charcot deformity.

Case 3

A 54-year-old diabetic male with a long history of Charcot deformity presented with a plantar ulcer (2.1 cm X 2.5 cm) of greater than 6 months duration. After the patient was offloaded in a Bledsoe® Walker (Bledsoe Brace Systems, Grand Prairie, TX), a granular bed was achieved after two weeks of aggressive debridement and topical wound care agents. (Fig. 3A) A GammaGraft® was then chosen to bring total closure to the wound site. The GammaGraft® was anchored to the wound site followed by AmeriGel®. (Fig. 3B) After one week, the initial dressing was changed and the patient was instructed to apply AmeriGel® every day thereafter, using dry sterile gauze as a secondary dressing. 3 weeks and 1 day later, the patient achieved complete healing. (Fig. 3C) Patient compliance with offloading and proper use of the prescribed dressings played a major role in this patient's quick healing time.

Learning points: Offloading wounds like the one above is the cornerstone to success in wound healing. Encourage patients to agree and be compliant with your treatment regimen.

Tip: Avoid using questionable cytotoxic agents over or on the BAT site.



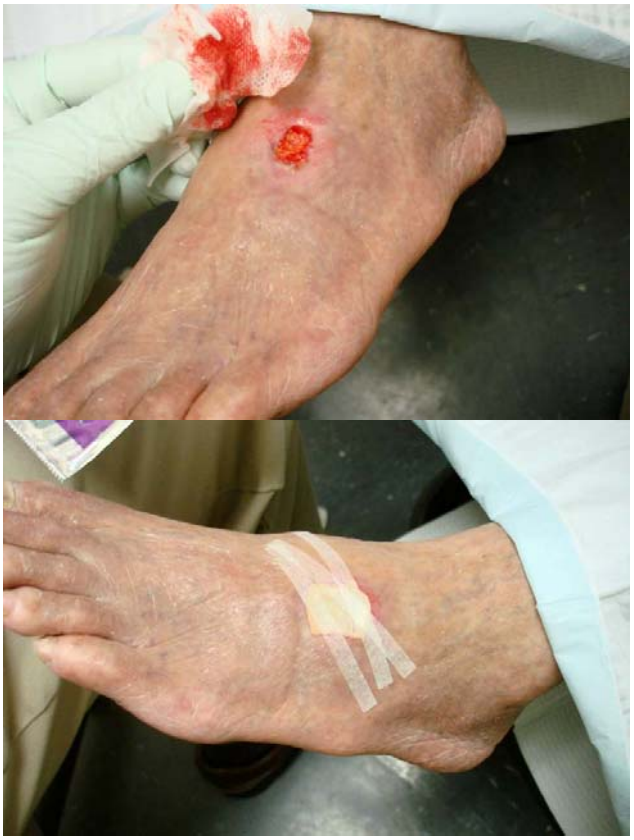
Figures 4ABC GammaGraft® and AmeriGel® were used to together to facilitate closure of this chronic heel ulceration that occurred as a result of dyshidrosis and neuropathy.

Case 4

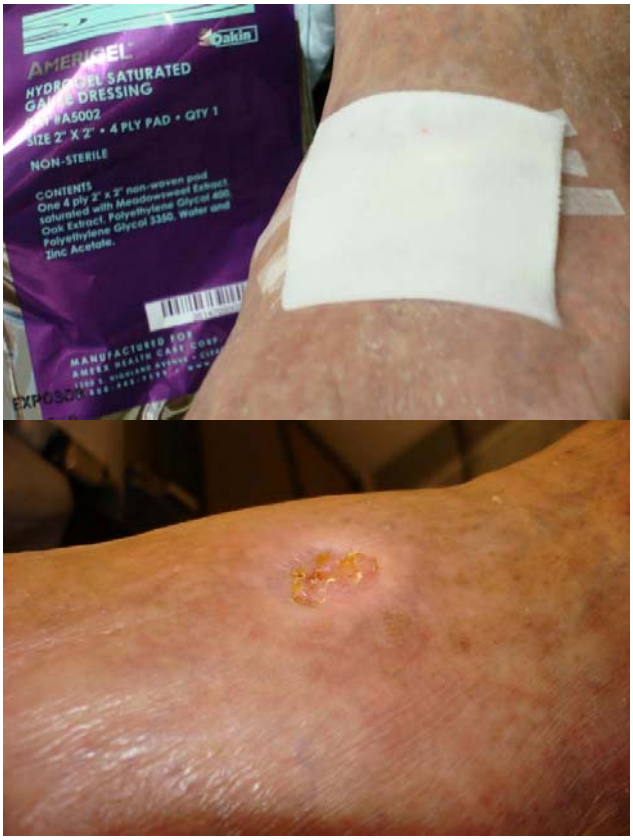
A 68-year-old diabetic female on dialysis presented with a chronic right heel ulcer (3.4 cm X 3.1 cm) of greater than 3 months duration. After thorough wound bed preparation over the course of 2 weeks (Fig. 4A), GammaGraft® and AmeriGel® was chosen to bring closure to the wound site. (Fig. 4B) The patient's dressing was changed at one week followed by daily applications of AmeriGel®, using dry sterile gauze as a secondary dressing. After 5 weeks and 3 days, the patient achieved total healing. (Fig. 4C)

Learning points: Initial dressing changes after application of a BAT should occur between 5-7 days. This may vary depending on the presence of drainage or infection.

Tip: The heel can be a very difficult place to heal a chronic wound for many reasons. Hydration was really the key to healing this wound as this patient developed the wound initially from excess dryness, cracking and fissuring.



Figures 5AB Application of GraftJacket® and AmeriGel® in the presence of vascular disease.



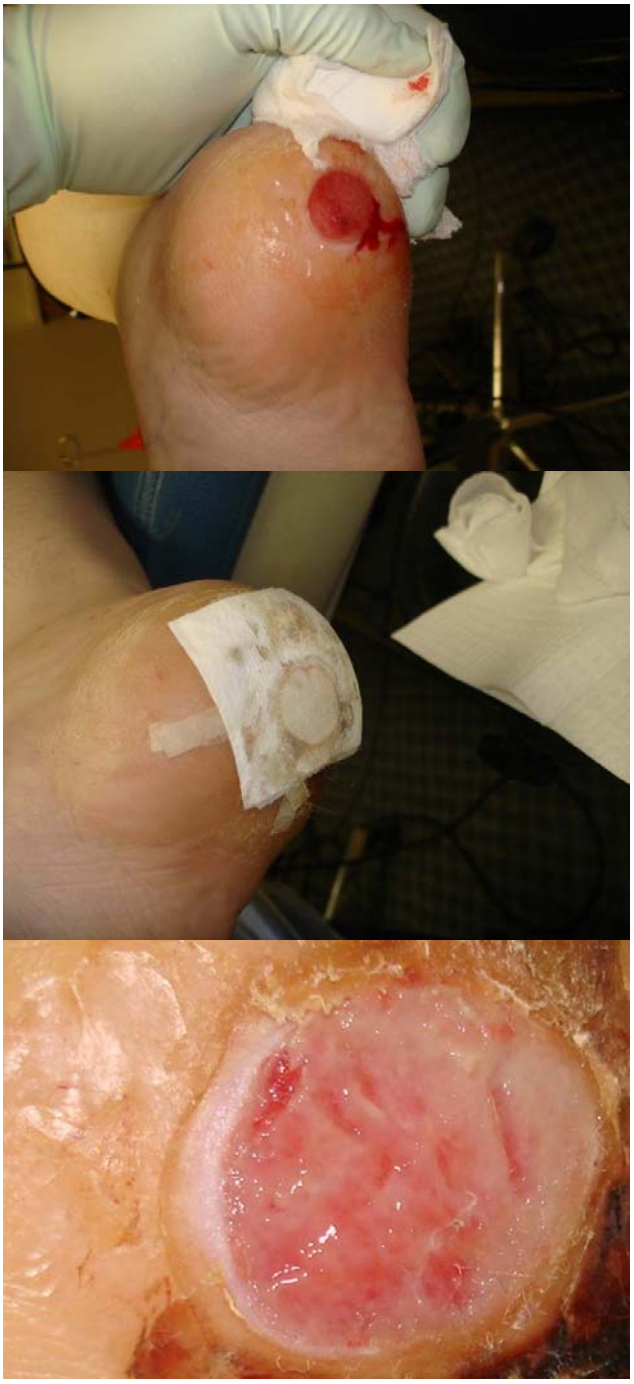
Figures 5CD Despite poor vascular status, early intervention and rigorous wound care helped heal this longstanding foot ulceration.

Case 5

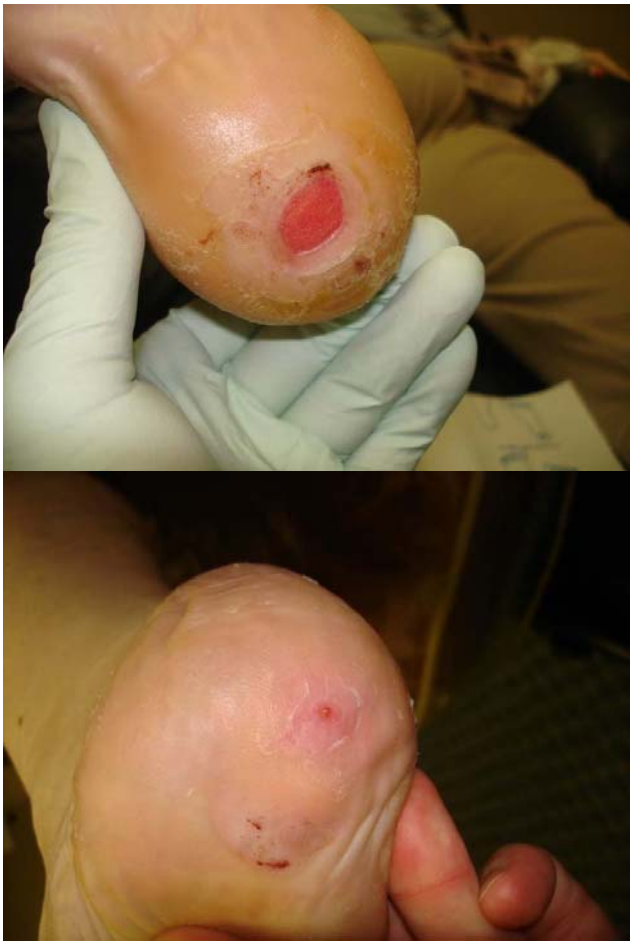
A 71-year-old diabetic male smoker with severe peripheral arterial disease presented with a dorsal foot ulceration (2.5 cm X 2.4cm) that had been chronically open for nearly 2 years. After months of treatment at 2 different wound care centers and several interventions by local vascular specialists, the patient was referred for consultation. After 2 weeks of aggressive wound debridements and the use of a collagen topical dressing, the wound bed improved to the point of accepting a BAT. (Fig. 5A) The GammaGraft® was anchored to the surrounding tissues with Steri-Strips™ (3M, St Paul, MN) (Fig. 5B) and covered with AmeriGel®. (Fig. 5C) After one week, the initial dressing was changed and daily applications of the AmeriGel® was performed using dry sterile gauze as a secondary dressing. The patient achieved complete healing in 6 weeks. (Fig. 5D)

Learning points: This patient's ABI demonstrated dismal PVR's, yet despite this, a rigorous wound care regimen was instituted that eventually led to complete healing.

Tip: Thoroughly assessing vascular status with each and every wound care patient is not only good practice; it can prevent limb loss with timely intervention.



Figures 6ABC After regular debridements, aggressive offloading and conservative treatments including the use of collagen dressings, Apligraf® was chosen for closure along with AmeriGel® per the BRAIN principals. Excellent incorporation was noted as early as one week (Fig. C).



Figures 6DE At two weeks, the wound size had been reduced by half and following daily applications of AmeriGel ®. The wound was closed 4 weeks and 4 days after the BAT was applied.

Case 6

A 47-year-old diabetic patient with profound peripheral neuropathy developed a blister on the plantar aspect of her right heel that became recalcitrant to conservative treatment. The patient's wound was debrided weekly and had Promogran™ (Johnson & Johnson Wound Management, Somerville, NJ) applied to the site until the wound developed a healthy granular base. Apligraf® (Organogenesis, Corp., Canton, MA) was chosen to close the wound. It was secured in place with Steri-Strips™ and covered with AmeriGel®, along with the use of a Bledsoe® boot and wheel chair.

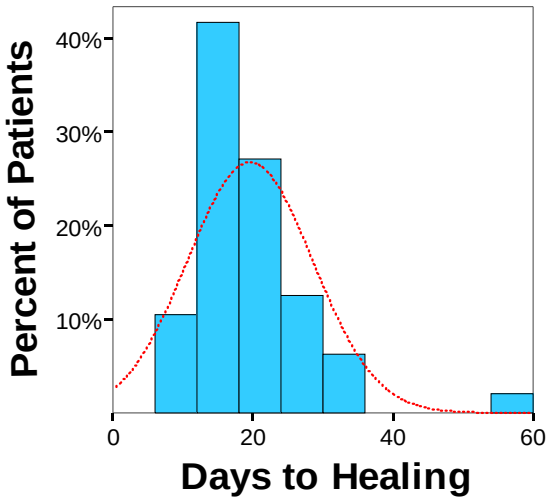
Due to the patient's severe neuropathy, among other balance concerns, the patient could not use crutches. (Fig. 6A) One week post application, the absorptive capability of the AmeriGel® was evident (Fig. 6B) as well as its ability to maintain a moist, healthy wound base. (Fig. 6C) At 4 weeks and 4 days, after daily applications of AmeriGel® and dry sterile gauze as the secondary dressing, the wound was healed. (Fig. 6DE)

Learning points: The above case illustrates well the concept of meeting the needs of the wound through the use of more than one product. Aside from regular wound debridements, collagen dressings were initially used to promote a healthy wound base followed by the Apligraf® and AmeriGel®.

Tip: Do NOT mechanically debride the wound bed for at least 4-6 weeks after applying a BAT [this may vary depending on the type of BAT being utilized (i.e. GammaGraft®)] unless the presence of significant exudate and colonization is present.

Discussion

Since using the BRAIN principles in my own clinics, successful incorporation rates have substantially improved when compared to conventional protocols used previously (i.e. petrolatum impregnated gauze, 4X4's and roll gauze). Over the past two years, 50 diabetic patients with similar ulcerations were treated using the BRAIN principles along with AmeriGel®. Approximately 90% of those patients had allograft tissue (GammaGraft® and GraftJacket®) applied while the other 10% had Apligraf® applied. To date, only two of the 50 patients have demonstrated BAT failure (non-healing of the wound). Failure in these two patients was attributed to peripheral vascular disease in one and non-compliance in the other.



Graph 1 This histogram shows that, with the exception of the extreme value (55 days to healing), healing times are reasonably normally distributed, represented by the dashed curve. Based on a log transformation the typical healing time is 17.8 days with a 95% confidence interval of 15.6 days to 20.2 days.

BATs applied to the legs healed quicker clinically than those applied to the foot. The legs being better vascularized in most cases constitute a viable reason for the comparably faster healing times. For chronic venous insufficiency ulcer patients, compression and a BAT covered by AmeriGel® allowed for healing in the majority of cases within two to three weeks. In some cases wounds were healed at one week. (Graph 1)

In all cases, only one BAT was used during the entire course of treatment, which certainly reduced costs. After application of the BAT, AmeriGel® continued to be employed as the primary dressing over the wound until closure.

Conclusion

Successfully combining BAT application along with other adjunctive therapies is not a new concept. Armstrong combined Dermagraft® (Advanced BioHealing, Inc., La Jolla, CA) with a vacuum-assisted closure system demonstrating quicker healing rates. [13]

One may also combine BAT's with hyperbaric oxygen treatment in wounds with local ischemia in turn improving the likelihood of BAT incorporation. [14] Furthermore, venous ulcerations in patients with edema may benefit from compression bandages in turn reducing healing times.

Clinical protocols incorporating the BRAIN principles will not only improve outcomes, but will also improve efficacy and patient satisfaction. No matter what your BAT of choice is, using the BRAIN principles to maximize the incorporation or transfer of the contents in the tissue to the wound will improve outcomes.[7] It has been evident in my patient population that the AmeriGel® gauze significantly helped to provide the ideal microcosm for the BAT after application. Reducing healing times will decrease wound infection rates and lowers the risk of amputation. When patients have faster healing wounds, the necessity for adjunctive diagnostic studies diminishes and patients may return more quickly to normal function thus reducing the costs associated with the increased number of supplies and physician office visits. [15]

Limitations

This study was retrospective and conducted out of a single multi-office practice. Furthermore, this study did not ascertain the impact of age, length of time the ulcer was present, nor previous treatment modalities. Although this case series is small, the results suggest that this protocol may be beneficial in ulcers from multiple causes, including those of diabetic and venous origin. Future studies may determine efficacy of this protocol as compared to a placebo group with traditional application of the BAT alone. The rapid healing noted in this study can be attributed not only to the use of the BRAIN principles, but also to the meticulous wound bed preparation and proper offloading that took place in every case prior to and after the BAT application.

References

1. Kim PJ, Dybowski KS, Steinberg JS. A Closer Look at Bioengineered Alternative Tissues. Podiatry Today - ISSN: 1045-7860 - Volume 19 - Issue 7: Pages: 38 – 55, July 2006.
2. Pham HT, Rich J, Veves A, Using Living Skin Equivalents for Diabetic Foot Ulceration: Lower Extremity Wound 1(1); 27-32, 2002.
3. Falanga V, Sabolinski M. A bilayered living skin equivalent construct (Apligraf) accelerates complete closure of hard to heal venous ulcers. Wound Repair Regen 7:201-7, 1999.
4. Bello YM, Falabella AF, Eaglstein WH. Tissue-engineered skin, current status in wound healing. Am J. Clin Dermatol 2(5):303-313, 2001.
5. Claxton MJ, Armstrong DG, Boulton AJM. Healing the diabetic wound and keeping it healed: modalities for the early 21st century. Cur Diab Rep. 2(6):510-8, December 2002.
6. Lee KH. Tissue-engineered human skin substitutes; development and clinical application. Yonsei Medical Journal 41(6):774-779, 2000.
7. Moore, J. The BRAIN Principle: Managing Wounds After Application of Bioengineered Alternative Tissues to Maximize Incorporation and Wound Healing, *doi: 10.3827/faoj.2008.0105.0003,* The Foot & Ankle Journal, 1(5):3, 2008
8. Loots MA, Lamme EN, Zeegelaar J, et al. Differences in cellular infiltrate and extracellular matrix of chronic diabetic and venous ulcers versus acute wounds. J Invest Dermatol 111:850–7, 1998.
9. Dinh T, Pham H, Veves A. Emerging Treatments in Diabetic Wound Care. Wounds 14(1) 2-10, 2002.
10. Eisenbud D, Hunter H, Kessler L, et al. Hydrogel Wound Dressings: Where Do We Stand in 2003. Ostomy/Wound Management 49(10) 52-57, 2003
11. Akiyama, H., Kazuyasu, F., Yamasaki, O., Oono, T., Iwatsuki, K., Antibacterial action of several tannins against staphylococcus aureus, Journal of Antimicrobial Chemotherapy 48: 487-491, 2001.
12. Cowan, MM: Plant Products as Antimicrobial Agents; Clinical Microbiology Reviews, 12(4) 564-582, 1999.
13. Espensen EH, Nixon BP, Lavery LA.. Armstrong, DG. Use of subatmospheric (VAC) therapy to improve bioengineered tissue grafting in diabetic foot wounds. *Journal of the American Podiatric Medical Association.* 92(7): 395-401, 2002.
14. Hopf HW, Humphrey LM, Puzziferri N, et al. Adjuncts to preparing wounds for closure hyperbaric oxygen, growth factors, skin substitutes, negative pressure wound therapy (vacuum-assisted closure). *Foot and Ankle Clinics.* 6: 661-682, 2001.
15. Harold Brem, MD; Jeroen Balledux, MD et al. Healing of Diabetic Foot Ulcers and Pressure Ulcers With Human Skin Equivalent, A New Paradigm in Wound Healing, *Arch Surg.* 135:627-634, 2000.