

# wound healing perspectives®

A CLINICAL PATHWAY TO SUCCESS

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➔ ADVANCED THERAPIES PART III

## Diabetes costs billions

The American Diabetes Association recently released their statement on the Economic Costs of Diabetes in the United States for 2007. The prevalence of diabetes is growing, with 17.5 million people in the U. S. diagnosed with diabetes. This report shows medical costs directly attributed to diabetes at \$27 billion and \$58 billion to treat the portion of diabetes-related chronic complications that are attributed to diabetes. The largest components of medical expenditures is attributed to diabetes and hospital inpatient care (50% of total cost).

In this issue of *Wound Healing Perspectives*, advanced therapies to treat chronic wounds are reviewed. Many of these therapies are viewed as expensive as compared to traditional wound dressings. But, as the ADA Economic data just released points out, the greatest expenditure for the diabetic patient is the inpatient hospital stays. If the addition of advanced therapies can help prevent infections or other complications, then they merit every consideration by the wound center team.

We hope the information in this issue helps you in your decisions to treat these complicated patients and the challenges you face each day evaluating new and advanced therapies.

Sincerely,



Katy Rowland, RN, MBA  
Chief Clinical Officer

## Using advanced therapies to treat non-healing, chronic wounds

For more than two decades, modern wound dressings have used a moist-healing environment for wound management. According to *Advanced Wound Management: Healing and Restoring Lives* [Advanced Medical Technology Association, June 2006], these dressings work by providing a bacterial barrier to prevent infectious organisms from invading the wound, among other tangible benefits. Dressings such as alginates, collagen, foam, hydrocolloids, and hydrogels are just some of the wound care technologies that provide this moist-healing approach. However, not all complex and chronic wounds respond to moist wound healing alone. In these cases, physicians can turn to many of the new technologies now available to help achieve proper wound healing. More importantly, these new advanced therapies can help to reduce the time and costs associated with the healing of extremely complex and/or non-responding wounds [Advanced Medical Technology Association].



**NEW ADVANCED THERAPIES CAN HELP TO REDUCE THE TIME AND COSTS ASSOCIATED WITH THE HEALING OF EXTREMELY COMPLEX AND/OR NON-RESPONDING WOUNDS.**

According to Woo, Ayello, and Sibbald (2007), scientific evidence increasingly reveals that cells in chronic, stalled

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# Growth factors: A mixed response

Although predicted in the 1990s that growth factors would some day revolutionize wound care, their use to stimulate healing has garnered only some appeal. Growth factors—subgroups of cytokines that are biologically active polypeptides—are recognized for their contribution to the cell activation process during wound healing [Woo et al]. Currently, platelet-derived growth factor, a dimeric protein composed of 2 disulfide linked polypeptide chains, is the only growth factor approved by the Food and Drug Administration (FDA). According to Woo et al, platelet-derived growth factor is a potent chemoattractant and mitogen for fibroblasts. It stimulates the production of fibronectin and

hyaluronic acid and is seminal to matrix formation and modulation of other growth factor activities in the wound. Platelet-derived growth factor (PDGF) is more active (catalyst) in acute wounds (or after sharp debridement) than in a chronic wound, where it is only one of many growth factors [Woo et al]. Other growth factors used in wound healing include fibroblast growth factor, keratinocyte growth factor, epidermal growth factor, transforming growth factor and vascular endothelial growth factor, nerve growth factor, hepatocyte growth factor, insulin-like growth factor, and granulocyte colony-stimulating factor [Woo et al].

Woo et al included the

results of four randomized clinical trials of 874 patients with diabetes and neurotrophic foot ulcers in their article to show that the growth factor was successful only in conjunction with adequate wound bed preparation. The trial compared the effect of topical becaplermin gel at a dose of either 30 or 100 µg/g with placebo gel, good ulcer care, or a combination of both. Healing occurred in up to 83% of patients treated with active surgical debridement and topical PDGF. Where surgical debridement was considered inadequate, only 20% of patients achieved healing with the PDGF treatment. These results suggest that wound debridement is a vital step when caring for

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## Using advanced therapies to treat chronic, non-healing wounds *(continued from page 1)*

wounds are altered phenotypically, with an increase in senescent cells that are less responsive to cellular signaling, decreased growth factors, and other diminished cellular responses. Woo et al also states that impaired cell migration and insufficient angiogenesis to support complete wound closure may also occur, leaving an imbalanced matrix

metalloproteases (MMPs) and their inhibitors, which will advance tissue destruction.

To improve wound healing, the addition of deficient components, such as growth factors and tissue matrix components can help. Cellular therapies such as autologous epidermis, allografts, and living skin equivalents are some examples of

advanced therapies [Woo et al]. Complementary therapies, such as growth factors, skin substitutes, the use of hyperbaric oxygen therapy, negative pressure therapy, electrical stimulation, laser therapy, ultraviolet light, and therapeutic ultrasound, among others, also may prove useful in patients with complex, non-healing wounds. ■

## What makes a wound chronic?



Chronic wounds are deficient in growth factors because of numerous mechanisms at work, including reduced growth factor expression, limited release from senescent cells, disproportionate degradation by MMPs, and possibly trapping within perivascular cuffs. The ability to synthesize and concentrate adequate quantities of growth factors has led to clinical trials that evaluate their use [Woo et al]. ■

# Summary of advanced therapy options

SUBSTANTIATED ADVANCED THERAPIES	INDICATION	RCT OR META-ANALYSIS AVAILABLE	RESULTS
OASIS	VLU	Yes	Complete healing
	DFU	Yes	Complete healing equal to PDGF
Growth factors (PDGF)	DNFU	Yes	Complete healing
Apligraf (epidermal cells, dermal, fibroblasts, bovine collagen)	DNFU	Yes	Complete healing
	VLU	Yes	Complete healing
Dermagraft (fibroblasts)	DNFU	Yes	Complete healing
Hyperbaric oxygen therapy (HBOT)	DNFU	Yes	Prevent amputation
Electrical stimulation	PrU	Yes	Complete healing
Therapeutic ultrasound	VLU	Yes	Faster healing
	DNFU	Yes	Complete healing
Negative pressure wound therapy (NPWT)	Post-surgical wounds	Yes	Complete healing
Promogran	VLU	Yes	Decrease wound size

PDGF = platelet-derived growth factor; DNFU = diabetic neurotrophic foot ulcer; VLU = venous leg ulcers; PrU = pressure ulcers; RCT = randomized controlled trial

SOURCE: WOO AND SIBBALD, 2006

## Growth factors (continued from page 2)

patients with chronic diabetic foot ulcers. What's more, the efficacy of becaplermin for pressure ulcer treatment has yet to be determined [Woo et al].

In certain cases, a combination of growth factors and platelet gels are necessary to promote wound healing [Woo et al]. Platelet gels or releasates are prepared from platelet-rich plasma obtained by differential centrifugation of whole blood. Cryoprecipitate may be added in the process to achieve a firmer consistency

of the gel (autologous platelet gel, APG). By adding gluconate calcium, thrombin, or batroxobine in platelet gels, the thrombocyte  $\alpha$ -granules are activated to release a wide range of growth factors, such as PDGF, transforming growth factor-beta, epidermal growth factor, insulin-like growth factor (IGF-1 and  $\beta$ -estradiol [E2]), and vascular endothelial growth factor. Platelet-derived growth factors will, in turn, activate signal transduction enzymatic pathways that up-regulate the tissue-re-

generation cascade [Woo et al]. Other studies have not seen beneficial results. According to the Woo et al article, in separate randomized, placebo-controlled studies, Senet et al and Stacey et al concluded that topical autologous platelets have no significant impact on the healing of chronic venous leg ulcers. In addition, Senet et al failed to demonstrate any modulation of growth factor levels by the platelet gel [Woo et al]. ■

## History of skin substitutes



Xenografts were first used to provide wound coverage as early as 1500 BC. Frog skin and then later water lizard skin were used in some parts of the world around 1600. By the 20<sup>th</sup> century, mammalian skins were used most frequently, including rabbit, dog, and pig skin products, the latter, in fact, are still used today. Xenografts would give way to homografts (in the form of cadaveric grafts and autografts) as the understanding of immunology, critical care, and resuscitation improved. As a result, large amounts of stable, permanent skin coverage were used on patients who were increasingly surviving acute phases of the disease process. ■

SOURCE: SHORES, GABRIEL, AND GUPTA, 2007

# Matrix metalloproteinases and their inhibitors

Matrix metalloproteinases or MMPs are enzymes from the metalloendopeptidases family, which are present in wound exudates. Wound fluids from chronic ulcers have been shown to be proteolytic or hastening the hydrolysis of proteins, due to an over expression and activation of MMPs and from a deficient level of the tissue inhibitors of MMPs. MMPs also are produced by bacteria that are present in chronic

wounds. MMPs may be responsible for the damage from critical colonization and infection in the inflammatory and proliferative phases of wound healing [Woo et al]. According to Ruston (2007), MMPs are expressed into the wound bed to allow dissolution (lysis) of dead tissue and damaged matrix components-the cells' membranes are destroyed making it easier for macrophages to engulf

and digest them. However, excessive accumulation and activation of MMPs can suppress cell proliferation and angiogenesis due to destruction of growth factors and matrix proteins that provide necessary substrates for cell migration and integrity of the tissue [Woo et al]. MMPs also help in cellular migration and extracellular matrix (ECM) remodeling. ■

## Benefits of Promogran Matrix



Promogran Matrix is intended for the management of exuding wounds including:

- Diabetic ulcers
- Venous ulcers
- Pressure ulcers
- Ulcers caused by mixed vascular etiologies
- Full-thickness and partial-thickness wounds
- Donor sites and other bleeding surface wounds
- Abrasions
- Traumatic wounds healing by secondary intention
- Dehisced surgical wounds

Promogran Matrix may be used under compression therapy with professional medical supervision. ■

SOURCE: JOHNSON & JOHNSON GATEWAY WEB SITE

## Combination anti-inflammatory matrix

Prepared from bovine collagen impregnated in oxidized regenerated cellulose/collagen, Promogran (Johnson & Johnson, New Brunswick, New Jersey) is a matrix that restores the balance at the microenvironment level through binding and inactivation of proteases (MMPs), while promoting a moist healing environment and protecting the biologic activity of endogenous growth factors [Woo et al and Johnson & Johnson].

In a study by Vin et al a total of 73 patients with venous leg ulcers were randomly allocated to receive ORC/collagen

(Promogran), while 36 received petrolatum gauze (Adaptic, ETHICON, Inc.). The study revealed that surface area reduction was greater in the Promogran group than in the Adaptic group (median decrease 82.4% versus 44.6%;  $P < .001$ ). Another study by Wollina et al found that both venous leg ulcers and wound microcirculation could be improved when Promogran was used. The authors also conducted a prospective trial that involved 40 patients with chronic venous leg ulcers (where the mean age was 74 years). Wound microcirculation was evaluated

using a technique based on noncontact remission spectroscopy. The mean reduction of the ulcer area was statistically significant in patients treated with Promogran between the initial and final measurements ( $P < .05$ ) [Woo et al]. However, the results of using Promogran in patients with diabetic plantar ulcers are somewhat equivocal, states.

Prisma Matrix (Johnson & Johnson) is another product used to control MMP. It contains 1% silver and kills bacteria in the dressing to help maintain bacterial balance. ■

# Types of skin substitutes and alternatives

Bioengineered skin substitutes (which consist of dermal cells, epithelial cells, or both, on a scaffold of collagen or another support material) were developed to emulate certain normal skin functions that can accelerate wound healing. Multifaceted in their approach, bioengineered skin substitutes not only assist in wound repair, they potentially can restore the biochemical balance and moist wound milieu, offer structural support for tissue regeneration, as well as the provision of cytokines and growth factors in physiologic concentrations, states Woo et al.

A variety of skin substitutes and alternatives to dressings are available to treat chronic wounds. Below are some viable options:

## AUTOGRAFTS

Autografts are tissues grafted to a new position on the same person/patient. They are usually divided into three main categories: split-thickness skin grafts (STSGs), full-thickness skin grafts (FTSGs), and cultured autologous skin, according to a 2007 study by Shores, Gabriel, and Gupta. Split-thickness skin grafts contain the epidermis and a variable thickness of the upper layers of dermis, leaving

the remaining layers of dermis in place to heal by secondary epithelialization from the wound edges and keratinocytes within the adnexa of the deeper dermis [Shores et al]. Full-thickness skin grafts (FTSGs) contain the epidermis and the entire dermis. These grafts are often used in areas where significant scarring has occurred or where contracture of the grafts would provide harmful aesthetic or functional consequences.

## ALLOGRAFTS

Allografts are grafts transplanted between genetically non-identical individuals of the same species. Allografts fall into three categories: epithelial/epidermal, dermal, or composite (epidermal and dermal). Within these categories, they may either be acellular, cellular/living, or cellular/nonliving. Acellular dermal allografts are products that consist of DED taken from human cadaveric donors. The grafts are cryopreserved, lyophilized, and glycerolized in preparation to remove donor cellular, infectious, and antigenic materials. The resultant acellular dermal structure serves as a scaffold or template for ingrowth of host fibroblasts and capillaries until it is replaced by host tissue [Shores et al].

## XENOGRAFTS

Xenografts are made up of tissues from one species and used as a temporary graft on another species. Today, porcine products are the most commonly used xenograft used on humans. These products consist of dermis in varying thicknesses where the epidermis has been removed (de-epithelialized/de-epidermized [DED]) [Shores et al]. Used only as temporary coverage, xenografts are indicated for application to clean partial-thickness wounds [Shores et al].

## ALLODERM

According to [www.life-cell.com](http://www.life-cell.com) (LifeCell Inc., Branchburg, New Jersey) AlloDerm is an acellular dermal matrix derived from donated human skin tissue supplied by U.S. AATB-compliant tissue banks, which follow the standards of the American Association of Tissue Banks (AATB) and FDA guidelines. Since AlloDerm is regarded as minimally processed and not significantly changed in structure from the natural material, the FDA has classified it as banked human tissue. According to Shores et al, AlloDerm is used for varied applications it has been studied extensively in burn patients where it

*(continued on page 6)*

## Characteristics of the ideal skin substitute



- Able to resist infection
- Able to withstand wound hypoxia
- Cost-efficient
- Easy to prepare
- Easy to store
- Easy to use
- Flexible in thickness
- Lack of antigenicity
- Offers long-term wound stability
- Provides permanent wound coverage
- Recreates dermal and epidermal components
- Able to resist shear forces
- Widely available ■

SOURCE: SHORES, GABRIEL, AND GUPTA, 2007

was used for deep partial and full-thickness injuries and has allowed the use of thinner STSGs. AlloDerm's role in chronic wound care, however, remains unclear.

availability of donor autograft tissue, the temporary silicone layer is removed and a thin, meshed layer of epidermal autograft is placed over the "neodermis."

the donor cells and tissue [Woo et al].

#### **APLIGRAF**

Apligraf (Organogenesis, Inc, Canton, Massachusetts), also

## Integra

Considered to be the first and only FDA-approved tissue engineered product for burn and reconstructive surgery, Integra Dermal Regeneration Template is an innovative bilayer matrix that provides a scaffold for dermal regeneration and is a biodegradable template that induces organized regeneration of dermal tissue by the body.

According to the Integra website, it's the only approved skin substitute that regenerates dermis because it allows for the:

- Early wound excision
- Immediate closure of the wound
- Controls fluid loss
- The patient is physiologically improved, allowing for early ambulation and rehabilitation ■

SOURCE: INTEGRA WEB SITE (WWW.INTEGRA-LS.COM)

**MULTIFACETED IN THEIR APPROACH, BIOENGINEERED SKIN SUBSTITUTES NOT ONLY ASSIST IN WOUND REPAIR, THEY POTENTIALLY CAN RESTORE THE BIOCHEMICAL BALANCE AND MOIST WOUND MILIEU, OFFER STRUCTURAL SUPPORT FOR TISSUE REGENERATION, AS WELL AS THE PROVISION OF CYTOKINES AND GROWTH FACTORS IN PHYSIOLOGIC CONCENTRATIONS, STATES WOO ET AL.**

#### **OASIS**

OASIS (HEALTHPOINT, Ltd., Fort Worth, Texas) is a natural, extracellular matrix—a biomaterial used to manage a variety of wounds by providing an environment that allows a patient's body to rebuild and repair damaged tissue [Healthpoint]. OASIS can be used in the management of partial and full-thickness wounds, such as pressure, venous, and chronic vascular ulcers, diabetic ulcers, surgical and trauma wounds, second-degree burns, abrasions, and autograft donor sites.

#### **INTEGRA**

The INTEGRA Dermal Regeneration Template (Integra LifeSciences Corporation, Plainsboro, New Jersey) is a bi-layer membrane system for skin replacement. Upon adequate vascularization of the dermal layer and

Cells from the epidermal autograft grow and form a confluent stratum corneum, which then closes the wound, reconstituting a functional dermis and epidermis. Integra has been used extensively in the treatment of burns and Moiemmen et al described the use of Integra for reconstructive surgery [Woo et al].

#### **DERMAGRAFT**

According to Woo et al, dermagraft (Advanced Biohealing, Inc, La Jolla, California) is the first single-layer product that consists of metabolically active dermal structure and is approved only for diabetic foot. Remaining viable in the product after wound implantation, the fibroblasts continue to secrete growth factors and recruit host cells until fibrovascular tissue in growth gradually replaces

called Graftskin, is approved for venous leg ulcer and diabetic foot. It is a bilayered, living-skin construct composed of cornified differentiated keratinocytes that constitute an epidermis and a lattice of type 1 bovine collagen containing viable fibroblasts that constitute a dermal matrix. It must be applied clinically within five days of delivery. ■

# Negative pressure wound therapy

Negative pressure wound therapy (NPWT)-the delivery of intermittent or continuous subatmospheric pressure to the wound-is considered to be a useful adjunct in the treatment of wounds.

According to a 2007 article by Hunter, Langemo, Hanson, Anderson, and Thompson, the subatmospheric pressure helps to remove exudate, increases local blood flow and granulation tissue formation, decreases bacterial load, and promotes wound closure by applying mechanical stress on edges of the wound. NPWT has been cleared by the U.S. Food and Drug Administration for the treatment of chronic, acute, traumatic, subacute, and dehisced wounds, as well as pressure ulcers, diabetic ulcers, partial-thickness burns, flaps, and grafts [Hunter et al, 2007].

However, it should not be used on wounds that have necrotic tissue with eschar present, exposed veins and arteries, active bleeding, untreated osteomyelitis, or malig-

nancy. Additionally, careful consideration/evaluation should be made before using this type of therapy on patients with fistulas, open body cavities, and oncology-related resections, as well as those with abnormal clotting times.

Several types of NPWT devices are available. One example is vacuum-assisted closure (VAC, KCI, San Antonio, Texas), an open-celled sponge or foam that is composed of either polyurethane or polyvinyl alcohol foam which is cut and placed onto the surface of the wound. The foam is then sealed over with a transparent drape to create a closed, airtight system, maintaining a negative pressure environment through a regulated vacuum pump. Contraction of the foam dressing exerts a centripetal effect at the wound edges and a mechanical force at the interface of the foam and wound. The suction effect and mechanical stress



are transmitted to cellular and cytoskeletal levels, causing deformation of ECM and cells that is postulated to promote cellular proliferation [Woo et al]. According to Hunter et al, silver fabric dressings, microbonded silver foam, and the application of antibiotics and local anesthetics into the wound have been used in conjunction with the VAC. The negative pressure can be set at a continuous or an intermittent cycle.

Another NPWT device is the Versatile 1 Wound Vacuum System (BlueSky Medical, Carlsbad, CA), which uses gauze instead of foam. Its flat, round channel and irrigation/aspiration drains are designed to facilitate drainage and wound healing [Woo et al]. ■

## A cost-benefit analysis of Apligraf

A computer-modeled cost analysis of the use of Apligraf in chronic wounds analyzed direct treatment costs attributable to treatment using Apligraf with compression versus compression therapy alone from the perspective of a health insurer or health plan. The Schonfeld study (based on Falanga and Sabolinski's study of chronic venous ulcers), concluded that the Apligraf/compression treatment arm incurred annual costs of \$20,041, whereas the cost of the compression alone was \$27,493. What's more, the Apligraf group displayed three more months per year per patient in the healed state versus compression alone. This model used an average of 3.34 applications compared to approximately 1.5 applications to effectively heal these wounds with Apligraf, which also resulted in fewer direct costs when using Apligraf (check). Another cost-benefit study combining Falanga's data on diabetic foot ulcers with data from a Dutch trial attempted to extrapolate costs at one year, even though the source data was collected for only six months. Through data analysis and wound healing prediction for these populations at one year, the authors concluded that the Apligraf treatment group could ultimately lower costs by 12% with 12 months of treatment. ■

SOURCE: SHORES ET AL, 2007

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## QUESTIONS OR COMMENTS?

Contact Erica Park at 888.332.0202 or  
Erica.Park@nationalhealing.com

### Wound Healing Perspectives

#### STAFF

James E. Patrick, CEO

Erica Park, Editor

Lisa Sedelnik, Writer

Heather Cicero, Layout Design

#### CLINICAL ADVISORS

Katy Rowland, RN, MBA

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## Working with a Wound Healing Center specializing in advanced therapies

Wound Healing Centers have dedicated, skilled physicians trained specifically in the use of advanced wound technologies. Not only are these centers uniquely equipped to administer these therapies, they also are designed to help primary care physicians avoid upfront costs and the time-consuming training generally associated with advanced wound care.

For example, by partnering with a Wound Healing Center in offering advanced wound therapies, your practice can:

- Provide access to clinicians with experience dealing with extensive wounds
- Ensure follow-up patient education
- Avoid upfront costs
- Avoid storage problems
- Stay informed about

healing progress with regular reports from our Clinical Outcomes Database. ■



## CONSIDER REFERRING YOUR PATIENTS TO A WOUND HEALING CENTER FOR ADVANCED WOUND CARE IF:

- The wound persists for more than 30 days
- Your patient has a wound and also has circulatory problems, diabetes, or is obese
- Your patient has a wound or suffers from chronic pain and has had radiation therapy in the past
- Your patient has had a recent revascularization procedure or has a questionable vascular supply
- You are considering surgical procedures