CLINICAL MANAGEMENT extra

Skin Substitutes and Alternatives: A Review

CME CATEGORY 1
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Dr Shores has disclosed that he has no significant relationships with or financial interest regarding this educational activity. Dr Gabriel has disclosed that he is a member of the speaker's bureau for KCI. Dr Gupta has disclosed that he has no significant relationships with or financial interest regarding this educational activity. Drs Shores and Gupta disclosed that they plan to discuss unlabeled/investigational usage of a commercial product and will disclose this to the audience.

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PURPOSE

To provide the specialist in skin and wound care with a review of skin replacement alternatives and their most common uses.

TARGET AUDIENCE

This continuing education activity is intended for physicians and nurses with an interest in wound care and related disorders.

OBJECTIVES

After reading this article and taking this test, the reader should be able to:

1. Describe characteristics of skin and skin substitutes for grafting.

2. Identify indications for and uses of common grafting procedures and products.

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The integument is the largest single organ of the human body, and although composed of only 2 specialized tissue layers, it remains a reconstructive challenge in many cases when compromised. A set of rules, known as the reconstructive ladder, helps guide practitioners with reconstructive surgery of the integument. The philosophies of the reconstructive ladder and replacing like with like have led to the development of the treatment strategies used today. The reconstructive ladder starts with the simplest treatment of secondary closure and progresses to distant free tissue transfer at the most complex level.

Many different characteristics of the whole patient and the reconstruction itself must be considered before choosing any specific therapy. Analysis should include consideration of the

normal skin anatomy, the patient's condition, comorbidities, wound type, the tissue missing, and the level of contamination. Further analysis should include the visibility of the area, contour abnormalities, adjacent tissue laxity, vascularity of the wound bed, ability to immobilize the patient postoperatively, and aesthetics. Within this framework, a reconstructive plan may be formulated with the goals of wound closure, prevention of infection, and stable-robust coverage, which maximizes function while minimizing donor defects.

Until a layer of tissue mechanically similar to the integument is placed over a reconstruction site, the reconstruction is incomplete and prone to failure. In addition, primary genetic diseases of the skin present further challenges to reconstruction, making bioengineered skin substitutes a solution that has received much attention lately.

Skin substitutes are a heterogeneous group of substances that aid in the temporary or permanent closure of many types of wounds, depending on wound coverage that vary based on wound and product characteristics. Although these products are not substitutes for adequate surgical debridement or standard surgical therapies such as flap coverage, they offer alternatives when standard therapies are not desirable. Skin substitutes provide reconstructive solutions that may be superior to other available methods because they may require a less vascularized wound bed, increase the dermal component of the healed wound, reduce or remove inhibitory factors, reduce the inflammatory response, and provide rapid and safe coverage. They also allow flexibility within the reconstructive ladder, enabling practitioners to use an approach more analogous to a reconstructive elevator, rather than a ladder. The practitioner can advance up and down the reconstructive ladder from extremes of coverage options, skipping in-between steps if desired.

Table 1.
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

History of Skin Substitutes

Xenografts were first used to provide wound coverage as early as 1500 BC.[1] Frog skin was initially used and has been resurrected in modern times as Ranafilm, a bullfrog (*Rana catesbeiana shaw*) skin product,[2] in some parts of the world, such as Vietnam and South America. Water lizard skin was also used in western culture in the 1600s.[1] This progressed to the use of mammalian skins during the 20th century, including rabbit, dog, and the still-used pig skin products. Xenografts gave way to homografts in the form of cadaveric grafts and autografts as the understanding of immunology, critical care, and resuscitation improved to the point where large amounts of stable, permanent skin coverage were required as patients survived the acute phases of their disease processes. Newer technologies built upon the principles learned using cadaveric grafts and autografts, giving way to the creation of engineered substitutes using living allograft cells, as well as the combining of technologies to create composites.

No perfect or ideal skin substitute exists. The qualitative ideal properties of the perfect product are listed in Table 1. These characteristics are not easily quantified in individual products; however, practitioners may consider how these tenets affect product selection and availability in individual practice environments and cases. Each type of product has applications, strengths, and disadvantages that vary depending on the clinical scenario. The variety is so great that a true head-to-head comparison of all products is not feasible. This article provides health care practitioners with a basic familiarity of the available products and processes, including a brief review of the history (see *History of Skin Substitutes*) and available technology of skin replacement alternatives, as well as their most common uses (Table 2).

XENOGRAFTS

Xenografts are tissues from one species used as a temporary graft on another species. Xenografts were first used to provide wound coverage as early as 1500 BC.[1] Frog skin was initially used and has even been resurrected in modern times in some parts of the world, such as Vietnam and South America.[2] Porcine products are the most commonly used xenograft in today's market.[3] They consist of dermis in varying thicknesses in which the epidermis has been removed (de-epithelialized/de-epidermized [DED]). Depending on the preservation process, xenografts are stored frozen or refrigerated to maintain adhesiveness, and the dermis may be meshed to allow drainage of transudates. Xenografts are indicated for application to clean partial-thickness wounds and are used

Table 2.
SKIN SUBSTITUTES

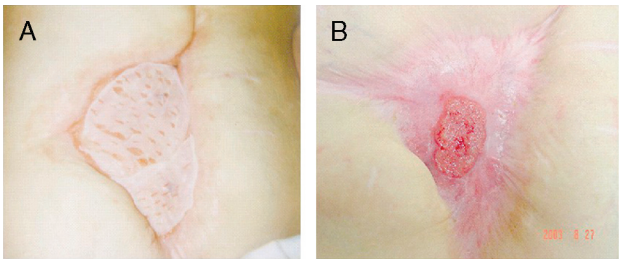
Product	Company	Tissue of origin	Layers	Categories	Uses	Cost estimate (cm^2)[78*,†]
Permacol	Tissue Science Laboratories, Andover, MA	Xenograft	Dermis	1. Xenograft 2. Dermis 3. Processed xenograft	• Temporary burn coverage • Clean partial-thickness wounds	$$-$$$
Epicel	Genzyme Tissue Repair Corporation, Cambridge, MA	Autogenous keratinocytes	Cultured autologous keratinocytes	1. Autograft 2. Epidermis 3. Cultured autogenous	• Deep partial- and full-thickness burns > 30% TBSA	$$$$$
Laserskin Vivoderm	Fidia Advanced Biopolymers, Abano Terme, Italy ER Squibb and Sons, Princeton, NJ	Allogenic keratinocytes	Cultured allogenic keratinocytes	1. Allograft 2. Epidermis 3. Cultured allogenic	• Deep partial- and full-thickness burns > 30% TBSA	
Cadaveric skin	Various	Allogenic dermis	Acellular dermis	1. Allograft 2. Dermis 3. Processed allogenic	• Deep partial- and full-thickness burns • Soft tissue replacement, suspensory materials • Interpositional grafts • Tissue patches	$$-$$$
Alloderm	LifeCell, Branchburg, NJ	Allogenic dermis	Acellular dermis	1. Allograft 2. Dermis 3. Processed allogenic	• Deep partial- and full- thickness burns • Soft tissue replacement • Suspensory materials • Interpositional grafts • Tissue patches	$$$
TransCyte (Dermagraft-TC)	Advanced BioHealing, Inc, La Jolla, CA	Allogenic dermis	1. Silicone 2. Nylon mesh 3. Collagen seeded with neonatal fibroblasts	1. Allograft 2. Dermis 3. Cultured allogenic	• Partial-thickness burns not requiring graft • Temporary coverage of excised burns	$$$$ (currently unavailable)
Dermagraft	Advanced Biohealing, Inc, La Jolla, CA	Allogenic dermis	Dexon or Vicryl seeded with neonatal fibroblasts	1. Allograft 2. Dermis 3. Cultured allogenic	• Chronic wounds • Full-thickness burns with STSG	$$$$
ICX-SKN	Intercytex, Ltd, Manchester, UK	Allogenic dermis	1. Human-based ECM 2. Allogenic fibroblasts	1. Allograft 2. Dermis 3. Cultured allogenic	• Phase II trials pending	

Table 2.
SKIN SUBSTITUTES, CONTINUED

Product	Company	Tissue of origin	Layers	Categories	Uses	Cost estimate (cm^2)[78*,†]
Apligraf	Organogenesis, Inc, Canton, MA	Allogenic composite	1. Neonatal keratinocytes 2. Collagen seeded with neonatal fibroblasts	1. Composite allograft 2. Epidermis + dermis 3. Cultured allogenic	• Chronic wounds • Excision sites • Used with STSG to improve function/ cosmesis	$$$$$$
OrCel	Ortec International, Inc, New York, NY	Allogenic composite	1. Neonatal keratinocytes 2. Bovine collagen sponge 3. Neonatal fibroblasts	1. Composite allograft 2. Epidermis + dermis 3. Cultured allogenic	• Skin graft donor site • Hand contractures with epidermolysis bullosa • Chronic wounds	
Suprathel	Institute of Textile and Process Engineering, Denkendorf, Germany	Synthetic	1. DL-Lactatide monolayer	1. Synthetic 2. Epidermis	• Partial-thickness burns and skin graft donor sites	
Biobrane	UDL Laboratories, Inc, Rockford, IL	Synthetic	1. Silicone 2. Nylon mesh 3. Collagen	1. Synthetic bilayer 2. Dermis	• Superficial partial-thickness burns • Temporary cover of excised burns	$
OASIS	Healthpoint, Fort Worth, TX	Xenograft	Acellular extracellular matrix	1. Xenograft 2. Dermis 3. Processed	• Temporary cover of superficial and deep burns/injuries • Partial- and full-thickness chronic wounds	$$
Integra	Integra Life Science Corporation, Plainsboro, NJ	Synthetic	1. Silicone 2. Collagen and GAG matrix	1. Synthetic bilayer 2. Dermis	• Deep- or full-thickness soft tissue defects for coverage • Requires definitive ''closure'' with skin graft	$$$
Cultured skin substitute	University of Cincinnati, Cincinnati, OH	Autogenous keratinocytes fibroblasts	1. Autogenous epidermis 2. Autogenous dermis	1. Composite autograft 2. Epidermis + dermis 3. Cultured autogenous	• Permanent cover of large TBSA burns/injuries • Partial deep- and full-thickness wounds	Not yet commercially available

TBSA indicates total body surface area; STSG, split-thickness skin graft; GAG, glycosaminoglycan.
*Some costs per unit cm^2 were obtained by contacting manufacturers/distributors and may vary by size, thickness, quantity, distributor, and region.
†$: 0-$1; $$: $2-5; $$$: $6-10; $$$$: $11-15; $$$$$: $16-20; $$$$$$: $21-30 (all costs in US dollars).

Figure 1.
AN 8-YEAR-OLD MALE WITH LUMBAR WOUND DEHISCENCE AFTER SPINAL INSTRUMENTATION



A. Covered with porcine xenograft. B. Wound contraction after multiple applications of porcine xenograft.

only as temporary coverage (Figure 1). Recent modifications to pig skin include aldehyde cross-linking and impregnation with silver ions to provide longer-lasting and more antimicrobially resistant grafts. Although xenografts may be left in place to become adherent until sloughing with re-epithelialization, many practitioners advocate changing the graft every 2 to 4 days for wound monitoring.

Permacol (Tissue Science Laboratories, Hampshire, UK) and OASIS Wound Matrix (HEALTHPOINT Ltd, Fort Worth, TX) are the most recent additions to the xenograft armamentarium.

• ***Permacol***. Permacol is a product derived from porcine dermis that has undergone a proprietary manufacturing process to create an acellular collagen matrix similar in concept to the allograft product AlloDerm.[4] Although Permacol has been used more extensively in the United Kingdom for implantation-related purposes, it is now being distributed in the United States and is approved by the US Food and Drug Administration (FDA) for rotator cuff repair and head and neck applications. It is also being marketed for urologic and gynecologic applications.

• ***OASIS.*** OASIS Wound Matrix is an acellular dermal regeneration matrix featuring small intestine submucosa technology. OASIS is prepared from porcine jejunum that has been processed to remove the cellular components, leaving a scaffolding structure with extracellular matrix including glycosaminoglycans, fibronectin, proteoglycans, and growth factors (basic fibroblast growth factor and transforming growth factor β).[5] It is most commonly used for chronic wounds of the lower extremity, although case reports, including the authors' experience, on the use of this product for other applications have yielded mixed results (Figure 2).

Mostow et al[6] performed a randomized controlled trial on 120 patients with chronic venous leg ulcers comparing compression therapy with OASIS to standard compression therapy and wound care for 12 weeks or until wound closure. Fifty-five percent of patients in the OASIS group demonstrated complete healing versus 34% of patients who received standard compression and wound care alone (P = .0196). On average, 8 sheets (3 7 cm) of OASIS were used per patient treated. After 6 months, 30 of 62 patients in the OASIS group were evaluated. Of these 30, 19 had healed ulcers during the 12-week study period, and 0 of 19 patients had recurrent ulcers at the follow-up examination. In another study by Niezgoda et al,[7] OASIS was compared with Regranex gel in the treatment of diabetic foot ulcers. This randomized, controlled, multicenter trial recruited 73 patients who were followed up weekly for 12 weeks. In the OASIS group, 49% of ulcers healed, compared with 28% in the Regranex group. This difference was not statistically significant because of the small sample size.

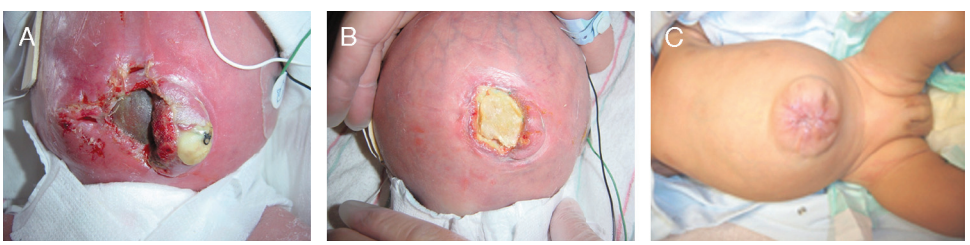
AUTOGRAFTS

Autografts are tissues grafted to a new position on the same individual. They are commonly divided into 3 main categories: split-thickness skin grafts (STSGs), full-thickness skin grafts (FTSGs), and cultured autologous skin.

Split-thickness skin grafts

Split-thickness skin grafts contain the epidermis and a variable thickness of the upper layers of dermis, leaving the

Figure 2.
A. GASTROSCHISIS WOUND WITH EXPOSED VISCERA. B. APPLICATION OF OASIS. C. RESULTANT FULL-THICKNESS HEALING.



remaining layers of dermis in place to heal by secondary epithelialization from the wound edges and keratinocytes within the adnexa of the deeper dermis.

Full-thickness skin grafts

Full-thickness skin grafts (FTSGs) contain the epidermis and the entire dermis.[8] These grafts are preferred in areas where significant scarring or contracture of the grafts would provide harmful aesthetic or functional consequences. Because there are a limited supply of FTSG donor sites, they are usually reserved for reconstructing wounds of the head, neck, hands, and areas of the genitals and breasts.

Cultured autologous skin

Cultured autologous skin substitutes are frequently referred to as cultured epidermal autografts (CEAs). This nomenclature includes epidermal grafts and excludes dermal/epidermal grafts.

• ***Epicel.*** Epicel (Genzyme Biosurgery, Cambridge, MA) is an autologous cultured keratinocyte product indicated for deep partial- and full-thickness burns of total body surface area (TBSA) greater than 30% and large congenital nevus excisions. It requires a biopsy (2 6 cm) from the patient. The manufacturing process then isolates, expands, and cultures the autologous keratinocytes in sheets for grafting by coculturing with murine keratinocytes.[9] Because of this process, patients with vancomycin, amikacin, and bovine protein product sensitivities are not candidates. The entire TBSA can be recreated (1.8 m^2) in up to 4 weeks, although the minimal preparation time for smaller surface areas is 16 days.

Advantages of Epicel include the availability of autologous tissue with permanent cover from a small amount of donor tissue. This is theoretically ideal for patients with high TBSA injuries who have few or no adequate donor sites. Disadvantages of Epicel include relatively high expense, time required for preparation, fragility of the resultant skin secondary to the thinness of the epidermal grafts, and a short window availability for grafting. Practically speaking, patients with high TBSA injuries have the highest potential benefit from this product. However, these patients are also the least stable for grafting secondary to burn sepsis and other medical problems. If patients are unstable for grafting in the 24- to 48-hour window present after receiving the CEA product, the grafts may go to waste.

In a study by Carsin et al[10] of 30 burned patients, CEA achieved coverage of 26% TBSA with an average take of 69%. Mechanical fragility was considered the largest drawback, with blistering seen during the period of dermal-epidermal junction maturation.[10] These patients also required meticulous wound care with noncytotoxic antimicrobial agents.

• ***Laserskin.*** Laserskin (Fidia Advanced Biopolymers, Abano Terme, Italy) is an epidermal autograft composite using autogenous keratinocytes from the patient that are cultured in a lab and seeded onto membrane consisting of 100% esterified hyaluronic acid, which is laser microperforated. (Skin substitute literature frequently cites VivoDerm [ER Squibb and Sons, Princeton, NJ] as an example of the same product, which may no longer exist as a separate entity as it has always appeared aligned with Fidia Advanced Polymers.) This product requires premanufacture biopsy of the patients for whom autogenous keratinocytes may be cultured and expanded. After approximately 10 days, autogenous keratinocytes are seeded onto the membrane and sent back to the clinical site for engraftment. Recent studies have evaluated its use with other hyaluronic acid-based dermal regeneration products from Fidia Advanced Biopolymers that have been branded HYAFF. Use of Laserskin has been investigated in a small pilot study of chronic diabetic foot ulcers.[11] The authors reported complete healing of 11 of 14 ulcers by 64 days. However, this study was preliminary, had no internal controls, and no long-term follow-up.[11] A large, multicenter, retrospective uncontrolled study was performed in Italy by Uccioli et al[12] evaluating the TissueTech Autograft System (Fidia Advanced Biopolymers), which consists of a combination of autologous fibroblast cultures within a HYAFF based 3-dimensional matrix (Hyalograft-3D, Fidia Advanced Biopolymers) with Laserskin applied as the epidermal layer. Diabetic lower extremity ulcers, venous ulcers, arterial ulcers, traumatic wounds, pressure ulcers, and other wounds were studied in 975 patients for 4 years. Diabetic wounds and venous ulcers demonstrated 70.3% and 56.4% healing at approximately 1 year, respectively. Because this study was purely descriptive, there were no controls for comparison. Experimental use of Laserskin in burn reconstruction has also been reported. One study examined the efficacy of allogenic fibroblasts on Laserskin;[13] another attempted staged application of Laserskin seeded with autologous keratinocytes to burn wounds treated with Integra bilaminate wound matrix (Integra Life Sciences, Plainsboro, NJ) with results varying from 50% to 100% survival of Laserskin grafts.[14]

• ***Cultured skin substitute.*** Cultured skin substitute (CSS) is a CEA with the addition of a cultured autologous dermal layer, making it a more anatomically correct skin substitute.[15] This product was created at the University of Cincinnati and Shriners Hospitals for Children, Cincinnati, OH, and is still in clinical trials but does represent, theoretically, the most advanced autologous skin substitute available. The product is created by culturing autologous fibroblasts and keratinocytes with collagen and glycosaminoglycan substrates. While

passenger melanocytes may be present in the cultures, reports indicate that pigmentation can be uneven and unpredictable. CSSs have the potential to offer up to 60- to 70-fold expansion of donor skin.

In 2002, Boyce et al[16] compared CSS with STSG and found no statistical differences at 28 days and 1 year. The authors became more successful with engraftment as their study progressed. However, the last 12 patients demonstrated an average take of 75% for CSS during the first 2 weeks after engraftment. This dropped to 71.5% by postoperative day 14. Up to 1-year postoperative, the CSS group demonstrated less raised scarring, and at 1 year, there was no qualitative difference between autograft and CSS. These results were further improved in the study of Boyce et al[16] performed in a pediatric population. Engraftment rates were 81.5% at postoperative day 14, and Vancouver Scar Scale scores were not statistically different at 1 year.[17] Although this product is not yet commercially available, CSS remains the most significant advancement in autologous-engineered skin.

ALLOGRAFTS

Allografts are grafts transplanted between genetically nonidentical individuals of the same species. Most human skin substitute allografts come from cadaveric sources. Allografts fall into 3 categories: epithelial/epidermal, dermal, or composite (epidermal and dermal). Within these categories, they may either be acellular, cellular/living, or cellular/nonliving.

Epithelial/epidermal allografts

• ***Human amniotic membrane.*** Human amniotic membrane has been used since 1910 to provide epidermal barrier function.[18,19] Use tapered off after it was largely replaced by porcine xenograft in the 1960s, but it is still occasionally used at present. The epithelium in human amniotic membrane provides good protection from evaporative loss, as well as barrier function, whereas the fibronectin and collagen matrix provide some dermal function. It is transparent, which offers good wound surveillance capabilities, and is minimally adherent, which facilitates dressing changes every 2 days. However, it is difficult to obtain, prepare, and store; it must be changed frequently; and it has more significant potential for infectious disease transmission than other products.

Acellular dermal allografts

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. Both commercially patented products and skin-banked products are available. Skin-banked cadaveric skin is an acellular dermal allograft used for temporary coverage of deep partial- to full-thickness burns (Figure 3). Although application helps with pain control and some insensible loss, the barrier function of all acellular dermal allografts is incomplete.

• ***AlloDerm.*** AlloDerm (LifeCell, Branchburg, NJ) is a commercially available acellular dermal allograft processed in a proprietary fashion and is used for varied applications. AlloDerm has been studied in burn patients where it was used for deep partial- and full-thickness injuries and has allowed the use of thinner STSGs.[20–22] In fact, a single-stage procedure of meshed AlloDerm placement at the time of skin grafting was shown to be a successful algorithm. AlloDerm-grafted burns also showed less scarring, a property possibly related to its ability to act as an adhesion barrier. Although acellular dermal allografts were originally intended for the treatment of skin defects, their ability to reconstruct other fibrous tissue of the body has been capitalized in many surgical specialties. AlloDerm is used for soft tissue replacement and augmentation, reconstruction of abdominal wall defects (Figure 4), coverage of implantable prostheses, interpositional grafts, tissue patches, and as suspensory materials in urologic and gynecologic surgeries. AlloDerm requires no special refrigeration or freezing for storage and has a shelf life of 2 years.

Figure 3.
TEMPORARY COVERAGE WITH CADAVERIC DERMAL ALLOGRAFT

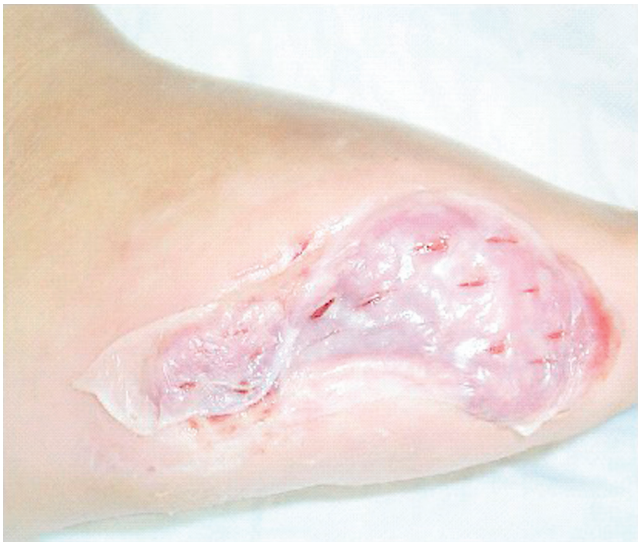
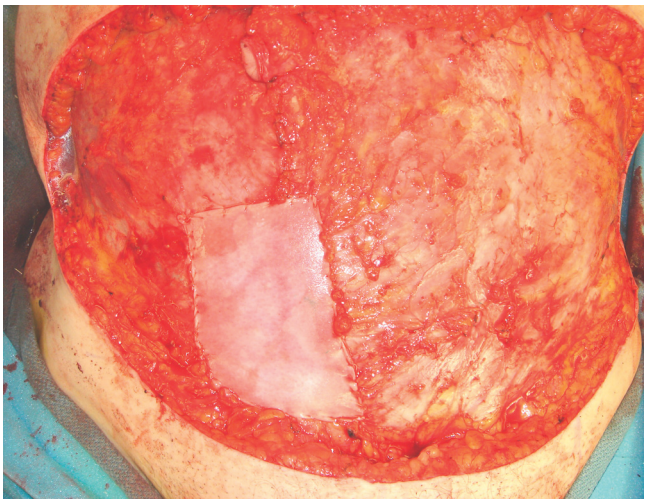


Figure 4.
ABDOMINAL WALL FASCIAL DEFECT REPAIR WITH ALLODERM



Although there is a theoretical disadvantage in that it is human donor tissue and therefore bears a small risk of infectious disease transmission, there have been no cases reported in more than 1 million product uses (Unpublished data from LifeCell Corporation, Branchburg, NJ, 2007; http://www.lifecell.com).

• ***GraftJacket.*** GraftJacket (Wright Medical Technologies, Inc, Arlington, TN) is a newer acellular dermal allograft product in the biomedical market. GraftJacket has been studied for use in lower-extremity wounds, as well as orthopedic applications, including tendon and rotator cuff repair. In a study of 40 patients with diabetic lower-extremity wounds of greater than 6 weeks' duration, Brigido et al[23] found that a single application of GraftJacket resulted in statistically significant decreases in wound dimensions and surface area over 4 weeks when compared with control wounds that received standard wound care. Although the study of Brigido et al illustrates the possibility of a dermal regeneration template in diabetic lower-extremity wounds, questions about long-term follow-up examinations and the actual number of wounds healed remain to be answered.

Citing similarity to LifeCell's AlloDerm, Mentor Corporation (Santa Barbara, CA) and Synthes, Inc (West Chester, PA) have recently brought to market human dermal products for implantation with the last year. Mentor's ***NeoForm*** is a human cadaveric dermal product that is solvent dehydrated and gamma irradiated in its manufacturing process by Axis-Tutoplast.[24] Its main indication is to provide extra soft tissue coverage for implanted breast prosthesis in breast reconstruction following mastectomy, a technique currently performed by many plastic surgeons with the product AlloDerm. Cadaveric dermal material processed by the same company has been used successfully in urogynecologic procedures as well as dental procedures.[24,25] Although the solvent dehydration and gamma-irradiation processing of products by Axis-Tutoplast has been shown to result in a lower percentage of large segments of intact DNA versus total DNA content of donor tissue compared to other products such as AlloDerm, their overall total DNA content was still higher than that of AlloDerm (767.5 mcgs/mg vs 526 mcgs/mg).[26] Furthermore, the clinical significance of this finding is unknown as LifeCell self-reports implantation of more than 1 million pieces of AlloDerm without known transference of infective DNA or other particle.

• ***DermaMatrix*** is another acellular allogeneic dermal product processed and manufactured by the Musuloskeletal Transplant Foundation and distributed through Synthes, Inc. This product uses the same raw cadaveric dermal material as AlloDerm and NeoForm but is processed using a combination of detergent and acid washes and is then freeze dried and packaged terminally sterile. Its purported uses include craniofacial, abdominal wall, and breast reconstruction. Synthes hopes to market it for the same indications as AlloDerm. Although there are no published studies that support or dispute its efficacy, it is another acellular monolayer dermal product that has recently become available.

Cellular dermal allografts

Cellular dermal allografts use only donor cells to help create a regenerative structure composed of a scaffold of various materials. This structure is then seeded with donor fibroblasts that synthesize proteins and other components of extracellular matrix that serve to help stimulate cells within the host's wound to promote healing.

• ***ICX-SKN.*** ICX-SKN (Intercytex Ltd, Manchester, UK) is an allogenic living monolayer dermal substitute comprised of a collagen-based scaffold populated with living fibroblasts.[27] Phase I trials of ICX-SKN have been completed demonstrating efficacy in healing full-thickness wounds created on small number of healthy volunteers. After implanting ICX-SKN, each subject successfully epithelialized the wound. Up to 28 days after wounding, the wounds were excised and analyzed histologically. Each wound had fully epithelialized and each ICX-SKN graft had been successfully incorporated into the recipients body with complete vascularization.[27] Intercytex is in the process of beginning phase II clinical trials and also indicates the possibility of creating a bilayer product with

epidermal cellular components (keratinocytes), in addition to the dermal cellular construct.

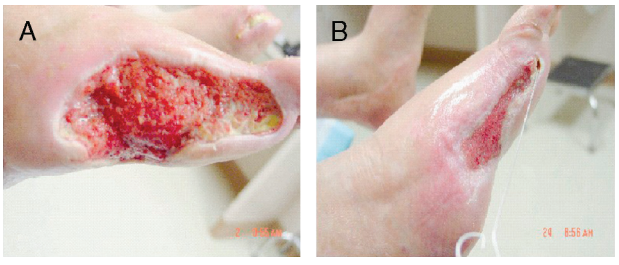
• ***TransCyte***. TransCyte (also known as Dermagraft-TC, Advanced BioHealing, Inc, La Jolla, CA; previously available through Advanced Tissue Sciences, La Jolla, CA) uses a nylon mesh covered with porcine dermal collagen (similar to Biobrane (UDL Laboratories, Inc, Rockford, IL), that is seeded with neonatal fibroblasts. These cells are allowed to proliferate and synthesize fibronectin, type I collagen, proteoglycans, and growth factors for 17 days. The fibroblasts are then cryopreserved, with preservation of the newly synthesized extracellular matrix and growth factors.[28] Because it uses porcine collagen and bovine protein in its growth medium, a hypersensitivity to these products is a contraindication to its use. TransCyte is indicated for definitive coverage of superficial partial-thickness wounds not requiring skin grafts or temporary coverage of deeper wounds requiring skin grafting at a later time. Advantages of TransCyte have been shown in multiple studies demonstrating that when used as temporary cover before skin grafting, it was easier to remove and resulted in less bleeding than allograft; ultimately, TransCyte maintained graft survival equal to allograft.[29] In a study of pediatric populations with partial-thickness burns, TransCyte reduced the number of skin grafts and showed better cosmesis and less hypertrophic scarring in wounds not grafted when compared with hydrodebridement and topical ointment treatments.[30] With TransCyte, patients reported less pain, and wound healing was shown to be faster, both of which were statistically significant.[29,31] TransCyte availability has been a challenge in the past few years as the original manufacturing company declared bankruptcy and Smith & Nephew (Largo, FL) acquired the rights to the former companies products. Although production of TransCyte's ''sister product,'' Dermagraft, has resumed in La Jolla, CA, by Advanced Biohealing, Inc, no public plans to resume production of this product are known at press time.[32]

• ***Dermagraft.*** Dermagraft (Advanced Biohealing, Inc, La Jolla, CA) is a living cellular dermal allograft derived from neonatal fibroblasts seeded onto a resorbable polyglactin polymer scaffold. The fibroblasts secrete growth factors, including collagens, tenascin, citronectin, and glycosaminoglycans. Remaining viable in the product after wound implantation, the fibroblasts continue to secrete growth factors and recruit host cells until fibrovascular tissue ingrowth gradually replaces the donor cells and tissue.[33] The exact extent to which donor fibroblasts continue to survive in the wound is not known, but these cells have been found up to 6 months after application.[34] Dermagraft is primarily indicated to stimulate healing of chronic lesions such as diabetic ulcers of more than 6 weeks' duration that are not overlying bone, tendon, muscle, or joint capsule (Figure 5). It may be applied weekly for up to 8 applications. Many clinicians trim a wound-size portion of the Dermagraft and store the excess in a medical refrigerator and later apply the remaining product to the same patient. However, this practice is not specifically approved by the US Food and Drug Administration or recommended by the manufacturer.

After Hanft and Suprenant's[35] initial single-center study demonstrating efficacy for diabetic foot ulcers was performed in 2002, Marston et al[36] followed 314 patients at multiple centers in a randomized controlled trial that demonstrated 30% complete healing with Dermagraft versus 18% healing with conventional methods after 12 weeks (P = .023). Wounds were 1.6 to 1.7 times more likely to heal in the Dermagraft group, and the median percentage of wound closure was 91% in the Dermagraft group versus 78% in the control group (P = .044). Although overall complications were fewer in the Dermagraft group, this difference was not statistically significant; however, complications directly related to the ulcer (cellulitis, osteomyelitis, and local wound infection) were significantly lower with Dermagraft (19% vs 32.5%, P = .007). Although these results sound promising, long-term follow-up studies are necessary to prove valid efficacy as well as cost benefits. Other non–FDA-approved uses for Dermagraft that have been reported in the literature include venous ulcers (50% vs 12.5% healing, P = NS) in a very small Egyptian 12-week study of 18 patients, which sought to show that a larger trial was warranted. Other reported uses include outpatient treatment of fasciotomy wounds, buccal fat pad graft donor site healing, pediatric postsurgical abdominal wound healing, and vestibuloplasty.[38–41]

As with almost all products, Dermagraft is contraindicated for placement on infected wounds or wounds that require

Figure 5.
A. DIABETIC FOOT WOUND AFTER DEBRIDEMENT OF INFECTION AND GRANULATION. B. INTERIM HEALING AFTER 3 APPLICATIONS OF DERMAGRAFT OVER 6 WEEKS.



surgical debridement. It is also contraindicated in persons with bovine protein allergies.

Composite allografts

Composite allograft products are the most advanced and closest products to living skin that are *currently commercially* available. The 2 prototypical products of this line are Apligraf and Orcel.

• ***Apligraf.*** Apligraf (Graftskin; Organogenesis, Inc, Canton, MA) is a composite bilayer product that uses a combination of bovine type I collagen gel and living neonatal fibroblasts as the dermal component, with a cornified epidermal layer composed of neonatal keratinocytes.[42] It is available and ready to use and has a shelf life of 5 days. It is approved by the US FDA for chronic venous ulcers of more than 1 month's duration and diabetic lower extremity ulcers of more than 3 weeks' duration.[43] It can also be used with meshed STSGs.[43] Apligraf may be applied every 4 to 6 weeks, and the number of applications required to treat wounds may vary by practitioner experience, wound type, and location (Figure 6).

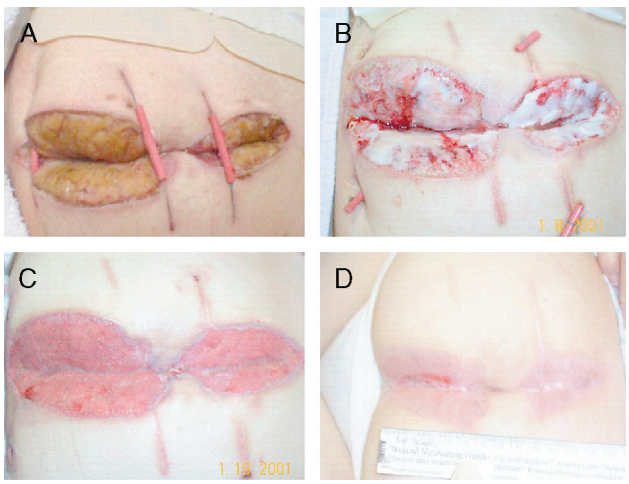
Apligraf has been most extensively studied in venous and diabetic ulcers. In 2000, Falanga[44] published a prospective, randomized, multicenter study of 214 patients with chronic venous ulcers that evaluated the efficacy of Apligraf with compression therapy versus compression therapy alone. The subjects were followed up for 6 months, and those who received treatment with Apligraf were 3 times more likely to have complete healing of wounds older than 1 year (defined as difficult wounds) by 8 weeks ($P = .008$) and were 2 times more likely to have complete healing by 24 weeks ($P = .002$).[44] In 1999, Falanga and Sabolinski[45] published similar results in a smaller, prospective, randomized, controlled trial that showed venous ulcers of more than 1 year's duration progressed to complete healing by 6 months with standard compression and Apligraf versus 19% of patients who received standard compression therapy alone ($P < .005$). In addition, subjects in the Apligraf group were twice as likely to heal by 6 months versus those who received standard compression therapy alone ($P < .005$).[45]

A number of researchers have also performed cost analyses of the use of Apligraf in chronic wounds (see *Cost-Benefit Analysis of Apligraf*). Schonfeld peformed a computer-modeled cost analysis based on Falanga's data analyzing direct costs attributable to cost of treatment of Apligraf with compression versus compression therapy alone from the perspective of a health insurer or health plan.[46] Schonfeld's study, which was dependent on several factors, concluded that the Apligraf/compression treatment arm incurred annual costs of $20,041, whereas the cost of the compression alone arm was $27,493. The Apligraf group displayed 3 more months per year per patient in the healed state versus compression alone. This model used an average of 3.34 applications, whereas the authors note that those studies using only 1.5 applications to efficaciously heal these wounds would result in fewer direct costs to the Apligraf group—resulting in more savings. In all cases, Apligraf was compared to standard therapy consisting of compression and a moist nonadherent dressing that is considered standard therapy and has been shown in a large meta-analysis of randomized-controlled prospective studies to be equivalent, if not superior, to all other topical non-skin substitute dressing types reviewed.[47]

The use of Apligraf in diabetic foot ulcers has also been evaluated. Veves et al[48] studied 208 patients in a 12-week, multicenter, randomized, controlled trial that compared Apligraf with moist gauze dressings, which was considered standard treatment and were recommended by the Consensus Conference on Diabetic Foot Wound Care[43–45] in 1999. On average, 3.9 applications of Apligraf per wound were used. At 12 weeks, 56% of patients treated with Apligraf had complete healing versus 38% of patients in the control group ($P = .004$). Median time to closure was sooner with Apligraf (65 vs 90 days; $P = .003$). The odds ratio for healing with Apligraf was 2.14 times greater than with moist gauze dressings (95% confidence interval, 1.23-3.74). There were no statistical differences in adverse outcomes such as wound complications or infections, except for osteomyelitis and pro-

Figure 6.
LAPAROTOMY WOUND TREATED WITH APLIGRAF

A. Dehisced laparotomy wound on immunosuppressed patient unable to tolerate other methods of wound closure. B-D. Showing progressive healing with application of Apligraf over the course of 30 days.



Cost-Benefit Analysis of Apligraf

A number of investigators have analyzed the cost benefits of using skin substitutes such as Apligraf compared with standard therapies.

Venous ulcers

Based on Falanga and Sabolinski's[45] study of chronic venous ulcers, Schonfeld et al[46] performed a computer-modeled cost analysis that analyzed direct costs attributable to treatment using Apligraf with compression therapy versus compression therapy alone from the perspective of a health insurer or health plan. Admittedly, the study depends on several fluid assumptions on cost and therapy that could be manipulated in many ways throughout the model. However, the results of the study of Schonfeld et al[46] showed that the Apligraf plus compression treatment arm incurred annual costs of $20,041; the cost of the compression-treatment-alone arm was $27,493. In addition, the Apligraf group displayed 3 more months per year per patient in the healed state versus compression therapy alone. However, the cost benefit could have proven to be more substantial in the Apligraf group because, as the authors point out, the more experience clinicians have with this product, the fewer applications that will be required. This model used an average of 3.34 applications; the authors point out that using an average of 1.5 applications would result in fewer direct costs to the Apligraf group, resulting in even more savings. In all cases, Apligraf was compared with a standard therapy consisting of compression therapy and a moist nonadherent dressing, which has been shown in a large meta-analysis of randomized controlled prospective studies to be equivalent, if not superior, to all other topical nonskin substitute dressings.[47]

Diabetic ulcers

Steinberg et al[52] also conducted a cost-benefit analysis based on Falanga's study of diabetic foot ulcers. This study, which also contained capacity for great variation and manipulation of key data points within its model, showed that while initial mean costs were higher in the Apligraf group ($7336 vs $2020 per patient), Apligraf costs were $6683 per ulcer-free month and $86,226 per amputation avoided. Costs were significantly lower when Charcot foot patients were excluded and ulcers treated were less than 2 months old. The study concluded that while the Apligraf costs estimated from trial data were based on an average use of 3.9 applications per patient, the costs could be lowered significantly if the use of Apligraf paralleled more recent clinical experience with the product using an average 1.5 applications per patient. This would theoretically decrease costs to $2356 per ulcer-free month and $30,403 per amputation avoided. Calculated cost-effectiveness ratios using Apligraf amounted to $30,403 to $86,226 per amputation avoided and $819 to $8181 per ulcer-free month in all patients (not subdivided by time or presence of Charcot foot).

Another cost-benefit study combining Falanga's data on diabetic foot ulcers with data from a Dutch trial attempted to extrapolate costs at 1 year, although the source data were collected for only 6 months.[53] When data were analyzed and wound healing patterns were predicted for these populations at 1 year, the authors surmised that the Apligraf treatment group could ultimately lower costs by 12% with 12 months of treatment. While these studies attempted to show tangible results based on theoretical applications of cost and generation of cost-benefit ratios, a more standard descriptive study is required to answer this question more convincingly.

gression to amputation, which were significantly lower in the Apligraf group (osteomyelitis: 2.7% vs 10.4%, $P = .04$; amputation: 6.3% vs 15.6%, $P = .028$). Six-month follow-up examinations showed no difference in rates of reulceration.

Cost-benefit analysis based on Falanga's Study of diabetic foot ulcers was also performed by Steinberg et al.[52] This study, which included the capacity for significant variation and manipulation of key data points within its model, found that whereas the initial mean costs with the Apligraf group ($7336 vs $2020 per patient), Apligraf costs $6683 per ulcer-free month and $86,226 per avoided amputation. Costs were significantly lower when Charcot foot patients were excluded and the ulcers treated were of less than 2 months' duration. The study concluded the although Apligraf costs estimated from trial data were based on an average use of 3.9 applications per patient, the costs could be significantly lowered if the use of Apligraf paralleled more recent clinical experience with the product using an average of only 1.5 applications per patient.

Another cost-benefit study combining Falanga's data on diabetic foot ulcers with data from a Dutch trial attempted to extrapolate costs at 1 year even though the source data was collected for only 6 months.[53] Through data analysis and wound healing prediction for these populations at 1 year, the authors concluded that the Apligraf treatment group could ultimately lower costs by 12% with 12 months of treatment.

Apligraf has also been used in the treatment of epidermolysis bullosa (EB).[54] In a study of 9 patients with 96 sites of skin loss, 90% to 100% healing was observed by 5 to 7 days, with clinically normal–appearing skin in place by days 10 to 14.[55] Young pediatric patients were able to meet developmental milestones after treatment, and hand range of motion in patients with hand involvement improved 50% to 90%. Studies of Apligraf use in EB have also shown that donor

deoxyribonucleic acid (DNA) was found in wounds up to the end of their 6-month study period, implying that donor cells could possibly be surviving longer. Another report on the use of Apligraf for treatment of cutis aplasia produced mixed results, and this application has met with some criticism.[56,57]

• ***OrCel.*** OrCel (Ortec International, Inc, New York, NY) is a composite bilayer product in which neonatal keratinocytes are cultured onto a coated, nonporous sponge composed of type I bovine collagen. Neonatal fibroblasts are also cultured onto the other, porous side of the collagen sponge. This bilayer composite serves as an absorbable matrix, with cytokines and growth factors secreted by the allogenic fibroblasts. The manufacturer claims no allogenic DNA is present in the transplanted wound after 3 weeks. Much less data are available on the use of this product, although it has been described for use in healing of STSG donor sites.[58] OrCel was compared with Biobrane application after graft harvesting and showed earlier time to donor site healing for purposes of earlier recropping of donor sites for further grafting.[58] OrCel has also been described for wound coverage after contracture release of the hands for EB.[59,60] The FDA has approved OrCel for the reconstruction or treatment of recessive dystrophic EB of the hands and also for treatment of skin graft donor sites of those patients. Studies evaluating its use in chronic venous and diabetic lower extremity ulcers are ongoing.

SYNTHETIC MONOLAYER SUBSTITUTE

Suprathel (Institute of Textile and Process Engineering, Denkendorf, Germany; Burn Department of Marienhospital, Stuttgart, Germany) is a monolayer acellular synthetic dressing based on DL-Lactide (>70%), trimethelcarbonate, and a-caprolactone. It is used to cover split-thickness skin graft donor sites and partial-thickness burns.[61] In a study of 22 patients in which Suprathel was used to dress skin graft donor sites and compared to paraffin gauze, Suprathel demonstrated such a significant decrease in pain scores that the study was stopped and patients received Suprathel.[62] In another study, 22 patients received either Suprathel or Jelonet (petroleum jelly impregnated gauze) and were monitored for the rate of epithelization and pain control of partial-thickness burns. Results demonstrated no differences in time to full epithelialization, but a statistically significant decrease in both pain and overall cost of treatment was observed with Suprathel as compared to Jelonet.[61]

SYNTHETIC BILAYER SUBSTITUTES

Synthetic bilayer substitutes are acellular products engineered without allogenic cells. They function as dermal templates or matrices that promote ingrowth of host tissues to repair defects or create a neodermis. They also contain a removable silicone epidermal layer to help protect the wound from moisture loss and contamination. Biobrane and Integra Bilayer Matrix Wound Dressings are both synthetic skin substitutes for which extensive clinical experience has been accumulated.

• ***Biobrane.*** Biobrane (UDL Laboratories, Inc, Rockford, IL) is a biosynthetic skin substitute consisting of a bilaminate membrane of nylon mesh bonded to a thin layer of silicone.[63] The mesh is coated with porcine type I collagen–derived peptides (dermal analogue). The silicone layer then functions as epidermis. Small pores are present to make Biobrane semipermeable to allow transudates to escape. The wound heals as host fibroblasts and capillaries invade the wound and repair the dermal defect, allowing re-epithelialization by wound margin and adnexal keratinocytes. As skin regeneration takes place, Biobrane separates from the wound, allowing easy removal. Biobrane benefits include firm adherence to wounds, a semipermeable barrier to evaporative losses, and permeability to topical antibiotics; however, it requires a vascularized wound base. Biobrane is indicated for clean, superficial partial-thickness burns not involving chemicals or petroleum-based products and for temporary coverage of freshly excised deep partial- or full-thickness wounds.[63,64] It may also be used for coverage of STSG donor sites.[64]

Compared with DuoDERM (ConvaTec, Bristol-Myers Squibb Co, Skillman, NJ), Xeroform (Tyco International, Inc, Mansfield, MA), and Scarlet Red Ointment Dressing (Sherwood Medical, St. Louis, MO), Biobrane was found to be more costly and was associated with more infections on donor sites in 2 studies.[65,66] Because of the large clinical experience of Biobrane since its development in 1979, Biobrane has become the standard for skin substitute coverage of thermal injuries by which other products are compared. It was first introduced as a low-cost alternative to cadaveric skin (allograft) for temporary coverage of wounds and has been refined to include 3 products: Biobrane; Biobrane-L, which is nylon mesh woven to be less adherent to wounds when this is desired; and Biobrane gloves for injuries involving the hands. Recent studies involving Biobrane include comparisons of this product to newer skin substitutes or alternative treatment forms.

A 2005 study by Cassidy et al[67] compared pediatric partial-thickness burns treated with Biobrane and DuoDERM, a hydrocolloid dressing, in patients with burns of less than 10% TBSA. Although long-term follow-up examinations that evaluated overall cosmesis and function were lacking in the study, short-term results indicated no difference in pain or time to healing between the 2 treatments. However, a substantial cost saving was demonstrated in the DuoDERM

group. Another pediatric study compared 33 children with 58 wounds who were randomized to receive Biobrane, TransCyte, or Silvazine cream (silver sulfadiazine and 0.2% chlorhexidine).[68] Patients who received Biobrane and TransCyte required fewer opioids for pain control. Ultimately, patients in the TransCyte group required significantly fewer skin grafts than patients in the Biobrane group. However, patients in the Biobrane group required significantly fewer grafts than the patients who received Silvazine.

Many wounds that are candidates for Biobrane are also candidates for treatment with other modalities. Wounds for which Biobrane may offer an advantage are wounds in which coverage is determined to be temporary, such as those that require grafts. In that case, however, TransCyte offers no clinical advantage and a prohibitive expense. In superficial partial-thickness wounds that are not expected to require grafting, however, Biobrane may offer a financial advantage over TransCyte. If these wounds unexpectedly progress to require grafting, the patient may have been better served by the more expensive TransCyte. Wounds that are located in cosmetically sensitive areas or not obvious as to whether they will require grafting may ultimately heal better with TransCyte.

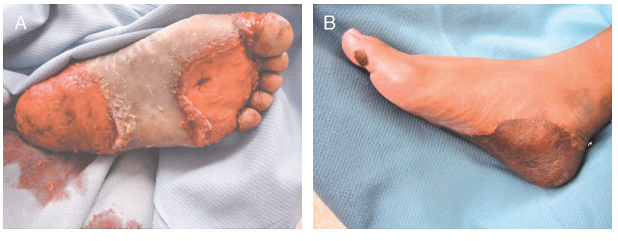
• ***Integra.*** Integra Bilayer Matrix Wound Dressing (Integra Life Sciences Corp, Plainsboro, NJ) is a synthetic bilayer acellular skin substitute composed of an outer silastic sheet (epidermal analogue) with a matrix composed of bovine collagen and glycosaminoglycan (dermal analogue).[69] The dermal matrix is engineered to have a pore size of 20 to 50 micrometers to promote fibroblast and endothelial cell ingrowth by the host wound bed. Integra provides a matrix and scaffolding for regeneration of the dermal structure. The wound gradually remodels or resorbs the matrix to create a neodermis as it is incorporated into host tissue over a 3- to 6-week period.[70] After adequate vascularization of the matrix has occurred and the neodermis has formed, the silastic sheet may be removed and skin grafting performed. This is usually accomplished 21 to 28 days after placement. The silastic sheet, however, may be left in place for up to 61 days, awaiting matrix incorporation or for patients to become suitable candidates for skin grafting for other reasons.[71] Alternatively, many smaller wounds may re-epithelialize without the need for grafting. Integra was first approved by the US FDA for wound coverage after excision of life-threatening deep partial- or full-thickness burns when sufficient autograft was not available for wound coverage or when autograft is not desirable because of other circumstances, as well as reconstruction after excision of postburn scar contractures.[72] Integra Life Sciences Corporation lists other indications including pressure ulcers, venous ulcers, diabetic ulcers, surgical wounds (eg, donor sites/grafts, post-Moh's surgery, and post-laser surgery), traumatic wounds, and draining wounds, with numerous case reports that seem to demonstrate its use for almost endless applications (Figure 7). It has also been used to reconstruct high-risk and radiated wound beds in older adult patients after tumor resections.[71]

Integra has long been known to offer reliable immediate coverage after excision of deep burns, improve take of thin epidermal autografts, decrease hypertrophic scarring by limiting the inflammatory response, show better function and range of motion of joints and extremities, and offer improved cosmetic outcomes for patients.[70,73,74] A recent study by Klein et al[75] showed that for deep facial burns, Integra offers the same benefits as thick autografts. For the face, the traditional 3-week waiting period to perform the graft may not apply because the face is so vascular it tolerates grafting after 7 to 10 days with unmeshed STSGs. Groos et al[76] demonstrated improved results using Integra for reconstruction of burn scar contractures in 22 grafts in children. Although this was not a case-control study, the short-term results showed excellent clinical improvement.

Outside burn literature, few randomized controlled trials involving Integra exist that evaluate its efficacy, but case reports abound. Advantages of Integra include its immediate availability for wound coverage, improved cosmesis and tissue elasticity compared with STSG alone, reduced donor site morbidity and scarring due to the use of thinner STSGs (0.005 in), and avoidance of the theoretical risk of infectious disease transmission present with allograft material. Integra may be ideal for use with autogenous cultured keratinocytes because the bilaminate substitute requires

Figure 7.
ADULT AFRICAN AMERICAN MAN WITH KERATODERMA OF PLANTAR FEET

After full-thickness excision of involved plantar skin down to uninvolved fascia, Integra Bilayer Matrix Wound Dressing was placed, allowing 21 days to incorporate. A. The silicone layer was removed, and the superficial surface was cleansed. B. One year after split-thickness skin grafting.



3 weeks for maturation before it is suitable for graft take. This enables an appropriate time for CEA culture. In a small case series, Chan et al[14] demonstrated the feasibility of such an endeavor in 3 patients with moderate to high success.

Disadvantages of Integra include its relative expense, learning curve for use, and its higher risk for seroma/hematoma formation after initial placement because of its use on acute wounds. In the authors' experience, however, meshing Integra 1.5:1 helps to enable some efflux of accumulating fluid from beneath the product. Time to graft and take rates of skin grafts on Integra may be shortened with the use of negative-pressure wound therapy (NPWT).[77] Jeschke et al[77] observed near 100% take rates in as few as 10 days when Integra was applied to acute and chronic wounds with a combination of fibrin glue and NPWT.

Integra Life Sciences Corporation is marketing a single-layer product, the Integra Matrix Wound Dressing (IMWD), which consists of the same dermal regeneration matrix as the bilayer product without the silicone epidermal layer. This product is intended for use beneath intact epithelium, in open wounds, and below another sheet of bilayer Integra for deeper wounds. Although no specific peer-reviewed literature has been published about this product, many surgeons have been using a version of this product for years. Before availability of IMWD, the bilayer product could be carefully and tediously separated from the silicone layer to which it is bonded and then used as a monolayer product. It currently has FDA permission to be marketed for the same indications as the bilayer product.

CONCLUSIONS

Skin substitutes are a heterogeneous class of therapeutic devices that vary in their biology and application. Although there is no single perfect skin substitute, certain characteristics can be considered when evaluating alternatives. A long shelf life and easy storage at a cost-efficient price translate to ubiquitous availability. The product should be easy to prepare and apply without intensive training. Flexibility of thickness allows the product to be tailored to specific wound needs. The substitute should be able to withstand a hypoxic wound bed as well as present some level of resistance to infection to allow relatively ischemic tissues to be candidates for application. The ideal skin substitute should allow resistance to shear forces and provide permanence and long-term wound stability. It should reproduce both components of the skin (epidermis and dermis) and provide no antigenicity that could compromise the graft or host or present difficulties with future applications.

Because no single product meets all these criteria, each patient case requires careful evaluation to determine the most appropriate solution. For instance, the product that will ultimately prove most biologically similar is CSS, created from expanded fibroblasts and keratinocytes from the individual patient. This product provides permanent, nonantigenic dermal/epidermal layers. However, the product is not readily available; is likely to be expensive; is not easily created, prepared, or stored; and may require special techniques for usage. Its ability to withstand shearing forces and infection may be lacking, and it requires a vascularized wound bed. Its long-term stable wound coverage ability is being ascertained.

On the other hand, Integra Bilayer Matrix Wound Dressing is readily available and is easy to prepare and use. It avoids dessication and can be applied to less vascularized wound beds because it is a synthetic acellular product with a silicone epidermal layer. These characteristics allow for its use on difficult wounds when few other options exist. However, it has disadvantages in expense, potential for infection, and secondary operations such as skin grafting.

Although many acute and chronic wounds may benefit from a tailored multidisciplinary approach that utilizes one or more of the products discussed, each patient should be evaluated for other possible therapies before use of skin substitutes. There is no alternative for adequate surgical debridement and infection control. In addition to patient-related factors, lower-extremity wounds require evaluation for peripheral arterial and venous disease. This may necessitate transcutaneous oximetry tests, noninvasive arterial studies, venous duplex ultrasonography, angiography, and consultation with a vascular surgeon. Only after surgical treatment of wounds with techniques such as local or regional flaps, or microvascular (free tissue) transplantation have been considered, should the incorporation of a skin substitute be implemented to a patient's treatment plan. If a patient is not considered a candidate for wound or defect reconstruction, creative applications of skin substitute technologies may not only significantly benefit a patient, but may also be the only option for wound closure and, in some cases, limb salvage.

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