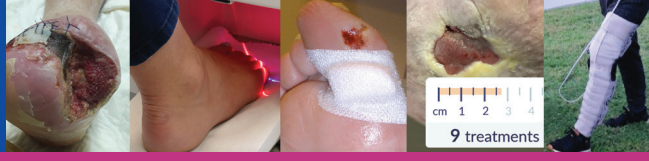

Maximizing Outcomes in Diabetic Limb Salvage with the Use of Cellular and Tissue-Based Products

Here's a review on which, when, and how to use CTPs.

BY CRAIG J. VERDIN, DPM, THOMAS MILISITS, DPM, MPH, AND JOHN S. STEINBERG, DPM

Goals and Objectives

1) Review the history of CTP development and gradual evolution over time.

2) Recognize the molecular and cellular processes that are present in wound healing.

3) Recognize clinically evident obstacles and clinically available supplements to CTP usage and success.

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*Following this article, an answer sheet and full set of instructions are provided (pg. 104).—**Editor***

Introduction

The evolution of cellular and tissue based products (CTPs) began in the 1970s when the first bio-engineered wound care products were made available for the purpose of treating burn wounds by harvesting keratinocytes, multiplying them, and reapplying them to targeted wounds.[1] In the '80s, Eugene Bell pioneered the use of skin allografts and his work led to the development of the first FDA-approved tissue substitute called Apligraf (Organogenesis Inc., Canton, MA) in 1998.

The first FDA-approved tissue substitute called Apligraf (Organogenesis Inc., Canton, MA) was introduced in 1998.

Ever since the first skin substitute entered this large marketplace, the wound care space has undergone a "boom" of innovation and

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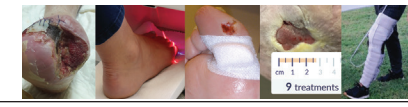

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technology that has resulted in 75+ CTPs that are available to clinicians today. While these scientific advancements are welcomed and needed in the wound healing field, there is a growing confusion as to the proper selection, utilization and even nomenclature we should employ in this topic.[2]

Acute wounds can be readily treated with standard wound care therapies, while chronic non-healing wounds may require more advanced treatment modalities. No absolute threshold exists as to when an acute wound becomes a chronic wound. However, the typical wound in a healthy patient is expected to heal either through primary intention or secondary intention within 10-14 days with continued remodeling that lasts several months to a year. The diabetic chronic wound often becomes stagnant and ceases to decrease in size and epithelialize.

As described by Sheehan in 2003, a wound may be considered chronic in nature when it ceases to decrease 10-15% every week or 50% over a one-month period. We now understand that this wound healing 'trajectory' is a highly reliable predictor of healing vs., non-healing. Further, as we know from Margolis in 2003, a wound that is larger than 2cm^2, greater than 2 months in duration, and is full thickness or deeper has a 79% decreased likelihood of healing within 20 weeks. Some of the more common reasons why an acute wound will transition into a chronic wound include ischemia, neuropathy, infection (including soft tissue and/or bone) and pressure.

A variety of treatment options are available to wound care specialists for healing the acute and chronic wound. The science of medicine helps guide the clinician in assessing the effectiveness of treatment therapies; however, it is the art of medicine that assists the wound care specialist in the proper treatment of a specific problem wound scenario. A flexible treatment algorithm which incorporates known evidence is necessary to effectively manage a problem non-healing wound. A wound that has stalled must be quickly recognized as a chronic wound and an appropriate change in the treatment plan should be implemented.

There are certain important considerations to take into account prior to the clinical application of CTP grafts. The first is timing, as it is not so much a matter of "which product should be used?" as it is "when is the appropriate time to use each product"? These products are not necessarily used in situations when a wound has been making good progress in healing, but rather in situations when a wound has become chronic in nature. This decision should be made based on the percent decrease in wound dimensions and/or the degree of granulation tissue noted in the wound bed.

Kumar devised the most commonly used CTP classification system.

The wound care space has undergone a "boom" of innovation and technology that has resulted in 75+ CTPs that are available to clinicians today.

Prior to application, the wound should be free of infection and an adequate blood supply must be confirmed or established. Each product may have some subtle differences in application; however, a general protocol can be followed. Application should begin with debridement of the wound in the operating room or in an appropriate clinical setting. The CTP product is then applied to the wound and often is secured with sutures, staples, Steri-Strips™ and/or a dressing. The wound should be evaluated on a weekly basis but the graft site should be left undisturbed and no debridements should be performed unless infection is suspected. Most products will integrate into the wound within three to four weeks. The product in the wound bed may have a slimy, coagulum appearance with mild to moderate drainage. This is part of the integration process and should not be misinterpreted as a graft failure.

Types of CTPs

According to the FDA, the term CTP is an umbrella term that consists of many different types of products that each have inherent differences in terms of their development and mechanism of action.[4-6] The first category is human skin allografts (HSA). HSAs are bioengineered products that are harvested from cadaveric tissue. After harvesting and in vivo culturing, these cells are typically projected onto a scaffold that provides a hospitable environment for their eventual growth and proliferation.

The next category is the allograft matrices (AM). Much like the HSAs, these are living cells that are typically derived from mesenchymal cells such as fibroblasts or components of native tissue membrane. AMs are unique because they have inherent structural benefits that allow them to be used in instances where wounds are structurally deficient. Composite matrices (CM) are another type of fibroblast-based product that often contains human keratinocytes. After harvest and multiplication, these viable cells are often set into a synthetic or even

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collageneous scaffold. The largest CTP category is the acellular matrices (ACM). These are typically derived from non-native and xenogenic tissue, which is typically collagenous in nature.

In Kumar's classification scheme there are three categories.

In 2008, Kumar, et al. created the most commonly used CTP classification system in an effort to better understand and organize CTPs. In this classification scheme, there are three categories.[7] The first category, or Class 1 skin substitutes, are temporary and impermeable dressings. The main function of this class type is to serve as a mechanical barrier while retaining moisture. Examples are these are cellulose, polyurethane, silicone, or cross-linked products.

Class II skin substitutes consists of epidermal or dermal substitutes but a key distinction is that they do not contain cellular components. However, Class II skin substitutes do contain necessary protein components for dermal healing, such as collagen and elastin, in an effort to facilitate a framework for which necessary processes like angiogensis, cell migration, and proliferation can occur. Examples are Apligraf and Alloderm.

Class III skin substitutes are very similar to Class II skin substitutes; however, they do contain cellular components. All skin grafts (xeno, allo, and auto) are included in this category as well as more synthetic grafts like Integra. While Kumar's classification continues to be ubiquitous, recent literature has suggested the need for a new classification system that reflects the growing complexity of graft function, composition, derivation, and use.[8]

Regardless of their mechanism of action and classification, the goal of all CTPs is to create a hospitable environment that allows for the proliferation and intracellular/extracellular stimulation of cells that ultimately result in wound healing.[9-13] The stimulatory or supportive effects of CTPs result in appreciable intracellular and extracellular changes. The intracellular effects of CTPs can largely be summarized as providing stimulatory factors such as cytokines, growth factors, and other means of intracellular signaling that result in downstream intracellular production of the necessary basic building blocks needed for wound healing.[9,10]

Extracellularly, CTPs have an effect on the more structural aspects of wound healing by which they can serve as a scaffold for which intracellular byproducts are built upon. Important components of the extracellular matrix include collagen and members of the glycan family.[10]

Organized wound healing is a function of communication between the intracellular and extracellular components which result in a well-organized cascade of events that allows the wound to progress through the inflammatory, proliferation, and remodeling phases of wound healing. Any disruption of these phases of wound healing can result in adverse outcomes in the form of delayed healing, incomplete healing, or failure of treatment.[9,10,12,13]

Clinical Practice

Currently, CTPs are indicated most commonly for diabetic ulcers, venous ulcers, and burns.[14] The use of CTPs has been shown to be a cost-effective adjunct to healing in the properly indicated wound.[15,16] Proper indications for CTPs are 1) wounds that have failed other more conservative modalities and/or 2) wounds that demonstrate significant depth that requires the wound bed reconstruction/optimization to allow for durable wound healing. In an article by Liu, et al., it is recommended that when a wound is deeper than the reticular dermis or roughly 0.55 mm, that CTPs be considered in an effort to provide a satisfactory scaffold to heal the wound from the "inside to out".[17]

When initially evaluating the targeted wound, it is important to understand the foundation for which CTPs may be placed upon. Unfortunately, CTPs are not largely indicated to be placed within or on tissue that is avascular such as bone, tendon, or fascia. Placing CTP over exposed bone is known to be a certain challenge due to the lack of available vascularity in the wound bed and the depth of the tissue defect. For this reason, the creation of a satisfactory wound bed or foundation may be necessary and can be performed with the use of flaps or uniquely indicated CTPs that do exist such as Integra.[18]

Once a wound foundation has been established, the clinician must ensure the environment is optimal for the increased survivorship of the CTP.

Once a wound foundation has been established, the clinician must ensure the environment is optimal for the increased survivorship of the CTP. Potential intrinsic barriers to CTP survivorship are the presence of biofilm, acute infection, or presence of non-viable tissue that disrupts continuity of healing.[19] Biofilms are known to create a poor environment for wound healing because they disrupt the normal physiologic inflammatory process that is associated with normal wound healing.[20] As a result, initial healing may occur but healing arrest is noted due to the wound progressing

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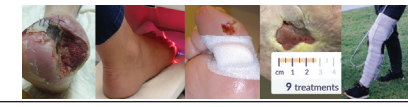

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to a more chronic phase of healing prematurely.[21]

On the other hand, more acute infection disrupts the normal physiology of wound healing and it too creates a rather hostile environment that would not allow satisfactory graft take. In the absence of infection, the presence of non-viable tissue that may potentially become a nidus for infection is often problematic because it serves as a barrier between healthy tissue and any product that is placed within it, therefore reducing the graft take rate and, if it does occur, results in a poorly constructed scaffold that is more inclined to break down and result in recurrent ulceration.[21]

While all of these factors are often inherent in the diabetic population, their effect can at least partially be mitigated with proper debridement and timing of intervention, which, in turn, can result in increased durability of wound healing.[22]

NPWT

After the wound bed is effectively optimized and the properly indicated CTPs have been targeted, adjunct and ancillary measures can be considered in an effort to expedite healing and ensure the increased survivorship of the CTP. Current and popular modalities that are often used in the wound care practice include negative pressure wound therapy (NPWT), hyperbaric oxygen therapy (HBOT), and nutrition optimization. The literature is heavily populated with the well-documented benefits of NPWT, which has been shown to decrease healing times and create an environment that is hospitable to wound healing by reducing exudate and wound edema.[23]

While the mechanism of its effect on the wound environment is not well understood, histological studies hint that the negative pressure environment results in histological changes that are conducive to wound healing such as increases in VEGF, pro-inflammatory cytokines, and neoangiogenesis.[24] Despite NPWT withstanding the test of time, however, and inducing a paradigm shift on how we treat wounds, its use does not always equate to a positive outcome.

Zinc is essential for successful wound healing to occur.

One of the most important considerations that a clinician must understand, especially in the context of potential application of a CTP, is that the granulation tissue that is produced by NPWT can be unstructured and poorly organized. Therefore, wound bed optimization is critical and can be done via a flap or other modality when there is significant depth and the patient is a candidate for surgical management.[25]

In the presence of a satisfactory and vascular wound bed/foundation, NPWT in conjunction with CTPs has been shown to have a significant positive effect on wound healing and durability of the wound.[22] The increased wound durability is directly tied to the scaffolding that the CTP provides for which granulation growth can be supported. For this reason, when possible, it is recommended to supplement CTP use with NPWT.[23]

HBOT

Another possible ancillary adjunct to CTP use is the utilization of HBOT. The use of HBOT has grown within the literature; however, more recent studies have demonstrated that the benefits of HBOT can be limited depending on patient type and wound presentation.[26-20] The principle behind HBOT revolves around maximal delivery of oxygen to wounds that may be largely deprived.[30]

Typical patients are vasculopaths who may or may not have been re-vascularized, but it must be stressed that the use of HBOT in patients with intact blood flow is largely unnecessary.[27] As it stands, the current recommendation for the use of HBOT is to serve as an adjunct in difficult wounds that are not healing via other more traditional means.[28] In the context of CTPs, the evidence for HBOT is sparse but what evidence does exist seems to chiefly support the use of HBOT in the "at-risk" flap or graft that is acutely ischemic for the purpose of salvage.[31] Under the assumption this does occur, the clinician needs to evaluate and identify potential host factors that may have preceded or developed during the course of treatment and be addressed.

Nutrition Optimization

Lastly, one of the most underappreciated or under-recognized intrinsic barriers to wound healing is nutrition optimization. It is well understood that wound healing is a well-orchestrated series of events; however, optimization of the wound microenvironment is impossible without the availability of micronutrients.[32] The creation of a durable wound collagenous scaffold is a function of the availability of crucial pro-collagenous vitamins A/B/C/D and elementary nutrients such as zinc, iron, glutamine, and arginine.[33]

1.0-1.5 g/kg is the current daily recommendation of protein consumption for patients with open wounds.

The current recommendation for patients with open wounds is 1.0-1.5 g/kg of protein daily in an effort to counter the protein loss

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that is typically associated with wound breakdown and to provide enough protein for wound healing.[33,34] While no literature exists on the effect of nutrition on graft take, it is largely intuitive that CTP success in the malnourished patient may be counterproductive; therefore, nutritional assessment and screening is important, especially in the diabetic patient.

While intrinsic factors to wound healing are typically the more significant impediments to successful limb salvage, there exist extrinsic factors that are inherent in CTP use that may place patients at risk for adverse outcomes. Given the nature of CTPs and their derivation (tissue-based), their use is largely regulated, monitored, and dictated by entities who are not directly treating the patient (home institution, regulatory bodies, and insurance).

Given the rapid growth and increasing intricacies of CTPs with respect to documentation, storage, acquisition, and access, certain providers and, in turn, patients may be restricted or limited. These difficulties may be further magnified for clinicians who are in a more rural area or who serve a more socioeconomically disadvantaged population. Unfortunately, for a singular provider, these issues may be difficult to navigate but communication with the involved entities should be paramount.[36,37]

Future Directions

The advent and recent growth of CTPs is exciting and offers clinicians a tool to encourage positive outcomes in the complex world of DFU treatment. Unfortunately, though, despite the rapid development of CTPs and the increased incentive to use them, recent evidence has demonstrated that the rate of limb salvage has not matched the rate of innovation, which is largely concerning. In a study by Geiss, et al. in 2019, there was a 62% increase in minor amputation rates over the period of six years (2009-2015).[38]

The advent and recent growth of CTPs is exciting and offers clinicians a tool to encourage positive outcomes in the complex world of DFU treatment.

While it is not clear why this is occurring, we believe that it could be largely a function of 1) improper selection of products and patients and 2) lack of recognition of the numerous variables in this complex patient population. Unfortunately, diabetic patients who have DFUs typically represent the "sickest" patients we encounter in our practice.[39]

Given the concurrent presence of multi-system dysfunction, there is often an overlapping set of intrinsic and extrinsic factors that negatively influence the efforts of the wound physician.[40] Regardless, the future of diabetic limb salvage is encouraging. With the proper use of CTPs and acknowledgement of other barriers to healing and care, it is only inevitable that we continue to see increased understanding of diabetic wounds and increased rates of positive outcomes. Proper use and selection is critical in addition to use of all ancillary measures that are available to the clinician in order to maximize the opportunity to achieve functional limb salvage and keep our patients walking.

A final thought is that the clinician needs to utilize CTPs (or any wound healing modality) only after the non-healing wound etiology has been identified and addressed to the highest degree possible. We certainly realize that not all of the underlying wound etiologies can be easily remedied, but often surgical intervention can be of great assistance in off-loading pressure, improving function, and delivering proper macrovascular flow to the area.

If the underlying etiology is a structural deformity, a reconstructive procedure, tendon lengthening procedure, or an exostectomy is absolutely critical. Without surgical intervention, the best efforts with local wound care will most often fail. Hence we have begun to utilize the nomenclature of 'limb salvage' over 'wound care' since there is much more that can be done when we incorporate the surgical elements with the proper medical and topical care for these complex wounds. **PM**

Given the concurrent presence of multi-system dysfunction, there is often an overlapping set of intrinsic and extrinsic factors that negatively influence the efforts of the wound physician.[40] Regardless, the future of diabetic limb salvage is encouraging.

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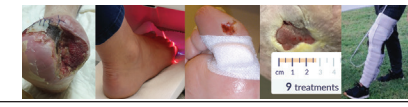

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Continuing Medical Education

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CME **EXAMINATION**

SEE ANSWER SHEET ON PAGE 105.

1) Which nutrient is essential for successful wound healing to occur?

- **A) Lithium**
- **B) Argon**
- **C) Zinc**
- **D) Silver**

2) Which is NOT a current indication for CTP use?

- **A) Surgical incisions**
- **B) Venous wounds**
- **C) Neuropathic wounds**
- **D) Burn wounds**

3) Which is NOT a currently accepted ancillary modality for wound healing to be used in conjunction with CTPs?

- **A) HBOT**
- **B) NPWT**
- **C) Nutrition consult or supplementation**
- **D) Hyaluronic acid injections**

4) What wound bed is least indicated for CTP placement?

- **A) Bone**
- **B) Muscle**
- **C) Tendon with intact vascularized periosteum**
- **D) Granular subcutaneous tissue**

5) Which is NOT a pro-collagenous vitamin?

- **A) Vitamin A**
- **B) Vitamin B**
- **C) Vitamin C**
- **D) Vitamin K**

6) What is the current daily recommendation of protein consumption for patients with open wounds?

- **A) 0.25-0.5 g/kg**
- **B) 0.75-1.0 g/kg**
- **C) 1.0-1.5 g/kg**
- **D) 2.0-2.5 g/kg**

Continued on page 104

(Continure from page 103)

7) Who devised the most commonly used CTP classification system?

A) Steinberg
B) Kumar
C) Winzeler
D) Attinger

8) In the previously mentioned CTP classification system in Question 7, how many classes are there?

A) 3
B) 4
C) 5
D) 6

9) How many CTPs exist on the market today?

A) ~ 25
B) ~ 75
C) ~ 100
D) ~ 200

10) What product was the first FDA-approved skin substitute made available to wound care clinicians?

A) Integra
B) Apligraf
C) Dermapure
D) Oasis

SEE ANSWER SHEET ON PAGE 105.

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EXAM #6/23
Maximizing Outcomes in Diabetic Limb Salvage with the Use of Cellular and Tissue-Based Products (Verdin, Milisits and Steinberg)

Circle:

1.	**A**	**B**	**C**	**D**	**6.**	**A**	**B**	**C**	**D**
2.	**A**	**B**	**C**	**D**	**7.**	**A**	**B**	**C**	**D**
3.	**A**	**B**	**C**	**D**	**8.**	**A**	**B**	**C**	**D**
4.	**A**	**B**	**C**	**D**	**9.**	**A**	**B**	**C**	**D**
5.	**A**	**B**	**C**	**D**	**10.**	**A**	**B**	**C**	**D**

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Strongly agree [5]	Agree [4]	Neutral [3]	Disagree [2]	Strongly disagree [1]

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2) The educational objectives were accomplished ____

3) I will apply the knowledge I learned from this lesson ____

4) I will makes changes in my practice behavior based on this lesson ____

5) This lesson presented quality information with adequate current references ____

6) What overall grade would you assign this lesson?

A B C D

7) This activity was balanced and free of commercial bias.

Yes _____ No _____

8) What overall grade would you assign to the overall management of this activity?

A B C D

How long did it take you to complete this lesson?

_____hour _____minutes

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_____

_____

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