Cellular and Tissue-based Products (CTP)

Effects on Wound Healing

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Special Thanks to Contributors

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Learning Objectives

• Review the basic definitions and properties of **Cellular and Tissue-based Products (CTP)**

• Examine the class of **acellular tissue-based** products and the clinical data

• Examine the class of **cellular tissue-based** products and the clinical data

• Understand the **documentation and coding requirements for use of skin substitutes in Wyoming**
Non-Healing Wounds

ADMIT IT
You always call them when you have a problem...
To Fix It......
Wound Management Products

Cleansing
- Saline, water
- Commercial cleansers

Basic Dressing Categories
- Gauze
- Films
- Hydrocolloids
- Hydrogels
- Calcium alginates
- Foams
- Composites
- Wound fillers

Advanced Dressings
- ECM components
  - Collagen
  - Hyaluronic acid

Active Products
- Growth factors
- CTPs
  - Cellular
  - Acellular

ECM = extracellular matrix
CTP = cellular and tissue-based products
Cellular and Tissue-based Products

• Can be classified as **cellular** (containing living cells) or **acellular** (biologically inert)

• May be **sourced** from
  – Biological tissue
    • **Animal** (e.g., equine/bovine/porcine/ovine)
    • **Human** (e.g., cadaveric skin, placenta, neonatal foreskin [keratinocytes and fibroblasts])
    • **Plant** (containing cellulose)
  – **Composite** (biological and synthetic)
Acellular Matrices

- Human and animal derived products are processed to remove cells leaving the collagen matrix and destroying pathogens
- Collagen may be cross-linked
  - Stabilize the matrix dressing
  - Inhibit degradation and prolong presence in the wound
- May function as a biological modulator
  - A material or substance derived from biological or synthetic sources that influences biological processes such as wound healing

Acellular Mode of Action

• Provides scaffold
  – For matrix metalloproteinases to bind to and break down collagen in the product
  – To support cell ingrowth and granulation tissue formation
  – For epithelial cells, fibroblasts and endothelial cells to migrate into and proliferate
  – To contain/protect growth factors
• Optimal response will be achieved using a matrix that is closest to the tissue it is replacing

Human Amnionic (HCT/Ps)

HCT/Ps = human cells, tissues, and cellular and tissue-based products

• Can be obtained from human donors, processed, and used exactly in the same role in the recipient
  – Skin for skin, tendon for tendon, bone for bone
  – Uses are regulated as HCT/Ps
    • Homologous use
    • Minimal manipulation
    • Registration establishes donor eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases by the device

HCT/Ps = human cells, tissues, and cellular and tissue-based products.
Amniotic Acellular Products

- Conceptually similar to other acellular products
- May contain soluble mediators that recruit adult MSCs
- Provides biologically active ECM for cell ingrowth

Amnion, Chorion, Placenta, Uterus

- Amnion
- Chorion
- Placenta
- Uterus
Placental Membranes

• First described as a treatment for wounds in 1910 in a large case series

• Contain a combination of growth factors, collagen-rich ECM, and viable cells
  – Neonatal fibroblasts and epithelial cells
  – MSCs

MSCs = mesenchymal stem cells.
## Components of Amniotic Tissue

<table>
<thead>
<tr>
<th>Layer</th>
<th>Extracellular Matrix Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amnion</td>
<td></td>
</tr>
<tr>
<td>Epithelium</td>
<td></td>
</tr>
<tr>
<td>Basement Membrane</td>
<td>Collagen types III, IV, V; laminin, fibronectin, nidogen</td>
</tr>
<tr>
<td>Compact layer</td>
<td>Collagen types I, III, V, VI; fibronectin</td>
</tr>
<tr>
<td>Fibroblast layer</td>
<td>Collagen types I, III, VI; nidogen, laminin, fibronectin</td>
</tr>
<tr>
<td>Intermediate (spongy) layer</td>
<td>Collagen type I, III, IV; proteoglycans</td>
</tr>
<tr>
<td><strong>Chorion</strong></td>
<td></td>
</tr>
<tr>
<td>Reticular layer</td>
<td>Collagen types I, III, IV, V, VI; proteoglycans</td>
</tr>
<tr>
<td>Basement Membrane</td>
<td>Collagen types VI; fibronectin, laminin</td>
</tr>
<tr>
<td>Trophoblasts</td>
<td></td>
</tr>
</tbody>
</table>
Cleaned Tissue

Courtesy of William W. Li, MD.
EpiFix® is a dehydrated Human Amnion/Chorion Membrane (dHACM) allograft and is composed of multiple layers including a single layer of epithelial cells, a basement membrane and an avascular connective tissue matrix. EpiFix® is a minimally manipulated, dehydrated, non-viable cellular amniotic membrane allograft that contains multiple extracellular matrix proteins, growth factors, cytokines and other specialty proteins present in amniotic tissue to provide a barrier membrane that enhances healing. From MiMedx webpage
Attributes of Amniotic Tissue

- Immuno-privileged
- Anti-inflammatory
- Antibacterial
- Rich with growth factors and cytokines
- Provides a matrix for cellular migration and proliferation
- Non-immunogenic
- Natural barrier

Courtesy of Cutting Image Histology, LLC
## Immunohistochemical Analysis of Amnion/Chorion vs Collagen

<table>
<thead>
<tr>
<th></th>
<th>Laminin</th>
<th>Laminin-5</th>
<th>TGF-β</th>
<th>FGF-2</th>
<th>PDGF-α</th>
<th>PDGF-β</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amnion/Chorion (n=5)</strong></td>
<td>4.4 ± 0.55 (P&lt;.001)*</td>
<td>4.2 ± 0.45 (P&lt;.001)*</td>
<td>1.4 ± 0.9 (P&lt;.05)*</td>
<td>0.7 ± 0.45 (P&lt;.05)*</td>
<td>2.4 ± 0.55 (P&lt;.005)*</td>
<td>3.2 ± 1.1 (NS)†</td>
</tr>
<tr>
<td><strong>Porcine Collagen (n=5)</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3.0 ± 0</td>
</tr>
</tbody>
</table>

*Significant difference vs porcine. †No significant difference vs porcine. FGF-2 = fibroblast growth factor-2; TGF-β = transforming growth factor-β. Xenoudi P, et al. Presented at: 89th International Association of Dental Research; March 16-19, 2011; San Diego, CA. Abstract 146797.
Epifix: Acellular

- Dehydrated human amniotic membrane product
- Collagen types IV, V, and VII
- Structural collagen and extracellular matrix

Level 1 Evidence

**Epifix: Acellular**

**Single Center RCT (n=25), 4-6 Week Evaluation**

<table>
<thead>
<tr>
<th></th>
<th>Epifix (n=13)</th>
<th>Control (n=12)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Healed</td>
<td>92%</td>
<td>8%</td>
<td>.001</td>
</tr>
<tr>
<td>Time to Heal</td>
<td>17.5 days</td>
<td>35 days</td>
<td>.001</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>16.7%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Level 1 Evidence
Graftjacket: Acellular

- “Like-for-like" replacement of tissue
- Epidermis and fibroblast cell removal-human tissue
- Cryogenic preservation
- 2-year shelf-life

Level 1 Evidence
Graftjacket: Acellular

RCT, 12 Week Evaluation

<table>
<thead>
<tr>
<th></th>
<th>Graftjacket (n=47[46])</th>
<th>Control (n=39)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Healed</td>
<td>68% [69.6%]</td>
<td>46.2%</td>
<td>.048 [.02]</td>
</tr>
<tr>
<td>Time to Heal</td>
<td>39.9 days</td>
<td>47.6 days</td>
<td>? [.03]</td>
</tr>
<tr>
<td>Infection</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

OASIS: Acellular

• OASIS is comprised of porcine-derived acellular small intestine submucosa

Level 1 Evidence
Oasis: Acellular

5 RCTs: 1 VLU, 3 DFU, 1 Mixed

<table>
<thead>
<tr>
<th>DFU Study N = 71</th>
<th>Oasis (n=37)</th>
<th>Control (n=36)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Healed</td>
<td>49%</td>
<td>28%</td>
<td>.055</td>
</tr>
<tr>
<td>Time to Heal</td>
<td>67 days</td>
<td>73 days</td>
<td>.025</td>
</tr>
<tr>
<td>Infection</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Level 1 Evidence

INTEGRA™ Bilayer Matrix comprised of bovine tendon, glycosaminoglycan made from shark cartilage and a semi-permeable polysiloxane (silicone layer)
Integra: Acellular

Multiple RCTs in Burn Wounds
Only case studies in chronic wounds

<table>
<thead>
<tr>
<th>N = 11</th>
<th>Integra</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Healed</td>
<td>63.6%</td>
</tr>
<tr>
<td>Time to Closure</td>
<td>52 days</td>
</tr>
<tr>
<td>Infection</td>
<td>NS</td>
</tr>
</tbody>
</table>

Level 4 Evidence for chronic wounds

Primatrix: Acellular

- Acellular fetal bovine dermis
- High proportion of type 3 collagen

Level 4 Evidence
Primatrix: Acellular

Prospective Cohort Study

<table>
<thead>
<tr>
<th>N = 55</th>
<th>Primatrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Healed</td>
<td>64%</td>
</tr>
<tr>
<td>Time to Heal</td>
<td>53.1 days</td>
</tr>
<tr>
<td>Infection</td>
<td>NS</td>
</tr>
</tbody>
</table>

Level 4 Evidence

Kavros S. Adv Skin Wound Care.
Theraskin: Acellular

• Human skin allograft with both epidermis and dermis layers

Level 4 Evidence
Theraskin: Acellular

Randomized Controlled Double Blind Studies
Randomized Controlled Studies
Case Control Studies
Case Series
Case Studies
Ideas, Editorials, Opinions
Animal Research
In Vitro Research

Retrospective Cohort Study

<table>
<thead>
<tr>
<th></th>
<th>Theraskin (n=134) VLU</th>
<th>Theraskin (n=54) DFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Healed</td>
<td>60%</td>
<td>61%</td>
</tr>
<tr>
<td>Time to Heal</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Infection</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Level 4 Evidence

Amniotic Cellular Products

- Manufactured to preserve cells, ECM, and growth factors
  - Neonatal MSCs
  - Epithelial cells and fibroblasts
- ECM provides 3-dimensional support
  - Promotes cellular adhesion and migration

Cellular Therapy

Keratinocytes

TGF-α
PDGF-A
PDGF-B
FGF-1
IL-8
IL-12

Fibroblasts

PDGF-A, PDGF-B
TGF-β3, TGF-β1
IL-6, IL-8, IL-11
IGF-2
FGF-1, FGF-2, FGF-7

Function of Cellular Skin Substitutes

• Goal of use is to restore skin barrier
• Secrete ECM (collagen)
• Produce growth factors needed by the wound at the needed time and needed amounts
• Provide temporary wound coverage
• Products with differentiated keratinocyte layer provide protection from moisture loss, bacterial protection

ECM = extracellular matrix.
Cellular Devices Do Not “Take”

- They are not skin grafts
  - There is no vascularization
  - There is no integration
  - There is no persistence

Mesenchymal Stem Cells Decline with Age

Source Material Is Critical: Human MSCs Decline with Age

Mesenchymal Stem Cells (MSC)

• Provide matrix proteins, cytokines, and growth factors

• Coordinate tissue repair process
  – Down regulation of inflammation
  – Stimulation of blood vessel formation
  – Recruitment and support of fibroblasts and epithelial cells

Dermagraft: Cellular

- Cryopreserved human fibroblast derived from newborn foreskin
- Bioabsorbable polyglactin mesh scaffold
Dermagraft: Cellular

3 Multicenter RCTs: 2 DFU & 1 VLU, 12 Week Evaluation

<table>
<thead>
<tr>
<th></th>
<th>Dermagraft</th>
<th>Control (n=115)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Healed</td>
<td>30%</td>
<td>18%</td>
<td>.02</td>
</tr>
<tr>
<td>Time to Heal</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Infection</td>
<td>19%</td>
<td>32%</td>
<td>.007</td>
</tr>
</tbody>
</table>

Level 1 Evidence

Apligraf: Cellular

- Derived from newborn foreskin
- Bilayered-epidermal-dermal layers
- Collagen lattice overlaid with cornified epidermis
### Apligraf: Cellular

#### 3 Multicenter RCTs: 2 DFU & 1 VLU, 12 Week Evaluation

<table>
<thead>
<tr>
<th></th>
<th>Apligraf (n=112)</th>
<th>Control (n=96)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Healed</td>
<td>56%</td>
<td>38%</td>
<td>.004</td>
</tr>
<tr>
<td>Time to Heal</td>
<td>65 days</td>
<td>90 days</td>
<td>.003</td>
</tr>
<tr>
<td>Infection</td>
<td>22%</td>
<td>32%</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Level 1 Evidence**

Grafix: Cellular

- Amniotic Mesenchymal Stem Cells
- Placental tissue harvested from planned C-section
- Cryopreserved

Level 1 Evidence
Multicenter RCT (n=97), 12 Week Study Period

<table>
<thead>
<tr>
<th></th>
<th>Grafix (n=50)</th>
<th>Control (n=47)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Healed</td>
<td>62%</td>
<td>18%</td>
<td>.001</td>
</tr>
<tr>
<td>Time to Heal</td>
<td>42 days</td>
<td>70 days</td>
<td>.001</td>
</tr>
<tr>
<td>Infection</td>
<td>18%</td>
<td>36%</td>
<td>.04</td>
</tr>
</tbody>
</table>

Level 1 Evidence
# Cellular and Acellular Therapies

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>High Quality DFU RCT</th>
<th>High Quality VLU RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermagraft</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Apligraf</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Grafix</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Oasis</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Graftjacket</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>Epifix</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AlloDerm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Integra</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primatrix</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theraskin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## High Quality DFU RCTs

|                      | Grafix  
N = 97            | Dermagraft  
N = 245         | Apligraf  
N = 208        | Graft Jacket  
N = 86         |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>% Healed</td>
<td>62% v 21%*</td>
<td>30% v 18%*</td>
<td>56% v 38%*</td>
<td>68% v 46%*</td>
</tr>
<tr>
<td>Time to Closure</td>
<td>42 v 70 days*</td>
<td>Not stated</td>
<td>65 v 90 days*</td>
<td>40 v 48 days</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>18% v 36%*</td>
<td>19% v. 32%*</td>
<td>22% v 32%</td>
<td>Not stated</td>
</tr>
<tr>
<td>Odds Ratio</td>
<td>6.04 (2.45-14.88)</td>
<td>1.92 (1.05-3.51)</td>
<td>2.14 (1.23-3.74)</td>
<td>2.40 (0.99-5.81)</td>
</tr>
</tbody>
</table>


* significant
Cellular and Acellular Therapies

• Are cellular therapies better than acellular therapies?

• No prospective head-to-head comparisons
### Medicare Payment Changes: CTPs

<table>
<thead>
<tr>
<th>“High Cost CTPs”</th>
<th>“Low Cost CTPs”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apligraf</td>
<td>Oasis</td>
</tr>
<tr>
<td>Dermagraft</td>
<td>Integra</td>
</tr>
<tr>
<td>Alloderm</td>
<td>Theraskin</td>
</tr>
<tr>
<td>Graftjacket</td>
<td>Ezderm</td>
</tr>
<tr>
<td>Primatrix</td>
<td>Matristem</td>
</tr>
<tr>
<td>Hmatrix</td>
<td>Unite Biomatrix</td>
</tr>
<tr>
<td>Integuply</td>
<td>Alloskin</td>
</tr>
<tr>
<td>Arthroflex</td>
<td>Hyalomatrix</td>
</tr>
<tr>
<td>Dermaspan</td>
<td>Tensix</td>
</tr>
<tr>
<td>Tranzgraft</td>
<td>Surgiment</td>
</tr>
<tr>
<td></td>
<td>Repriza</td>
</tr>
</tbody>
</table>

Cell based therapies undergo rigorous randomized placebo controlled trials and must demonstrate clinical efficacy/safety in order to receive FDA approval. Each indication must be approved through the FDA. Currently there are 3 products that meet this standard (Apligraf®, approved for venous leg ulcers and diabetic foot ulcers, Dermagraft; approved for diabetic foot ulcers, and Regranex (a recombinant human platelet-derived growth factor) approved for diabetic foot ulcers. Collagen dressings are approved by the FDA, however they are not required to undergo randomized-placebo controlled trials, and are classified as non-interactive dressings.
Noridian Healthcare Solutions

JURISDICTION F

SKIN SUBSTITUTE POLICY

WYOMING MEDICARE PART B

Eric J. Lullove, DPM CWS FACCWS
DURATION OF WOUNDS

- FOR DFU: 3 WEEKS
- FOR VLU: 1 MONTH
• Document failure to respond to conservative measures (a failed response is defined as an ulcer that has increased in size or depth and no indication that improvement is likely e.g., epithelial in growth and progression towards closure.

• This is usually defined as DFU not attaining 30% of closure by week 4

• This is usually defined as VLU not attaining 40% of closure by week 4
Documentation Requirements

• Document measurement of the ulcer at baseline, following cessation of conservative management.
• Describe adequate treatment of the underlying disease process contributing to the ulcer.
• Diagnosis of patient.
• Document that wound is free of infection, redness, drainage, underlying osteomyelitis, surrounding cellulitis, tunnels and tracts, eschar or any necrotic material.
Vascular Documentation

• For DFU, document current HbA1C reading (HbA1C should not exceed 12%)

• Document adequate arterial blood supply as evidenced by an ABI of 0.65 or greater

Treatment
Vascular Documentation

• The Policy does not specifically mention anything regarding VLU standards of care, other than the provider should adhere to the SOC with venous patients:
  – Compression therapy
  – Venous duplex with reflux
  – Addressing varicose veins with venogram (if necessary)
Cellular and/or Tissue Products (CTP)

• The policy does not eloquently state any specific tissue product for use.

• In the contractor’s silence on this issue, manufacturer’s IFU should be strictly followed and provider prudence in the selection and use of product is clinically indicated for the use of the product.

• Retain all invoices, lot numbers and expiration dates.

• While this is not specifically listed, it is not expected that providers will be using more than 1 CPT-tissue type to closure in a 12-week period. (i.e. don’t use amniotic then switch to bovine then switch to recombinant therapy)
Coding Guidelines

• DO report the appropriate Q-code for the tissue and units used.

• Use of –JW modifier for waste will automatically trigger a manual review. Please use tissues that will have zero waste to avoid delays in processing claims.

• Over-utilization will trigger a automatic stop in the system for manual review of each claim.

• Use of 15002 and 15004 reported with CTP application (15271 or 15275) will trigger a non-payment of service.
Chronic Venous Ulcers

- 74 year old gentleman, referred for care with no-healing venous leg ulcers
- PMH: HTN, RA, type 2 Diabetes, Hx. of DVT
- Medications: Plavix, Lasix, Prednisone, Methotrexate, Atenolol, Lisinopril, Pravastatin
- Previous history of diabetic foot ulcers; resolved
- PSH: Hip replacement right, Lumbar spine surgery, CABG/Carotid surgery 2011
- Previous treatment: Various dressings, history of being unable to tolerate compression

Patient case provided by Lawrence A. Lavery, DPM, MPH
Venous Ulcers X2 Left Leg
14 Months

Initial Management: Collagenase, antimicrobial foam, edema management

Patient case provided by Lawrence A. Lavery, DPM, MPH
1st cellular application

Patient case provided by Lawrence A. Lavery, DPM, MPH
2 Weeks: 2nd Application

Patient case provided by Lawrence A. Lavery, DPM, MPH
Week 4: 3rd Application

Patient case provided by Lawrence A. Lavery, DPM, MPH
6 Weeks: 4th Application

Patient case provided by Lawrence A. Lavery, DPM, MPH
8 Weeks

Patient case provided by Lawrence A. Lavery, DPM, MPH