Advanced Wound Care Modalities for the Treatment of Pressure Ulcers

Improving the Standard of Care

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PVA Summit 2011
September 17, 2011
Disclosures

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- CME Staff Disclosures
  Professional Education Services Group staff have no financial interest or relationships to disclose.
Learning Objectives

At the conclusion of this activity, the participant will be able to:

A. Explain the physiology of wound healing and the pathophysiology of stalled wounds

B. Describe current standard of care for wounds, specifically pressure ulcers

C. Discuss advanced wound care modalities including biophysical modalities, growth factors, extracellular matrices, and bioengineered skin substitutes
Introduction

Pressure Ulcers are a major complication of SCI/D
Will develop in ≥50% of veterans with SCI/D
Overall prevalence of 39%
Majority of pressure ulcers are Stage IV (NPUAP)
Ischia most common anatomic site
Recurrence rate is significant (~40%)

Physiology of Wound Healing

Acute Wound Healing

Orderly and Timely Process

Proceeds through three general phases:

1. Inflammation
2. Proliferation
3. Remodeling

Results in restoration of skin/tissue integrity
## Major Growth Factors

<table>
<thead>
<tr>
<th>Growth factor family</th>
<th>Cell source</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transforming growth factor</strong></td>
<td>Platelets, Fibroblasts, Macrophages</td>
<td>Fibroblast chemotaxis, ↑ Collagen, TIMP synthesis, ↓ MMP synthesis</td>
</tr>
<tr>
<td>TGF-β1, TGF-β2, TGF-β3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Platelet-derived growth factor</strong></td>
<td>Platelets, Macrophages, Keratinocytes, Fibroblasts</td>
<td>Activates immune cells and fibroblasts, ↑ Collagen, TIMP synthesis, ↓ MMP synthesis, ↑ Angiogenesis</td>
</tr>
<tr>
<td>PDGF-AA, PDGF-BB, VEGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fibroblast growth factor</strong></td>
<td>Macrophages, Endothelial cells, Fibroblasts</td>
<td>↑ Angiogenesis, ↑ Keratinocyte proliferation and migration, ↑ ECM deposition</td>
</tr>
<tr>
<td>Acidic-FGF, Basic-FGF, KGF</td>
<td></td>
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<tr>
<td><strong>Insulin-like growth factor</strong></td>
<td>Hepatocytes, Skeletal myocytes, Fibroblasts, Macrophages, Neutrophils</td>
<td>↑ Keratinocyte and fibroblast proliferation, ↑ Angiogenesis, ↑ Collagen synthesis, ↑ ECM formation, ↑ Cell metabolism</td>
</tr>
<tr>
<td>IGF-I, IGF-II, Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Epidermal growth factor</strong></td>
<td>Keratinocytes, Macrophages</td>
<td>↑ Keratinocyte proliferation and migration, ↑ ECM formation</td>
</tr>
<tr>
<td>EGF, HB-EGF, TGF-α</td>
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</tbody>
</table>
Standard Wound Management

1. Wound Bed Preparation
2. Infection Control
3. Correction of Ischemia
4. Nutritional repletion
5. Correction of Hyperglycemia
6. Pressure Relief (Offloading)
Defining Therapeutic Goal

Wound Closure vs. Wound Maintenance

Maintenance Wound Goals (palliative):

1. Prevent further tissue loss
2. Prevent infection
3. Control exudate/drainage
4. Control odor
Multidisciplinary Wound Care Team
VA Long Beach SCI/D HCG

Plastic Surgery
WOCN
Physiatry
Physical Therapy
Primary Care Nursing
Nutritionists
Research
Wound Bed Preparation

**D**ebridement – Remove non-viable tissue

**I**nfection/Inflammation – Reduce bacterial load, inflammation

**M**oisture – Control for edema/maceration vs. desiccation

**E**dge Advancement – Support cellular proliferation/migration

Wound Assessment Tools

“Is this wound healing appropriately?”

“I know it when I see it…”

– SCOTUS Justice Potter Stewart
Wound Assessment Tools

Numeric scales to score pressure ulcer healing:

1. Bates-Jensen Wound Assessment Tool (BWAT)
   13 characteristic sub-scores

2. Pressure Ulcer Scale for Healing (PUSH)
   3 characteristic sub-scores

3. Spinal Cord Impairment Pressure Ulcer Monitoring Tool (SCI-PUMT)
   7 characteristic sub-scores
“How long will it take to heal?”

Depends on:

1. Fibroblast proliferation & migration
2. ECM deposition rate
3. Keratinocyte proliferation & migration
4. Myofibroblast wound contraction
Mathematical Modeling

Dermal Healing (fibroblasts):

\[
\frac{d}{dt} i(t) \equiv \dot{f}(t) = s \frac{\nu^i(t)}{\nu^i(t)}
\]

\[
u^i(t) = (1 - \rho) c( i(t), t) + \rho \frac{\dot{f}(t-\tau)}{\dot{f}(t-\tau)}
\]

where \( s = \) cell speed
\( \tau = \) time lag

Wound healing as exponential decay:

\[ N(t) = N_0 e^{-\lambda t} \]

where \( N_0 \) = initial wound size
\( \lambda \) = healing rate
\( t \) = time

Half-life, \( t_{1/2} = \frac{\ln 2}{\lambda} \)
Healing Rate of DFUs
Standard Wound Care Alone

Percentage of Patients in Whom Ulcers Healed During the 12-Week Period

- >53% area reduction at 4 week: 58%
- <53% area reduction at 4 week: 9%
Wounds that do not achieve 50% healing in 4 weeks

- or -

\[ t_{\frac{1}{2}} = \frac{\ln 2}{\lambda} > 4 \text{ weeks} \]

will likely fail to heal and result in a chronic wound.
The Chronic Wound
Non-healing/Stalled/Problem Wound

Pathways to Non-healing:

1. Infection – Biofilm, Osteomyelitis
2. Hypoxia – Edema, Scarring, Vasculopathy, Nicotine
3. Cellular Failure – Diabetes, Malnutrition
4. Trauma – Pressure

Suspect chronic inflammation in absence of above
Chronic Inflammation

- Fibroblast senescence hypothesized as major factor
- May result from prolonged exposure to reactive oxygen species
- Impaired synthetic and replicative capacity
- Decreased secretion of neutrophil attracting cytokines
- Increased fibroblast senescence in pressure ulcers
- Elevated plasmin production by pressure ulcer fibroblasts

## Biochemical Differences

### Healing Wounds
- ↓Pro-inflammatory cytokines
- ↓MMPs
- Normal matrix—fibronectin, collagen
- Cells capable of rapid response
- ↑Cell mitosis
- ↑Growth factors

### Chronic Ulcers
- ↑Pro-inflammatory cytokines
- ↑MMPs
- Degraded matrix—fibronectin, collagen
- Senescent fibroblasts
- ↓Mitogenic activity
- Disordered patterns of growth factors

Chronic Wound
Prevention/Treatment

- All risk factors addressed and corrected
- But wound still not healing at reasonable rate
  
  \[ t_{\frac{1}{2}} = \frac{\ln 2}{\lambda} > 4 \text{ weeks} \]

- Consider applying advanced wound care
Advanced Wound Care

AKA Adjuvant wound care, Advanced therapeutics

1. Biophysical
   - Hyperbaric O₂, Negative pressure wound therapy (NPWT), Electrical stimulation, Ultrasound, Radio Frequency, Ultraviolet Light, Low-level Laser Therapy

2. Growth Factors
   - Platelet-derived growth factor (Regranex), Platelet-rich plasma

3. Extracellular Matrix
   - Oasis, Integra, MatriStem, Unite Biomatrix

4. Bioengineered skin substitutes
   - Apligraf, Dermagraft
Hyperbaric Oxygen Therapy

- 100% Oxygen delivered at >1.5 atmospheres absolute
- Reverses tissue hypoxia
- Reverses edema
- Stimulates fibroblast proliferation, keratinocyte differentiation
- Promotes neovascularization
- Stimulates production of growth factors/cytokines
- Accelerates microbial oxidative killing
Hyperbaric Oxygen Therapy

Wound Indications:
1. Problem Wound
2. Refractory Osteomyelitis
3. Endangered Flap/Graft
4. Delayed Radiation Injury
   - 100% O$_2$ at 2.0-2.4ATA
   - 90 minutes, once a day
Hyperbaric Oxygen Therapy
Transcutaneous Oximetry (tcpO₂)

- Noninvasive estimation of pO₂ on skin surface
- Diagnostic tool for wounds and skin flaps
- Screening tool for HBO
- tcpO₂ < 40 mmHg suggests hypoxia-impaired healing
- In diabetes/renal failure hypoxia at tcpO₂ < 50 mmHg

Negative Pressure Wound Therapy (NPWT)
Electrical Stimulation

- Transepithelial potential of 20-50mV in unwounded skin
- Skin wounding results in DC voltage gradient
- Wound electric field stimulates:
  1. Cell migration
  2. Cellular proliferation rate
  3. Alignment of axis of cellular division
  4. Growth factor secretion
Electrical Stimulation

- Anode (+) attracts:
  1. Macrophages
  2. Neutrophils
  3. Keratinocytes

- Cathode (-) attracts:
  1. Activated neutrophils
  2. Fibroblasts
  3. Myofibroblasts
  4. Endothelial cells
Electrical Stimulation

Level A evidence strength

High-Voltage Pulsed Current (HVPC)

Wound filled with saline-gauze/hydrogel

50-100V at 100Hz

60 minutes once a day
Electrical Stimulation
Bioengineered Skin Substitutes

Products with living cells as functional skin equivalents

Mechanisms of action:

1. Colonization of wound bed with non-senescent cells
   Recruitment of stem cells

2. Production of growth factors
   Stimulation of angiogenesis

3. Re-epithelialization
   Substrate for keratinocyte migration

4. Modification of inflammatory processes
   Recruitment of neutrophils, prevention of biofilms

Apligraf®
Organogenesis, Inc.

- Living bi-layered dermal-epidermal skin substitute
- Dermal layer: fibroblasts in bovine type I collagen
- Epidermal layer: keratinocytes
- Cells from human neonatal foreskin tissue
- FDA-approved for venous leg ulcers, diabetic ulcers
- Shipped overnight, viable for 2-3 days
- Each circular unit measures about 7.5cm in diameter
Dermagraft®
Advanced BioHealing, Inc.

- Cryopreserved bioengineered dermal substitute
- Fibroblasts seeded into polyglactin (Vicryl™) mesh
- Cells derived from human neonatal foreskin tissue
- FDA-approved for diabetic ulcers
- Preserved at -70°C with 6-month shelf-life
- Each unit measures approximately 2”x3”
Bioengineered Skin Substitutes

Dermagraft®

Apligraf®
Dermagraft for Stalled Wounds
Long Beach SCI Experience

- Total 43 patients treated since December 23, 2009
- Total 65 wounds treated
  - 46 Pressure Ulcers
    - 6 Surgical Dehiscences
    - 3 Open Wound from Flap Loss
    - 2 Open Wounds after Abscess Drainage
    - 2 Open Digital Amputations
    - 1 Diabetic Foot Ulcer
    - 1 Open Wound after Skin Graft Loss
    - 1 Chronic Sinus Tract
    - 1 Non-healing Burn
    - 2 Other
  - 6 Other
Case #1
Coccygeal Pressure Ulcer, Stage IV

- 67 Year-old man with Multiple Sclerosis
- Followed by Wound Care Team as Inpatient
- Chronic Renal Failure, Ventilator-dependent
- Ulcer first noted on 4/27/2009
- Treated with: Granulex, Aquacel Ag, Cadexomer I₂
- First Dermagraft applied on 3/26/2010
Case #2
Planter Heel Ulcer, Stage III

- 62 Year-old man with Paraplegia (T2 complete)
- Followed by Wound Care Team as Outpatient
- Non-Diabetic, Non-Smoker
- Ulcer first noted on 12/30/2009
- Treated with: collagenase, hydrogel
- First Dermagraft applied on 4/14/2010
Collagenase

Hydrogel

1st Dermagraft

2nd Dermagraft

3rd Dermagraft

4th Dermagraft

5th Dermagraft

LxW (sq cm)

Width (cm)

Length (cm)

12/30/09

1/30/10

3/2/10

4/2/10

5/2/10

6/2/10
Healing with Dermagraft vs. without Dermagraft

Patient A: 52 year-old man, C3 tetraplegic, ASIA D stage IV coccygeal pressure ulcer initial size 4.4x1.6cm, 1.4cm deep initial volume of 9.86 cm³

Patient B: 25 year-old man, C4 tetraplegic, ASIA B stage IV coccygeal pressure ulcer initial size 5.2x5.4cm, 0.9cm deep initial volume of 25.27 cm³
Dermagraft for Pressure Ulcers
VA Long Beach SCI Initial Numbers

- 12 Patients: 7 tetraplegic, 5 paraplegic
- 15 pressure ulcers: 5 stage III, 10 stage IV
- 80% of ulcers older than 90 days
- 10 (67%) ulcers healed, with average 4.7 grafts
- Healers had smaller ulcers (4.1cm$^3$ vs. 14.7cm$^3$)
- Healed ulcers less chronic (237.8 days vs. 1,300 days)
Summary

1. Diagnose and correct reversible risk factors
2. Manage wound bed (DIME)
3. Assess healing after 4 weeks of standard wound care
4. If healing <50% consider advanced wound therapies
Pressure Ulcer

Infection Control
Correction of Ischemia
Nutritional repletion
Correction of Hyperglycemia
Pressure Relief (Offloading)

Surgical Candidate?

Flap Closure

Wound Bed Preparation (DIME)

Has Wound Healed ≥50% in 4 weeks?

YES

Advanced Wound Care
Biophysical Modalities
Growth Factors
ECM Products
Bioengineered Skin Substitutes

NO

Weekly Wound Assessment
Measurements
Photography
Validated Tool (e.g. BWAT, PUSH, SCI-PUMT)

NO

YES


References

Obtaining CME Credit

- If you would like to receive CME credit for this activity, please visit:
  http://www.pesgce.com/PVAsummit2011/
- This information can also be found in the Summit 2011 Program on page 8.