REDUCING THE BURDEN OF STALLED WOUNDS: PROGRESSING TOWARDS HEALING

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Disclosures

Dr. Herman: Grant/Research—Tufts University; Research—Smith & Nephew

Dr. Lehrman: Board of Directors—American Society of Podiatric Surgeons, American Professional Wound Care Association; Consultant—Endo, Smith & Nephew, Molnlycke, MTF; Speakers’ Bureau—BSN Medical, Smith & Nephew

Dr. Ruotsi: Speakers’ Bureau—Organogenesis, Smith & Nephew
Learning Objectives

- Describe the pathophysiology of chronic wounds
- Recognize the importance of aggressive wound management for chronic wounds
- Examine the role of enzymatic debridement as an adjunct to sharp debridement in progressing chronic wounds toward healing
- Recognize the impact of chronic wounds on healthcare costs and patient’s quality of life

The Chronic Wound Conundrum: Precipitating Factors and Pathophysiology

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Chronic Wounds: A Global Problem

<table>
<thead>
<tr>
<th>Wound Type</th>
<th>Prevalence</th>
<th>Annual Direct Cost (USD)</th>
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<tbody>
<tr>
<td>Venous</td>
<td>2.5 million</td>
<td>$Many billions*</td>
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<tr>
<td>Diabetic</td>
<td>882,000†</td>
<td>&gt; $6 billion‡</td>
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<tr>
<td>Pressure</td>
<td>10% to 18% (acute care)</td>
<td>$Many billions§</td>
</tr>
<tr>
<td></td>
<td>Up to 28% (extended care)</td>
<td>- Doctor visits: $520/pt §</td>
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<tr>
<td></td>
<td></td>
<td>- Hospital: ~$16,000/pt §</td>
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*Based on estimated prevalence of 2.5 million and actual mean direct cost of $9685/person; †Based on 14.7 million diabetics, 8% of whom expected to develop ulcers over 2 years; ‡Direct costs of treating noninfected diabetic foot ulcers; §Costs in 1996 and 1998.

Many billions

- Doctor visits: $520/pt §
- Hospital: ~$16,000/pt §

10% to 18% (acute care)
Up to 28% (extended care)

Regulation of Wound Healing: Dynamic and Reciprocal Signaling

\[ u-PA = \text{urokinase plasminogen activator}; \ MMP = \text{matrix metalloproteinase}; \ t-PA = \text{tissue plasminogen activator}. \]


Phases of Wound Repair

Coagulation: provisional matrix
Inflammation: cytokine release
Migration/proliferation
Matrix/tissue remodeling

Normal Repair: Achieving an Equilibrium between Synthesis and Degradation
Overview of Chronic Wounds

Non-Sequential Progression through Wound Healing Phases

- Phase 1: Hemostasis (0 to ~3 hours)
- Phase 2: Inflammation (Prolonged)
- Phase 3: Proliferation/Epithelialization (Slow or Failed)
- Phase 4: Maturation/Remodeling

Chronic Wounds: A Disrupted Equilibrium

PROTEASES DEGRADATION

INHIBITORS SYNTHESIS

CHRONIC WOUND CONUNDRUM
- Infection & Immunity
- Necrosis
- Perfusion
- Metabolism & Nutrition
- Pressure
Acute vs Chronic Wound Healing

Excessive inflammation
MMP production
Matrix degradation
Cell senescence
Impaired angiogenesis

Cell proliferation
Apoptosis
TIMP production
Matrix remodeling

TIMP = tissue inhibitor of metalloproteinase.
How Chronic Wounds Differ from Acute Wounds

• Within chronic wounds, several issues can affect healing, ie, quantity and activity of inflammatory cytokines, MMPs and their inhibitors, all of which can lead to decreased levels of certain growth factors (eg, PDGF, EGF and TGF-β), when compared to acute/normal wounds.

• Bacteria and biofilms contaminating chronic wounds may be deleterious compared to those beneficial bacteria found in acute wounds.

• Excessive MMPs can degrade the cytokines, eliminating the mediators of cellular processes that are critical to wound healing.

EGF = epidermal growth factor; PDGF = platelet-derived growth factor; TGF-β = transforming growth factor beta.


Chronic Wounds: Inflammatory Cycle

• Elevated levels of TNF (neutrophils, macrophages)
• Elevated levels of ILs (IL-1β, IL-6)
• Imbalanced protease and inhibitor profiles
  – Elevated MMPs
  – Decreased TIMPs
• Destruction of key survival agents (growth modulators and receptors)
• Altered microenvironment (ECM)
  – Perturbation of cellular responses to injury (migration and growth)

ECM = extracellular matrix; TNF = tumor necrosis factor; IL = interleukin.


Signaling through the Inflammatory Network: Role of Immune Modulators and Host Enzymes

Bacterial Signals: Amplify Inflammation

Immune Surveillance Cells: Elevated Extravasation?

Elevated Proteases—Decreased TIMPs

ICAM = intercellular adhesion molecule; LFA = lymphocyte function; VLA = very late antigen; VCAM = vascular cell adhesion molecule; PMN = polymorphonuclear neutrophils.

Reversal of ECM Degradation: Active Healing in Venous Ulcers

Fibronectin absence


Pressure Ulcers: Can Wound Fluid Protease Activity Predict Healing Efficacy?


Acute vs Chronic Wound Healing

EPC = endothelial progenitor cell; FGF = fibroblast growth factor; ROS = reactive oxygen species; VEGF = vascular endothelial growth factor.

Importance of Aggressive Wound Management for Chronic Wounds

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The Importance of Aggressive Wound Bed Preparation

Triple Aim

1. Improved Patient Experience
2. Improved Cost
3. Improved Population Health
Wound Bed Preparation: Restoring the Balance

• Integrates proven concepts to build a platform for the treatment of chronic wounds
• Organizes medical procedures into a holistic approach that can be used to evaluate and remove barriers to the wound healing process
• Ultimate aim of the formation of good quality granulation tissue leading to complete wound closure
• Optimal management of a wound in order to accelerate endogenous healing, or to facilitate the effectiveness of other therapeutic measures

The Microenvironment of the Chronic Wound is Imbalanced

HEALING WOUNDS
Low inflammatory cytokines
Low proteases, ROS
Functional ECM and growth factors
Mitotically competent cells
Apoptotic clearing (without necrosis)

CHRONIC WOUNDS
High inflammatory cytokines, bacteria
High proteases, ROS
Degraded ECM and growth factors
Quiescent and senescent cells
Necrosis (without regulation of apoptosis)

Treat the Cause

• Determine the etiology
  – Assess ability to support
    • Offloading / pressure redistribution
    • Compression
    • Glucose control
    • Re-establish blood flow
  • Assess potential for healing
  • Assess comorbid conditions

Treat the Cause

- Determine the etiology
  - Assess ability to support
    - Offloading / pressure redistribution
    - Compression
    - Glucose control
    - Vascular interventions
    - Nutritional support
- Assess potential for healing
- Assess comorbid conditions

TIME

- Tissue
- Infection
- Moist wound environment
- Edge *Don’t waste it*

Necrotic Tissue

- Devitalized tissue that supports the growth of pathological organisms
  - Bacteria thrive in presence of necrotic tissue
- Perpetuates inflammatory response
- Acts as a barrier to new tissue growth
Why Debride Non-Viable Tissue?

- To remove dead, devitalized, contaminated tissue or foreign material, senescent cells
- To reduce microbes, toxins, and other substances that inhibit healing
- To provide a clinician the ability to assess the depth of wound and the condition of surrounding tissue
- To remove the physical barrier to healing and reduce bacterial growth
- To adequately prepare for advanced agents, CTPs
- Recommended in all guidelines

Types of Debridement

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
<th>Examples</th>
</tr>
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<tbody>
<tr>
<td>Surgical (Excisional/Sharp)</td>
<td>Removal by surgical instrument</td>
<td>Scalpel, scissors, hydrotherapy, lasers, curettes</td>
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<tr>
<td>Mechanical</td>
<td>Removal of necrotic tissue by mechanical means</td>
<td>Wet to dry dressings, hydrotherapy, ultrasound, abrasion</td>
</tr>
<tr>
<td>Biosurgical</td>
<td>Sterile larvae selectively digest necrotic tissue and bacteria</td>
<td>Sterile blowfly or housefly larvae</td>
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<tr>
<td>Autolytic</td>
<td>Uses the body’s own enzymes to dissolve necrotic tissue; assisted with moisture-retentive dressings</td>
<td>Moisture-retentive dressings</td>
</tr>
<tr>
<td>Enzymatic</td>
<td>Topical application of enzymes to liquefy necrotic tissue</td>
<td>Collagenase</td>
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Debridement is a Key Component of Adequate Wound Bed Preparation
Advantages of Sharp Debridement

- The fastest way to remove necrotic tissue
- Able to completely remove surface debris, biofilm
- May re-ignite an inflammatory response
  - Return wound to healing trajectory
Adjunctive Debridement with Collagenase

- Daily debridement adjunct to weekly or bi-weekly sharp debridement
- Exogenously applied agent works directly on devitalized tissue or indirectly by dissolving collagen anchoring devitalized tissue to wound bed
- Little to no effect on healthy collagen or tissue
- Easily applied by patient or caregivers
- Collagenase is the only enzymatic debriding agent approved by the FDA

Collagenase

- Collagenase belongs to a family of MMPs
  - Naturally occurring enzymes produced by in response to bacteria, debris, and are produced by activated inflammatory cells and certain wound cells
- Exogenous collagenase is a derived from fermentation by clostridium histolyticum
  - Complex biologic that requires a year-long manufacturing process in a sterile environment
  - Digests collagen in the necrotic wound environment
  - Targets only devitalized collagen
- Continuously removes necrotic tissue from the wound while allowing normal granulation to proceed
- Selectively attacks and cleaves collagen strands anchoring cellular debris
- Enables it to work from the "bottom up"

Debridement with and without Adjunctive Clostridial Collagenase Ointment

• Objective
  – Provide descriptive outcomes data regarding chronic diabetic foot ulcers treated with 6 weeks of serial sharp debridement with or without adjunctive CCO debridement

• Endpoints
  – Primary
    • Percent change in ulcer area from baseline at end of the treatment period (Week 6) and after an additional 6 weeks of follow-up (Week 12)
  – Secondary
    • Wound appearance at Week 6 and Week 12 using a standardized wound assessment tool

Debridement with and without Adjunctive Clostridial Collagenase Ointment (cont’d)

• Aim was to generate rather than test a hypothesis based on sample size (N = 55)

• Objective decision making relative to sharp debridement
  – Bates-Jensen Wound Assessment Score
    • Edges
    • Undermining
    • Necrotic tissue type and amount
    • Exudate type and amount
    • Periwound skin color
    • Granulation tissue
Debridement with and without Adjunctive Clostridial Collagenase Ointment: Results

- Wound appearance scores improved in both treatment groups
- On average, ulcers receiving serial sharp debridement decreased in size more rapidly with the addition of CCO
  - The CCO group demonstrated a 68% decrease in ulcer area from baseline at Week 6 (P < .001) vs 36% in the control group (P = NS)
- This was designed as a descriptive study; further work underway


Precautions

- The optimal pH range of collagenase is 6 to 8
- Adversely affected by certain detergents, and heavy metal ions such as mercury and silver which are used in some antiseptics
- Soaks containing metal ions or acidic solutions should be avoided because of the metal ion and low pH
- A slight transient erythema has been noted occasionally in the surrounding tissue, particularly when CCO was not confined to the wound. Therefore, the ointment should be applied carefully within the area of the wound


With that said…

- Thoroughly flush with saline if agents are used
- Awareness of compatibility with cleansers and antimicrobial dressings/agents helpful

Case Study 1

- 24-year-old male spent a morning pouring a cement sidewalk in sneakers with no protection from the wet cement and lime contained therein. These are lime-related chemical burns with associated eschar.
Case Study 2

- 44-year-old male with leukocytoclastic vasculitis and hospitalized after several weeks of ineffective treatment
- Biopsy done in hospital and seen in Wound Center 5 days later
- Thick, broad-based hard black eschars were cross-hatched on Day 1
- Concomitant systemic steroids and CCO

Case Study 3

- 82-year-old Egyptian male presented to hospital with huge bulla on foot
- Bulla decompressed at bedside
- Cultures unremarkable and vascular workup satisfactory
- Discharged with conservative wound care and initially reluctant to come for follow-up
Case Study 4

- 62-year-old male awoke on Saturday morning with intense redness and warmth around his ankle
- Took a shower and the skin peeled off in affected area
- Went to urgent care center and sent home with cephalexin 500 qid
- Saw me 48 hours later
Case Study 5

- 82-year-old female tripped going up stairs striking her leg on edge of stair
- Developed huge hematoma and went to orthopedist as she had total knee replacement
- He debrided the eschar leaving huge underlying wound and referred to me
- Remained on prophylactic antibiotics for about a month
Impact of Chronic Wounds on Healthcare Costs and Quality of Life

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Neuropathic Ulcer 5-Year Mortality Rate


Quality of Life
Chronic Wounds


6.5 Million Individuals affected and growing annually in the United States

Estimated at $33 Billion annually in the United States

BMI = body mass index.


Age
Population > 65 years
82% projected increase (2000 – 2030)
12.1% ≥ 19%

Diabetes
1990 – 2010
Increase of x 3

Obesity
Two-thirds with
BMI > 25

MACRA
ACI = Advancing Care Information; MIPS = Merit-based Incentive Payment System.
Comparative Effectiveness of Clostridial Collagenase Ointment vs Honey for Treatment of Pressure Ulcers

- 517 CCO Treated Pressure Ulcers
- Matched to Honey Treated Pressure Ulcers

- CCO group: 38% more likely to achieve 100% granulation at 1 year
- CCO group: 47% more likely to epithelialize at 1 year
**Clostridial Collagenase Ointment vs Honey**

- **CCO group:**
  - Fewer office visits
  - Fewer debridements
  - Less likely to require NPWT

NPWT = negative pressure wound therapy.

**Summary**

- Pathophysiology
- Aggressive Management!
- Enzymatic Debridement + Sharp Debridement
- Quality of Life
- Healthcare Costs

**Q & A**