Diabetic Foot Ulcers: Strategies for Prevention and Treatment

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EPIDEMIOLOGY

- 25.8 million in US diagnosed with diabetes
- 18.8 million persons currently diagnosed
- 7 million undiagnosed
- 79 million people have pre-diabetes
- 26.9% incidence over age 65

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EPIDEMIOLOGY

- Race and ethnic differences in prevalence of diagnosed diabetes
  - 7.1% of non-Hispanic whites
  - 8.4% of Asian Americans
  - 12.6% of non-Hispanic blacks
  - 11.8% Hispanics
  - 16.1% in Native Americans


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EPIDEMIOLOGY

- Ulceration occurs in up to 25% of people with diabetes in the US
- Ulceration leads to amputation in 30% of people with diabetes who are 40 or older
- Medicare spends more than 1.5 billions dollars on care of diabetic foot ulcer
- Each ulcer is associated with direct costs of $45K
- Recurrence rate of ulcerations is very high
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EPIDEMIOLOGY

- Amputation
  - More than 60% of non-traumatic lower-extremity amputations occur in people with diabetes.
  - Amputation rates among American Indians are 3 to 4 times higher than those for the general population.
  - It has been estimated that perhaps 50% of lower-extremity amputations could be prevented by improving foot care among individuals with diabetes.
  - people with diabetes annually (180/day)


Risk Factors for DFU

- Peripheral neuropathy - sensory, motor, autonomic.
  - Associated with 78% of DFU
- Foot deformity
- History of previous amputation
- Male
- Race (Native American)
- History of prior foot ulceration
- High vibration score
- High foot pressures
- Vascular Insufficiency
- Limited joint mobility
- Long duration of diabetes
- Long history of smoking
- Poor glucose control
- Impaired vision
- Increased age
- Poor footwear
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Amputation Risk

- Peripheral sensory neuropathy
- Vascular insufficiency
- Infection
- Prior amputation
- Foot deformity
- Trauma
- Impaired vision
- Poor glycemic control
- Poor footwear
- Older age
- Male Sex
- Charcot deformity
- Ethnicity

Pathophysiology of DFU
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Pathophysiology of DFU

- Neuropathy:
  - glucose, sorbitol and fructose and a reduction in myo-inositol needed for nerve conduction
  - Affects microvascular component innervations

Pathophysiology of DFU

- Sensory Neuropathy:
  - Presents in stocking and glove pattern.
  - Have loss of protective sensation,
  - lack of awareness of pain, temperature change,
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Pathophysiology of DFU

Motor Neuropathy:
- Affects the muscles required for normal foot movement
- Can result in muscle atrophy.
- Causes collapse of arch
  Charcot’s foot, claw toes, hammer toes with subsequent with redistribution

Ankle joint equinus-
- Defined as less than 0 degrees of ankle joint flexion
- Occurs in about 10.3% patients with DPN
- Results in increased plantar pressures increasing the risk for ulceration

Charcot foot with equinus deformity
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**Peripheral Arterial Disease**

- Major risk factor for amputation
- Incidence of ischemic diabetic ulcerations is relatively low
- Little is known about biology of PAD in patients with diabetes,
- Have macrovascular and microvascular changes
- Medium sized arteries are affected mainly at popliteal trifurcation

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**Diabetes Mellitus**

**Neuropathy**
- Motor: Weakness/Atrophy, Deformity, Abnormal Stress, High Plantar Pressures, Callus formation
- Sensory: Loss of Protective Sensation
- Autonomic: Anhidosis, Dry Skin, Fissures, Decreased sympathetic tone (Altered blood flow)

**Trauma**

**Vascular Disease**
- Microvascular: Structural: Capillary BM Thickening, Functional: A-V shunting
- Macrovascular: Atherosclerosis
- Ischemia: Decreased blood flow, Edema

**Osteoarthropathy**

**Impaired Responses to Infection**

**Amputation**

**Diabetic Foot Ulceration**

Reduces nutrient capillary flow

Amputation
**Components of Normal Wound Healing**

<table>
<thead>
<tr>
<th>Process</th>
<th>Cell Types Involved</th>
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<tbody>
<tr>
<td>Coagulation process</td>
<td>Platelets</td>
</tr>
<tr>
<td>Inflammatory process</td>
<td>Platelets, Macrophages, Neutrophils</td>
</tr>
<tr>
<td>Migratory/Proliferative process</td>
<td>Macrophages, Lymphocytes, Fibroblasts, Epithelial cells, Endothelial cells</td>
</tr>
<tr>
<td>Remodeling process</td>
<td>Fibroblasts</td>
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Injury/hours/days \[\rightarrow\] weeks

“Abnormalities in healing:
- Diabetic foot is stalled in the inflammation phase of healing
  - Causes cessation of epidermal growth and migration over the wound surface
  - High levels of MMP resulting in increased proteolytic activity and inactivation of the growth factors

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Kane & Krasner, 1997
Abnormalities in Healing:
- Morphologic changes that impair function are present in:
  - Macrophages
  - Keratinocytes
  - Results in keratinocyte proliferation without differentiation

Abnormalities in healing:
- Collagen-balance between synthesis and degradation in wound repair is tenuous
- Diabetes shifts the balance to one side disrupting the healing cycle
- Resultant collagen production deficits can be seen in thickening of vascular basement membrane, limited joint mobility, and poor wound healing
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**Primary Goals of Care:**
- Prevent limb loss
- Maintain quality of life

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**Global History**
- Duration of diabetes
- Glycemic control
- Cardiovascular, renal, ophthalmic evaluation
- Other comorbidities
- Social Habits
  - Alcohol/tobacco, etc

**Global history**
- Current Medications
- Allergies
- Previous hospitalizations
- Previous surgeries
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History
- Foot-Specific
  - General
  - Daily activity
  - Footwear
  - Callus formation
  - Deformities
  - Previous foot surgeries
  - Neuropathy symptoms
  - Ischemic symptoms

Physical Examination
- Peripheral pulses
- Shape of foot and pressure points
- Semms Weinstein test
- Joint mobility
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Physical Examination

Semms Weinstein test

Ulcer Assessment:
- Wound size
- Depth
- Presence of sinus tracts
- Probing to bone
- Amount of granulation tissue/dysvascular tissue
- Type and amount of drainage
- Amount of hyperkeratotic tissue surrounding the wound
- Signs of infection
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ULCER ASSESSMENT

Modified Wagner Classification System

- 0 No open lesions: may have deformity or cellulitis
- 1 Superficial ulcer
- 2 Deep ulcer to tendon, or joint cellulitis
- 3 Deep ulcer with abscess, osteomyelitis, or joint sepsis
- 4 Localized Gangrene
- 5 Gangrene of entire foot
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Assessment of Vascular Status

- No universal noninvasive test that can completely evaluate vascular health
- Palpation of pulses: provides evidence for presence of PAD but not absence
- ABI: ADA recommends as reproducible and quantitative test, however should be performed with an understanding of limitations of test in diabetics
- Segmental Pressure Volume: Used for patients with poorly compressible vessels
- TCPO$_2$: used to assess probability of healing, and in conjunction with HBO

Diagnostic Testing

- Vascular testing as indicated-ABI, Arterial Duplex, TCPO2
- Plain film X-Ray if indicated
- MRI if indicated
- Lab work including
  - CBC with diff
  - CMP
  - pre-albumin,
  - Hgb A1c,
  - sedimentation rate
# TIME Principles of Wound Bed Preparation

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## Diabetic Foot Ulcers: Strategies for Prevention and Treatment

**Debridement**
- Sharp Debridement: surgical, hydro surgical
- Enzymatic debridement
  - Collagenase
- Autolytic debridement: The process by which a wound bed clears itself of debris
- Biotherapy: describes the use of live organisms (maggots and leeches) to assist in the medical regimen
- Mechanical-hydrotherapy, wet to dry dressings
- Ultrasonic MIST

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Debridement

- Debridement widely recognized as one of the most important techniques in wound bed preparation
- Targets complete removal of all necrotic, non-viable, dysvascular tissue to achieve red, granular wound bed
- Promotes release of growth factors that contribute to more progressive wound healing

Infection/Inflammation
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Signs of Infection

- **Classic Signs**: Heat, pain, redness, swelling
- **Secondary Signs**: Exudate, delayed healing, friable tissue, discolored granulation tissue, foul odor, pocketing at wound base, wound breakdown
- **Probe to bone test**
- If osteomyelitis suspected, ESR, C-reactive protein
- Not recommended: routine culture as an evaluation unless infection is apparent or sensitivities are required for ABX selection

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### Signs of Infection

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<th>Agent</th>
<th>Pathogen</th>
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<tr>
<td>Dicloxacillin</td>
<td>QID, narrow spectrum</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Limited evidence for severe SA</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>QID dosing</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Once daily</td>
</tr>
<tr>
<td>Doxycycline</td>
<td></td>
</tr>
<tr>
<td>TMP/SMX</td>
<td></td>
</tr>
<tr>
<td>Amox/sulbactam</td>
<td>relatively broad spectrum, covers anaerobes</td>
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<tr>
<td>Linezolid</td>
<td>Expensive, increased toxicities greater than 10 days</td>
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Guidelines for Diabetic Foot Infection. CID 2012:54 (June 15) e151
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Recommendations for Collection of Specimens for Culture From Diabetic Foot Wounds

Do
- Obtain an appropriate specimen for culture from almost all infected wounds
- Cleanse and debride the wound before obtaining specimen(s) for culture
- Obtain a tissue specimen for culture by scraping with a sterile scalpel or dermal curette (curettage) or biopsy from the base of a debrided ulcer
- Aspirate any purulent secretions using a sterile needle and syringe
- Promptly send specimens, in a sterile container or appropriate transport media, for aerobic and anaerobic culture (and Gram stain, if possible)

Do not
- Culture a clinically uninfected lesion, unless for specific epidemiological purposes
- Obtain a specimen for culture without first cleansing or debriding the wound
- Obtain a specimen for culture by swabbing the wound or wound drainage

Guidelines for Diabetic Foot Infection. CID 2012:54 (June 15) e151

Topical Anti-microbial – Why Silver Dressings?

Centuries of proven anti-microbial activity.

Traditional delivery methods provided high levels of silver which rapidly binds with chlorine and proteins.
- SSD delivers in the range of ~3000 ppm (µg/ml) of Ag+.
- Required dressing changes 2-4 times per day.

Proven bactericidal against >150 clinically relevant pathogens

Demling and Desanti (2001)
Understanding the chemistry
How does silver work?

Silver must be in ionic form to provide antimicrobial effect

Silver species
- Ag⁺ most common form released from dressing - antimicrobial
- Ag⁰ only released from nanocrystalline silver and occurs as clusters of atoms/ions

Multiple mechanisms of action


ACTICOAT - MRSA Death Curve
Wright et al (1998) AJIC 26(6), 572-577
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**Moisture Imbalance**

Choice of dressings must be made with the goal of controlling exudate while maintaining optimal wound bed moisture

Moisture Imbalance

- Moist wounds heal 40% faster
- Moist wound environment facilitates epithelial migration, maintains optimal temperature, decreases pain, and provides better cosmetic result
- Excess exudate has negative effect on wound, slows migration of epidermal cells, limits epidermal regeneration
- Chronic wound fluid is biochemically distinct from acute wound fluid.
  - Slows down or blocks the proliferation of cells such as keratinocytes, fibroblasts, endothelial cells

Moisture Balance

Hydrogels provide high level of moisture contained in polymers
Best choice for dry, sloughy wounds with minimal to moderate exudate
Reapply 24-72 hours
Facilitate autolytic debridement
Absorb Exudate: Foams and Hydrofibers

- Foam dressings provide thermal insulation, high absorbency, moist environment, moderate to heavy exudate
- Have polyurethane backing to prevent excess fluid loss
- Hydrofibers are highly absorbent, good tensile strength
- Hydrofibers do not shed fibers in the wound bed
- Both can be worn for up to a week

Moisture Imbalance

Absorb Exudate: Alginites

- Best on heavily exudative wounds.
- Form gel upon contact with exudate
- Donate calcium to wound bed facilitating hemostasis.
- Made from brown seaweed.
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**Edge of Wound Non-advancing or Undermined Collagen**

- Available as sheet, gel or in particles
- Provides hemostasis
- Attracts macrophages and fibroblasts
  - Fibroblasts demonstrate increased proliferation and synthesis when attached to a collagen matrix
- May enhance tissue strength
- Modulate effects of excess MMP's?
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Edge of Wound Non-advancing or Undermined
Advanced Wound Healing

APLIGRAF

Apligraf®

- Only bioengineered, bilayered living cell-based product
- Contains 2 cell types relevant to healing
  - 11 million fibroblasts in an ECM
    - 8,780 fibroblasts per mm³
  - 4 million keratinocytes with a differentiated stratum corneum barrier
    - 10,608 keratinocytes per mm³
  - >90% cell viability maintained throughout shelf-life
- Used in >12 years of clinical practice
  - Over 425,000 units of Apligraf have been supplied to wound care and outpatient centers throughout the United States
Edge of Wound Non-advancing or Undermined

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OASIS® Wound Matrix
SIS biomaterial provides a natural extracellular matrix scaffold with 3 dimensional structure and a biochemical composition that is attractive to host cell infiltration and conducive to tissue regeneration.

**OASIS®**
- Small Intestine Submucosa (SIS)
- Derived from porcine small intestine
- Complex matrix of collagen and other proteins
- Acellular collagen sheet
- Processed to remove serosa, smooth muscle, and mucosa layers
- Sterilized with ethylene oxide

Edge of Wound Non-advancing or Undermined

From: Brown-Etts, M; Cutsall, W; Hiles, M in Wounds 14(4):150-166, 2002
**Edge of Wound Non-advancing or Undermined**

**Autologous Platelet Concentrate**

- Autologous concentration of platelets in small volume of plasma
- Has concentration of seven fundamental growth factors proven to be secreted by platelets for wound healing
- Also contains fibrin, fibronectin, cellular adhesions molecules
Edge of Wound Non-advancing or Undermined

Open wound following Ray amputation of digits 3-5 on Feb. 16

Edge of Wound Non-advancing or Undermined

Oasis application on March 14
Edge of Wound Non-advancing or Undermined

First application of APC April 20

2nd application of APC April 29

Edge of Wound Non-advancing or Undermined

Healed June 22
Mist Ultrasound Therapy

- Multiple RCTs supporting efficacy in wound healing
- Decreased bioburden
- Facilitates debridement
- Increase angiogenesis

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HYPERBARIC OXYGENATION

- Monoplace chamber
- Multiplace chambers
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**Hyperbaric Oxygen:**
- **Patient breaths 100% oxygen** in hyperbaric environment (2.0-2.4 ATA)
- **Cochrane review:** reduces risk of amputation and may improve healing

**HYPERBARIC OXYGENATION**

**Physiological Effects**
- Hyperoxygenation of plasma (0.03-6.0MG)
- Vasoconstriction resulting in edema reduction
- Reduction of gas bubble size
- Bacteriostatic

**Indications for HBO**
- Gas Gangrene
- Acute traumatic peripheral ischemia
- Crush injury
- Suturing of severed limbs
- Progressive necrotizing infections
- Preservation of skin grafts or flaps
- Chronic refractory osteomyelitis
- Osteoradionecrosis, soft tissue radionecrosis
- Diabetic wounds of the lower extremities in patients who meet the following three criteria:
  - a. Patient has type I or type II diabetes and has a lower extremity wound that is due to diabetes;
  - b. Patient has a wound classified as Wagner grade III or higher; and
  - c. Patient has failed an adequate course of standard wound therapy.
Pressure relief or offloading is critical to healing of DFU. Multiple comparative studies have shown that Total Contact Cast is preferred method of offloading.

OTHER METHODS FOR OFFLOADING

- CROW Boot
- IPOS OR OTHOWEDGE
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OTHER METHODS FOR OFFLOADING

- CAM WALKER
- POST OP SHOE

Diabetic Foot Ulcer Summary

- Goals are to preserve limb, maintain quality of life
- Early Diagnosis and Treatment by knowledgeable provider essential to prevent amputation
- Most amputations could be prevented if treated appropriately when ulcer first developed
- Referral to Wound Center for offloading and advanced wound care decreases amputation rates and length of time to heal