Diabetic Foot Ulcer Management and Predictive Markers for Using Advanced Therapies

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Objectives

• To discuss the epidemiology of the diabetic foot
• To learn about the pathophysiology of diabetic foot ulcer formation
• To review predictive markers when considering advanced therapies
• To learn about vascular disease and the angiosome concept in the diabetic foot
• To discuss interesting cases

“Think like an internist, before you act like a surgeon” — Wm. Ennis, DO

• Wound management often requires a subtle balance between medical and surgical interventions.

Sometimes Clinicians Become Confused

Core Healing Principles

- Patient factors
- Physical aspects
- MACROscopic environment
- MICROscopic environment
Wound specialists have to be medical detectives

Don’t get caught with your pants down!

Acute Wounds

Examples
- Lacerations
- Abrasions
- Punctures
- Burns
- Surgical Incisions

Characteristics
- Heal in an expected time frame
- Cause is transient
- Usually lack significant impediments to healing
- Repair is sustained

Chronic Wounds/Ulcers

Examples
- Pressure ulcers
- Diabetic neuropathic ulcers
- Venous Insufficiency ulcers
- Arterial Insufficiency ulcers
- Inflammatory ulcers

Characteristics
- Non-healing, slow healing
- Cause is ongoing
- Multiple systemic and local impediments to healing
- Wound often recurs

Proposed Mechanisms for Chronicity in Diabetic Foot Ulcer

Unresponsive and/or Senescent Cells
- Deficient and/or unavailable growth factors/receptor sites

Non migratory, hyperproliferative edge epithelium
- Proteolytic/Inflammatory environment
- Bacterial interference

Address the etiology
Incidence of Common Chronic Wounds

- Diabetic Neuropathic Ulcers: > 340,000/yr
- Venous Stasis Ulcers: > 500,000/yr
- Pressure Ulcers: > 2.1 million/yr

Impact of Diabetes

- 1.3 million new cases (incident cases) of diabetes are diagnosed annually in the US in people aged 20 and over
- Prevalence of total diabetes in the US for all ages was 6.3%-7%
- Economic burden of diabetes:
  - Patients with diabetes in a Medicare population incur 1.7 times the health care expenditures of those without diabetes
  - Diabetic employees within a private health insurance group incur higher mean annual costs than their non-diabetic counterparts ($7,778 vs $3,367)

Diabetic Foot Ulcers

- One of the most common complications of diabetes
- Annual incidence varies from 1% to 4%
- Lifespan after diagnosis:
  - 5 years: Up to 90% may develop diabetic foot infections
  - 8 years: 100% may develop diabetic foot infections
- Peripheral neuropathy is a major contributing factor in diabetic foot ulcers
  - Other factors: foot deformity, callus, trauma, infection, and peripheral vascular disease
- 1 million amputations globally in patients with diabetes (every 30 seconds)
  - In the US, 1200 amputations weekly

Infection Contributes to Various Complications Including Amputation

- Risk factors for infection:
  - Wounds that penetrate to the bone
  - Wounds with a duration > 30 days
  - Recurrent foot wounds
  - Wounds with a traumatic etiology
  - Peripheral vascular disease
  - Pain
  - Deterioration of the wound

Infection plays a role in about 60% of the DFU cases that result in amputation

Diabetic Ulcers

- Once amputation occurs:
  - 50% of patients develop an ulcer in the contra-lateral limb within 18 months of the amputation

Post-op Mortality Rates Among Diabetic Amputees

- 1 Year: 13-40%
- 3 Years: 35-65%
- 5 Years: 39-80%

Data from 9 studies, Reiber & Weiler, 2001

References:

1. Centers for Disease Control (CDC) 2000
2. Weiler, 1999
3. Reiber, 2002
Consequences of Unhealed Neuropathic Ulcers

- Nearly half of all unhealed neuropathic ulcers result in death within 5 years


History of Foot Ulcer Increases Mortality Among Individuals with Diabetes

Ten Year Follow-up of the Nord-Trøndelag Health Study, Norway

- A large population-based study examined the association between foot ulcers in patients with diabetes and mortality risk while controlling for disease factors
- Foot ulcers were independently associated with increased mortality risk
  - Patients with diabetes and a foot ulcer had an increased mortality risk of 2.3-fold (229%) compared to non-diabetic subjects
  - In patients with diabetes, presence of a foot ulcer alone increased mortality risk by 47%


Population Mortality Hazard Risk; Db+HFU vs. Non Db Hazard Risk; Db+HFU vs. Db-HFU
Non-Db (N=53,632) 16.5% 2.29 [95% CI 1.82–2.88] 1.47 [95% CI 1.14–1.89]
Db-HFU (N=132) 49.0% 3.23 [95% CI 2.11–4.64] 2.29 [95% CI 1.14–4.64]
Db+HFU (N=1339) 35.2%

Db = Diabetic; HFU = History of foot ulcer
Hazard risk calculated via Cox regression analyses, adjusted for demographic and lifestyle factors.

Just having a neuropathic foot ulcer is a marker for death!

Snyder RJ(2010) Podiatry Management

Sometimes it is hard to get ahead of the curve

The extent of the problem of “problem wounds”...Diabetic Foot Ulcers

- In Denmark a multidisciplinary wound management program integrating vascular intervention and wound care has reduced LEA rate by 75%


Healing Neuropathic Ulcers: Results of a Meta-analysis

- These data provide clinicians with a realistic assessment of their chances of healing neuropathic ulcers
- Even with good, standard wound care, healing neuropathic ulcers in patients with diabetes continues to be a challenge
Continuing Research: Healing of Diabetic Foot Ulcers After 4 Weeks

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

- Wounds achieving less than 53% closure at week 4 have minimal chance of healing with conventional therapy


Association Between PAR at Week 4 & DFU Closure at Week 12

- Data was dichotomized by PAR of <50% or ≥ 50% by week 4 to assess the association of PAR with DFU closure by 12 weeks

Number of DFUs that healed by 12 weeks

- Results suggest that PAR at week 4 is the best prognostic indicator of healing by 12 weeks because it provides the highest specificity and sensitivity

2010 Consensus Panel
2010 Consensus Panel on Treatment

“The panel recognizes the prognostic value of 50% percent area reduction of the wound at four weeks and recommends utilization of this parameter as a clinical decision point for the use of advanced therapies in healing DFUs. Use of advanced modalities, when indicated, should be viewed as the new standard of care and these advanced modalities should not be a ‘last resort’ in the treatment of DFUs.”


DFU...Understanding the pathophysiology

Essential!!!
Diabetes Mellitus: Mechanisms of Cellular Failure

- Protein glycation and advanced glycation end products (glycosolated Hgb)
- Accelerated atherosclerosis
- Hyperglycemia
  - Impaired leukocyte function
  - Increased platelet aggregation
- Altered pattern of GF and GF receptor expression
- Impaired collagen synthesis
- Impaired angiogenesis

Account for Spectrum of DFU Presentation

- Probable contamination, no infection
- Local infection with adjacent cellulitis
- Progressive, necrotizing infection

Account for Spectrum of DFU Presentation

Moderate to Severe Ischemia/Hypoxia
Mild to moderate Ischemia/hypoxia
Severe Ischemia/hypoxia

DFU...Pathophysiology

- Infection
- Ischemia/hypoxia
- Cellular failure
- Pressure/trauma
- Inflammation

All final common pathways are implicated in DFU healing failure!!

The 2 circulatory systems impacting wound healing...

- Macrovascular Microcirculation

Macrovascular Arterial Occlusive Disease

- Microvascular dysfunction related to stress of nociceptive reflex and inflammatory response
- Vasomotor dysfunction with AI shunting
- Capillary basement membrane thickening with altered capillary exchange
- Ischemia due to tributary arterial occlusion disease
- Toes curled in "toe" position
- Diminished sensation
- Capillary density with increased pressure under maternal loads
Patterns of Peripheral Arterial Occlusive Disease in Diabetics

- Earlier age of onset
- Characteristic distribution pattern (Strandness, 1964)

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<tr>
<th></th>
<th>Aortoiliac</th>
<th>Tibial/Peroneal</th>
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<tr>
<td>Non-diabetics</td>
<td>68%</td>
<td>57%</td>
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<tr>
<td>Diabetics</td>
<td>27%</td>
<td>81%</td>
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“Small vessel disease” is a misnomer

- Thickening of the basement membrane creates some inelasticity and decrease in capillary size however this does not cause narrowing of the capillary lumen
- Disease is functional rather than obstructive (Microcirculatory dysfunction (MD))
- MD may also decrease the movement of leucocytes, thus theoretically making diabetics more susceptible to infection

Vascular disease in Patients with Diabetes

- Distribution of large vessel disease is different in diabetic patients
- Trifurcation disease with tibial vessel involvement
- The distal vessels are often spared at the level of the ankle (e.g.: PT, AT, Peroneal) making distal bypass and endovascular intervention possible
- Often the goal of an operative intervention is to improve microcirculatory dysfunction

Microcirculatory abnormalities not always reversed by correction macrovascular abnormalities...

- Post revascularization diabetic patients may still be at risk for foot ulceration and may fail to heal the ulcer despite adequate correction of macrovascular flow
The Angiosome Concept

• A new paradigm in evaluating and treating vascular disease in patients with diabetes
• Taylor and Palmer (1987)
• Dr. Chris Attinger: Pioneered the angiosome model in the diabetic foot

Angiosomes in the Diabetic Foot

• There are 6 angiosomes in the foot that originate from the three major arteries in the lower leg (PT, AT/DP, Peroneal)
• Choke vessels mark the boundary of any angiosome and can supply blood to an adjacent angiosome through the delay phenomenon
• Arterial-arterial connections: Allow uninterrupted blood flow to the entire foot despite the occlusion of one or more arteries (vascular redundancy; vascular rescue)

The distribution of 6 angiosomes in the foot create vascular redundancy. This generates multiple pathways to augment blood supply to an injured/ulcerated area

Anterior Tibial to Dorsal Pedal Artery Angiosomes

Medial Plantar Angiosome

Choke vessels in a rat model
Foot ulcers in patients with diabetes can be classified as neuropathic, neuroischemic, or ischemic; however, there is often an overlap between macro and microvascular disease that "blurs the lines" between these entities.

Neuropathic (Plantar with callus)

Ischemic (distal)

Neuroischemic (foot margins)

Wagner Classification Diabetic Foot Ulcers

- **Grade 0**: Intact skin
- **Grade I**: Superficial without penetration deeper layers
- **Grade II**: Deeper reaching tendon, bone, or joint capsule
- **Grade III**: Deeper with abscess, osteomyelitis, or tendonitis extending to those structures
- **Grade IV**: Gangrene of some portion of the toe, toes, and/or forefoot
- **Grade V**: Gangrene involving the whole foot or enough of the foot that no local procedures are possible

Wagner FW. Foot & Ankle 1981, 64-122

Wagner Grade I
Superficial without penetration deeper layers (some portion of dermis intact, no subcutaneous involvement)

Problem with Wagner Grading System…this is anatomically a Wagner I but is infected and clearly has a different risk presentation than the previous example.

Wagner Grade II
Full thickness reaching tendon, bone, or joint capsule without infection of ischemia

What about "probe to bone"?

Wagner Grade III
Full thickness with abscess, osteomyelitis, or tendonitis (any infection) extending to those structures
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Grade I & II w/Infection = Grade III

Wagner FW. Foot & Ankle 1981, 64-122

Wagner Grade IV
Gangrene of some portion of the toe, toes, and/or forefoot

Evaluation and Classification

Foot and Ulcer Evaluation
- Initial event and wound healing history should be considered
- Foot ulcer examination should include:
  - Dermatological changes
  - Ulcer characteristics, dimensions, and condition
  - Probe Test
  - Presence of Necrosis and wound associated pain

Wound Classification
- The University of Texas system which uses a matrix of grades is recommended
- The Wagner System may be needed for reimbursement

Wagner Grade V
Gangrene involving the whole foot or enough of the foot that no local procedures are possible

DFU… Critical Principles

- **ALL** patients with a neuropathic diabetic foot ulcer should be assessed for arterial disease with revascularization (endovascular or surgical) completed when indicated.
**DFU…Assessment**

Clinically significant arterial disease should be ruled out by establishing that pedal pulses are clearly palpable and there is an ABI > 0.8 or by completing additional vascular screening. The presence of pedal pulses does not preclude significant vascular disease.

**DFU…Critical Principles**

- Effective offloading should be achieved using total contact casting or removable orthotic walkers affixed in such a way as to prevent removal.

**DFU…Offloading**

Ensure adequate offloading of pressure through wound closure. Acceptable methods of therapeutic offloading in decreasing order of effectiveness (Level I):

- Total contact casting (TCC) and variants (TCC-EZ™, Med-Efficiency)
- Removable orthotic walkers affixed to prevent removal (Armstrong “instant TCC”)
- Post operative shoes, half shoes, felt and foam dressings with crutch walking or use of walker in Wagner grade I ulcers.

Often it is not what you put on the wound but what you take off the wound that facilitates healing.

**DFU…Critical Principles**

- Early closure is the single most important intervention to prevent significant wound infection, secondary osteomyelitis, and necrotizing soft tissue infections. Debridement plays a critical role.

**Wound Bed Preparation**

Wound bed preparation is an important step in treating and protecting against wound infection.
Indications for Debridement in DFU Care

- Presence of callous
- Presence of undermining of ulcer edges (margination of keratinocytes)
- Presence of necrotic tissue in the wound bed

- Remove biofilm, debrided osteo

Surgical Planning

- The importance of blood flow and oxygen delivery to a wound bed cannot be overstated
- Despite heroic efforts by wound care specialists, ulcerations will not heal in the presence of pronounced peripheral vascular disease
- Vascularity therefore remains of prime importance when evaluating a patient for an operative intervention.

Palpable Pedal Pulses

- There is no single noninvasive parameter that will reliably predict healing
- A palpable pulse does not always indicate appropriate vascularity
- It therefore, remains imperative to have vascular and endovascular consultation


Classification of the Surgical Patient

- Surgical patients may be classified as emergent, elective, or palliative
- In the two latter scenarios, vascular work-up and intervention when necessary should be performed before surgery commences
- However, emergent cases often require life and limb saving intervention before vascular issues are addressed.

Example of Emergent Surgical Intervention

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Snyder et al. Ostomy Wound Management, April, 2010 “Consensus Recommendations for Advancing the Standard of Care for Treating Neuropathic Foot Ulcers in Patients with Diabetes.”
GROUP ONE: The Ideal Patients
Clinical Targets: The Stalling Ulcer
(4 Weeks < 50% Progress)

GROUP TWO: The Ideal Patients
Clinical Targets: Ulcers that are doing “good” or “ok” (4 Weeks < 50% Progress)

Clinic Case Studies

- Clinical Case Studies

Clinical Case Studies

Rapid Wound Closure NPWT & HSE 5 weeks

Dehisced Surgical Wound

- 68 year-old male with IDDM
- H/O osteomyelitis and ischemia
- Treated with multiple angioplasties and stents; bypass to plantar arch
- Multiple wound and bone debridements culminating in a Transmetatarsal amputation utilizing part of the great toe as the flap / percutaneous TAL
- Wound became dusky and dehiscence observed
- H/O heart disease, hypertension, PVD, generalized arthritis, renal insufficiency
Dehisced Wound

78 year-old male with diabetes presented with decubitus heel ulcer of 1 month duration
• Diabetes liable; IDDM
• Non-palpable pedal pulses, foot cool, capillary refill delayed
• Semmes-Weinstein greater than 5.07
• Non-ambulatory; no pacemaker
• H/O heart disease, hypertension, dyslipidemia, and renal insufficiency requiring dialysis

Patient had angioplasty, then underwent wound and bone debridement. A cadaveric allograft was applied and NPWT was instituted. Infection was treated with antibiotics.

Neuropathic ulcer with bone exposed

67 year old male with IDDM
• H/O blockage of posterior tibial opened with angioplasty
• Burned his foot with a heating pad
• Severe neuropathy
• Presented to the office with an infection requiring hospitalization

Wound Bed Preparation and sequential/combination therapy create significant clinical improvement. This represents a perfect scenario for the use of serial applications of an advanced therapy.
Negative Pressure Wound Therapy in conjunction with several human skin equivalents applied weekly, HBO
Split Thickness Skin Grafts were ultimately utilized for complete closure

- Ulceration in Male with Diabetes, PVD and Neuropathy
- H/O BKA contralateral limb
- H/o remote MI, renal insufficiency, hypertension, dyslipidemia
- Non-palpable pedal pulses, foot cool, capillary refill delayed
- Semmes-Weinstein greater than 5.07

S-P angioplasty and extensive wound debridement. IV antibiotics and PMMA beads were used. NPWT therapy and HBO started

Serial human skin substitutes utilized; NPWT therapy and HBO continued through placement of split-thickness skin graft

Day - 0: Presented at ER
Day - 10: post Debridement prior to application of EpiFix

- Wound size was 18.75 cm²
- Application of EpiFix® Graft with 30% area reduction at 7 days
- Additional 15% area reduction at Day 14
- Additional application of EpiFix® Graft and wound closed at day 28
- At 3 months wound remains fully closed and patient walking with custom molded shoe

Abscessed foot in a neuropathic patient with diabetes: a stepwise approach
What we are trying to prevent!

At the end of the day

Its all about the patient