What’s New in Wound Care in the Diabetic Foot and Combined Arterial and Venous Ulcerations

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Introduction

Significance:
• Roughly 9.6% of the population over the age of 20 suffers from diabetes
• Economic cost burden: ~ $200 billion dollars per year
• ~ 1/3 cost burden related to peripheral wounds
• Impaired wound healing is the leading cause of lower extremity amputation
• 5 year survival following amputation for a diabetic foot ulcer is ~46%
  – “Worse than most cancers”

The Diabetes Epidemic

Annual Number (in Thousands) of New Cases of Diagnosed Diabetes Among Adults Aged 18–79 Years, United States, 1980–2013 (cdc.gov)

Multiple etiologies for impaired DFU healing

• Ischemia
• Neuropathy
• Impaired immune cell function/inflammation

Diabetes andPeripheral Ischemia

• Risk of Amputation in patients with wounds
  – Diabetes =21% (5-7x the risk)
  – Non-diabetics =3%
• Microvascular disease improved with tight glucose control (UKPDS); Macrovascular disease less clear (ACCORD)

Diabetes and Neuropathy

• The WHO now estimates 60% of diabetics have neuropathy and it is accelerating at an alarming rate
• Peripheral sensory neuropathy is the strongest risk factor for DFU
Introduction

- Impaired ability to clear infection
- Chronic inflammation due to impaired monocyte/macrophages
- Impaired vasculogenesis/angiogenesis

Diabetes and Immune Cell Dysfunction

Hemostasis
Wound Healing
Progression
Inflammation
Proliferation Maturation

Current Treatment Strategies - Prevention

- Prevention
  - Local- screening for neuropathy/foot exams
  - Systemic- Hgb A1C under 7

Early Recognition/Screening

- It is recommend that patients with DFU have pedal perfusion assessed by ABI, ankle and pedal Doppler waveforms, and either toe systolic pressure or TcPO2 (1B)

Early Recognition/Treatment

- In patients with plantar DFU, it is recommended to offload with a total contact cast or irremovable fixed ankle walking boot (1B)

Treatment

- In patients with DFU who have adequate perfusion that fails to respond to 4 to 6 weeks of conservative management, hyperbaric oxygen therapy may be indicated (2B)

Revascularization

- Endovascular may be associated with worse outcomes because of poor distal runoff/reduced patency
- Better durability with surgery for tibial disease with autogenous vein conduit
- Meta-analysis demonstrates rates may be more similar
- 60% of ulcers healed at 1 year post-revascularization
Translational Therapies/Clinical Trials

• Stem Cell Therapy
  • Mesenchymal stem cells – promote angiogenesis, improve killing/phagocytosis/ decrease inflammation, promote VEGF/other factors
    – Bone marrow-derived MSC - Phase 2 – for DFU, need ABI > 3-6, early results with improved healing
    – BM-MSC – phase 1 – for non-revascularizable DFU
    – Adipose-derived MSC (ALAS-ASC-2003), phase 1 – need ABI > 7; early results show decreased amputation rates at 6 months
  • Cord Blood, Skin stem cells, Embryonic/iPSC
  • Problems with therapy - stem cells dissipate; need scaffolds

• Gene Therapy
  • Human growth factors (i.e., VEGF, HGF, GF-B) and enzymes added to wound site
    – HGF-0205 trial – IM injection HGF – improved wound healing, no change in limb salvage rates

• Bioengineered skin replacement
  • Applies living cells (fibroblasts)

• Immunotherapy
  • Cytokine-directed therapy
    

Mixed Venous/Arterial Ulcers

• 15-30% of Venous ulcers have an arterial component
  • How do we treat these?
    • Revascularize first?
    • Compression therapy?
  • Most recent data suggests the following algorithm:

  ABI < .5, ankle pressure < 70, Toe pressure < 50

  Revascularize first, percutaneous first line, avoid compression

  Compression (40 mmHg), May need to modify to 20-25 mmHg, Compression increases arterial flow to wound

Summary

• DFU are on the rise and are the leading cause of amputation
• Promising translational therapies looking at stem cells, growth factors and immune therapy
• Mixed venous/arterial ulcers are increasingly common – RCT needed to determine best therapy