Nonhealing wounds pose major challenge in clinical medicine

Estimated that 1-2% of population of developed countries will experience chronic wound during their lifetime

- Diabetic foot ulcers (DFUs), venous leg ulcers (VLUs) and pressure ulcers/injuries comprise majority of these chronic wounds

In US, chronic wounds affect more than 6.5 million people
Medicare spending for wound care alone in 2014 was about $35.3 billion

- Infections accounted for $16.7 billion
- Chronic ulcers for $9.4 billion
- Surgical wounds for $6.5 billion

This cost burden continues to grow due to increasing costs of health care, an aging population and a steep rise in incidence of diabetes and obesity worldwide.
CHRONIC WOUNDS

- Chronic wounds: wounds that fail to progress through the normal phases of wound healing
- The controlled sequence of events seen in acute wounds becomes stalled or stuck at one or more of the 4 different stages of wound healing (hemostasis, inflammation, proliferation, remodeling/maturation)
- Although these phases are typically described separately, the process is actually a gradual progression guided and regulated by the complex interaction of platelets, neutrophils, macrophages and other cells that respond to and produce growth factors, cytokines and proteases and inhibitors
CHRONIC WOUNDS

- All of the common causes of nonhealing wounds inhibit this orderly healing process
  - venous hypertension
  - arterial insufficiency
  - chronic pressure
  - chronic inflammation
- Usually in the inflammatory phase
- Chronic wounds are characterized by defective remodeling of the extracellular matrix, a failure to epithelialize and prolonged inflammation
(1) Hemostasis  (2) Inflammation  (3) Proliferation  (4) Remodeling

Epidermis

Dermis

Subcutaneous

Key

Fibrin  Cytokine  TGF-β  Adipose  Neutrophil  Fibroblast  Bacillus  Collagen
PDGF  GF  T-Cell  Macrophage  Myofibroblast  Debris  Coccus  GAG
WOUND HEALING – Normal Process

- **Hemostasis**
- **Inflammatory Phase**
- Inflammation develops within 24 hours of acute wounding and continues up to 2 weeks
- Mediated by mast cells, neutrophils and macrophages
- Cytokines are released by activated lymphocytes and macrophages into the tissue
- Results in further recruitment and activation of fibroblasts and epithelial cells in the wound
WOUND HEALING

- Neutrophils migrate into the wound and release matrix metalloproteinases (MMPs)
- MMPs clear damaged tissue from the wound area by breaking down collagen, gelatin and elastin
- MMP activity is closely controlled by tissue inhibitors of MMPs (TIMPs), produced principally by macrophages
WOUND HEALING

- **Proliferative Phase**
- Growth factors are secreted by multiple cell types, but primarily by macrophages
  - Platelet-derived growth factor (PDGF)
  - Transforming growth factor-β (TGF-β)
  - Vascular endothelial growth factor (VEGF)
- These growth factors are responsible for the recruitment of fibroblasts to commence the proliferative phase and for the initiation of angiogenesis required to support tissue regeneration and epithelial growth
WOUND HEALING

- Orderly capillary growth and networking must occur to support developing granulation tissue
  - Requires complex interplay of growth factors
- MMPs are also required for the normal progression of angiogenesis
WOUND HEALING

- Remodeling/Epithelialization Phase
- Epithelialization occurs most rapidly on a well-granulated, confluent tissue bed
- Epithelial cells migrate into the wound from the periphery by secreting MMPs to degrade nonviable tissue at the wound edge, allowing migration into the wound
- Normally, epithelial migration should continue until other epithelial cells are contacted
- Remodeling is a long-term process in which type III collagen is largely replaced by mature type I collagen
ABNORMAL WOUND HEALING MECHANISMS

- Chronic nonhealing wounds occur when normal healing process is disrupted.
- This is most frequently the result of an underlying disorder that causes a prolonged, unchecked proinflammatory state.
- These disorders include venous hypertension, chronic pressure, bacterial colonization, inadequate tissue perfusion, and cellular senescence.
ABNORMAL WOUND HEALING MECHANISMS

- Inflammation

- Recurrent or prolonged inflammatory stimuli result in chronic wounds that are characterized by persistent upregulation of proinflammatory cytokines and MMPs.

- This proinflammatory environment is necessary for a brief period of time for acute wound healing, the persistence of this environment has detrimental effects.

- Chronic wound fluid may contain high levels of MMP-2 and MMP-9 and abnormally low levels of TIMPs.

- In venous ulcers, MMP levels decrease after compression treatment.

- Patients with critical limb ischemia have lower levels of VEGF.
ABNORMAL WOUND HEALING MECHANISMS

- Cytokines
  - Upregulation of proinflammatory cytokines (TNF-α, IL-1, and IL-6) has been described in chronic venous wound fluid
  - These levels were found to improve when ulcers began to heal, with a decrease in size and improvement in granulation
  - Diabetic foot ulcers may also contain proinflammatory upregulation and lower expression of angiogenic factors
ABNORMAL WOUND HEALING MECHANISMS

- Cell Senescence
  - Cellular senescence has been reported in fibroblasts collected from chronic nonhealing ulcers
  - Fibroblasts from patients with increasing levels of venous disease displayed a progressively diminishing response to agonist-induced proliferation
  - Stimulation of senescent fibroblasts may be a key target of therapy for improving the healing potential of chronic leg ulcers
The successful treatment of patients with nonhealing leg ulcers requires the underlying cause of the ulceration be diagnosed. It has been reported that multiple causes are involved in more than 20% of leg ulcers. So each potential diagnosis must be considered in every patient. Early and accurate wound diagnosis is essential in determining the appropriate steps for treatment of a chronic wound. Successful wound care cannot take place without an accurate diagnosis. An incorrect or delayed initial diagnosis may harm the patient and increase the risk for serious complications.
What is an arterial ulcer?

Any wound on a (usually) lower extremity that results from reduced blood supply.

Typically, arterial disease accounts for 5-10% of leg ulcers.

Can be misdiagnosed as venous leg ulcers and therefore managed inappropriately.

Early identification of patients at risk for arterial disease can make a difference between salvage possibilities and limb loss.
Why do we care about arterial ulcers?
ARTERIAL ULCERS

- Characteristics of arterial ulcers vs venous ulcers
LOCATION

Arterial ulcers are usually on the tips of toes, outer ankle or lateral foot over pressure points.
Venous ulcers are typically on the lower leg (mid calf or below) and ankle.

Characteristically adjacent to or above the medial or lateral malleoli.
WOUND APPEARANCE

Arterial wound base typically doesn’t bleed
Is yellow, brown, grey or black
Characteristically deep
Punched out with well-defined, even wound margins
WOUND APPEARANCE

Venous wounds are often covered with fibrinous layer mixed with granulation tissue.
Shallow, superficial
Varying depths within ulcer
May be discrete or circumferential
PERIWOUND

Arterial
Skin and nails on extremity appear atrophic
Skin is pale, shiny, taut and thin
Minimal to no hair growth
Extremity may turn red when dangled (dependent rubor) and pale when elevated
PERIWOUND

Venous
Hemosiderin staining
Lipodermatosclerosis in long term venous insufficiency
Variable pigmentation
Venous eczema (erythema, scaling, weeping, itching) is common
# ULCERS

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>ARTERIAL</th>
<th>VENOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensation</td>
<td>Generally very painful</td>
<td>Throbbing, aching and heavy</td>
</tr>
<tr>
<td></td>
<td>Improves with dependency</td>
<td>feeling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improves with elevation and</td>
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<tr>
<td></td>
<td></td>
<td>rest</td>
</tr>
<tr>
<td>Exposure of deep</td>
<td>Often extends to underlying</td>
<td>None (maybe fat layer)</td>
</tr>
<tr>
<td>structures</td>
<td>tendon, muscle or bone</td>
<td></td>
</tr>
<tr>
<td>Temp and pulses</td>
<td>Limb cool/cold to touch</td>
<td>Higher temperature</td>
</tr>
<tr>
<td></td>
<td>Weak/absent pulse</td>
<td>consistent with chronic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>venous insufficiency</td>
</tr>
<tr>
<td>Exudate and Edema</td>
<td>Minimal exudate</td>
<td>Heavy exudate</td>
</tr>
<tr>
<td></td>
<td>Limited edema</td>
<td>Pitting edema often present</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and may predate ulcer</td>
</tr>
<tr>
<td>Location</td>
<td>Between or on tips of toes, outer ankle, or</td>
<td>Lower leg and ankle, around</td>
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<td></td>
<td>lateral foot</td>
<td>malleoli</td>
</tr>
<tr>
<td>Wound appearance</td>
<td>Deep, punched out</td>
<td>Shallow, superficial</td>
</tr>
<tr>
<td>Periwound</td>
<td>Atrophic, no hair</td>
<td>Hemosiderin staining</td>
</tr>
</tbody>
</table>
ARTERIAL ULCERS – Risk Factors

- Hypertension
- Dyslipidemia
- Smoking
- Obesity
- Advanced age
- CAD
- Diabetes

Fig. A4. Approximate magnitude of the effect of risk factors on the development of critical limb ischemia in patients with peripheral arterial disease. CLI – critical limb ischemia.
ARTERIAL ULCERS

- How do you diagnose arterial insufficiency?
Right ABI = ratio of
Higher of the right ankle systolic pressures (posterior tibial or dorsalis pedis)
Higher arm systolic pressure (left or right arm)

Left ABI = ratio of
Higher of the left ankle systolic pressures (posterior tibial or dorsalis pedis)
Higher arm systolic pressure (left or right arm)
When to refer to Vascular Surgery:

1. ABI < 0.8 or a dampened doppler waveform
2. TcPO2 < 40 mm Hg (reflection of local arterial perfusion pressure)
3. Toe pressure < 45 mm Hg (toe pressure normally 30 mm Hg less than ankle pressure)
4. Ankle systolic pressure < 50 mm Hg
ARTERIAL ULCERS – Wound Care

- Consider debridement – lightly!
  - Leave adherent eschar or dry gangrene in place
- Manage infection
- Moisture-balanced dressing (antiseptic solution-moistened gauze dressing)
- Off-loading
- Protection
Why do we care about arterial ulcers?
Fig. A3. Fate of the claudicant over 5 years (adapted from ACC/AHA guidelines\(^5\)). PAD – peripheral arterial disease; CLI – critical limb ischemia; CV – cardiovascular; MI – myocardial infarction. Adapted with permission from Hirsch AT et al. J Am Coll Cardiol 2006;47:1239–1312.
Fig. A8. Survival of patients with peripheral arterial disease. IC – intermittent claudication; CLI – critical limb ischemia.
ARTERIAL ULCERS

- Outcomes
- Data from several clinical trials studying critical limb ischemia have identified a risk of major amputation in 25-40% of pts at 1 year if revascularization is not performed.
- Separate study found that 34% of limbs with ABI of less than 0.5 and 43% of limbs with an ABI of less than 0.4 required amputation at 12 months (vs 15% of limbs with ABI between 0.5 and 0.7).
VENOUS ULCERS

- C0: No visible or palpable signs of venous disease
- C1: Telangiectases or reticular veins
- C2: Varicose veins
- C3: Oedema
- C4: a. Pigmentation and/or eczema: b. Lipodermatosclerosis and/or atrophie blanche
- C5: Healed venous leg ulcer
- C6: Active venous ulcer
VENOUS ULCERS

- **Venous leg ulcer**: an open lesion between the knee and ankle joint that occurs in the presence of venous disease.
- Venous disease is the most common cause of leg ulcers, accounting for 60-80% of all ulcers.
- Venous disease in any combination of anatomic sites may result in limb ulceration, including superficial venous insufficiency alone.
- Ruling out associated arterial disease in leg ulcers is critical for wound healing.
VENOUS ULCERS

- Characteristics – see above
  - Located in leg (mid-calf or below) and ankle; characteristically adjacent to or above medial or lateral malleoli
  - No deep tissue exposure
  - Covered with fibrinous layer mixed with granulation tissue
  - Periwound has hemosiderin staining
  - Heavy exudate
  - Pitting edema
VENOUS ULCERS – Risk Factors

- Previous DVT
- CHF
- Varicose veins
- Decreased mobility and/or ankle ROM
- Smoking, DM and higher BMI
- Reflux in deep veins
- Drug use injection in groin, legs or feet
Many investigators currently believe that venous insufficiency results in a chronic, recurring condition resulting in years of inflammatory upregulation in the soft tissues of the lower extremity.

The effects are most severe at the ankle, but the foot is spared because of the construction of the fascial compartments and the lack of major veins in the deep tissues.

Proinflammatory cytokines are chronically upregulated, resulting in the overexpression of proteases, leading to increased tissue fibrosis and the clinical appearance of lipodermatosclerosis.

Ulceration eventually occurs either spontaneously or due to minor limb trauma in the lower calf or ankle that cannot heal.
Risk factors for chronic venous disease

Venous hypertension
Venous dilation

Valve reflux

Increased hypertension

Valve and wall changes

Capillary hypertension

Capillary leakage

Edema

Valve distortion and leakage

Altered blood flow and shear stress

INFLAMMATION

Skin changes

Ulcera
Manifestations of chronic venous insufficiency

- Skin discolouration
- Eczema
- Induration
- Venous ulcers
- Varicose vein rupture
- Leg swelling

Mechanism of varicose vein formation

Incompetent venous valve
- Blood flows backward away from the heart and into the superficial system causing venous congestion and high pressures within the superficial veins

Competent venous valve
- Ensures the forward flow of blood by preventing reflux of blood during the relaxation phase of the calf muscles
VENOUS ULCERS

What do we have to do diagnose venous ulcer?
Venous Duplex

Check for DVT
Venous Duplex

- Check for venous insufficiency
Right ABI = ratio of
Higher of the right ankle systolic pressures (posterior tibial or dorsalis pedis)
Higher arm systolic pressure (left or right arm)

Left ABI = ratio of
Higher of the left ankle systolic pressures (posterior tibial or dorsalis pedis)
Higher arm systolic pressure (left or right arm)
VENOUS ULCERS - Treatment

- Debride appropriately
- Manage infection
- Moisture balanced dressing (antiseptic solution-moistened gauze dressing)
- COMPRESSION!
VENOUS ULCERS - Treatment

- Compression therapy via bandaging is the cornerstone of managing venous leg ulcers in the absence of significant arterial disease.
- Compression facilitates faster healing compared with no compression.
- High compression is better than low compression in improving venous ulcer healing rates.
- Compression is contraindicated in decompensated chronic CHF.
- Careful compression can be used in patients with an ABI as low as 0.5!
Indications

The multi-layer compression bandage system has been specifically designed for the management of venous leg ulcers and associated conditions. The system pack can be used on patients with ankle circumferences of greater than 18cm or 7¼ inches (padded).

Precautions

- Do not use on patients with an ankle brachial pressure index (ABPI) of less than 0.8, or on diabetic patients with advanced small vessel disease.
- Should the patient develop pain or pale, cool or numb extremities distal to the dressing, the bandages should be promptly removed. If the patient has a very thin ankle or very prominent tibial crest, extra padding should be applied to these areas to prevent pressure necrosis.
- Failure to detect significantly reduced arterial flow can result in pressure necrosis, amputation or even death.
- This product has components that contain natural rubber latex which may cause allergic reactions in some individuals.
- The risk of arterial as well as venous disease rises with age.
<table>
<thead>
<tr>
<th>ABI</th>
<th>Bandage</th>
<th>Sub-bandage pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.8</td>
<td>4-layer</td>
<td>35-40</td>
</tr>
<tr>
<td>0.7</td>
<td>2-layer</td>
<td>17-25</td>
</tr>
<tr>
<td>0.6</td>
<td>2-layer</td>
<td>17-25</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>Only with medical supervision</td>
<td>—</td>
</tr>
</tbody>
</table>

ABI: ankle-brachial index
VENOUS ULCERS - Edema

- In normal tissue, each cell is only a few cell diameters away from the nearest capillary and receives nutrients and oxygen by diffusion.

- With inflammation, venous insufficiency, or any other causes of edema formation, the sequestered extracellular fluid increases the diffusion distance for oxygen and results in a lower tissue PO2.

- With lower extremity venous insufficiency, the chronic protein leak from the capillaries results in pericapillary deposition.

- This ‘cuffing’ is a further barrier to oxygen and nutrient diffusion and possibly functions as a site of nonspecific binding of growth factors, making them less available to the wound environment.
Edema reduces microvascular blood flow and the clearance of bacteria and protein from the wound.

The impact of edema is to eliminate or reduce the likelihood of healing, and until edema is eliminated, other management is often futile.

Removal of edema fluid in an ischemic extremity increases blood flow to the entire limb, including the toes.
VENOUS ULCERS - Treatment

- Refer to Vascular Surgery when venous insufficiency identified in superficial venous system (GSV or SSV) or perforator veins
- Venous interventions reduce the incidence of ulcer recurrence whenever superficial venous reflux is prominent component of the abnormal venous function
- Treatment with compression bandaging using any number of systems results in healing in about 60-70% of patients after 4-6 months of consistent therapy
- Interventions cannot be recommended for most patients to accelerate venous wound healing – old adage?
A Randomized Trial of Early Endovenous Ablation in Venous Ulceration

Manjit S. Gohel, M.D., Francine Heatley, B.Sc., Xinxue Liu, Ph.D., Andrew Bradbury, M.D., Richard Bulbulia, M.D., Nicky Cullum, Ph.D., David M. Epstein, Ph.D., Isaac Nyamekye, M.D., Keith R. Poskitt, M.D., Sophie Renton, M.S., Jane Warwick, Ph.D., and Alun H. Davies, D.Sc. for the EVRA Trial Investigators*

Abstract

May 31, 2018
DOI: 10.1056/NEJMoa1801214
Abstract

BACKGROUND Venous disease is the most common cause of leg ulceration. Although compression therapy improves venous ulcer healing, it does not treat the underlying causes of venous hypertension. Treatment of superficial venous reflux has been shown to reduce the rate of ulcer recurrence, but the effect of early endovenous ablation of superficial venous reflux on ulcer healing remains unclear.

METHODS In a trial conducted at 20 centers in the United Kingdom, we randomly assigned 450 patients with venous leg ulcers to receive compression therapy and undergo early endovenous ablation of superficial venous reflux within 2 weeks after randomization (early-intervention group) or to receive compression therapy alone, with consideration of endovenous ablation deferred until after the ulcer was healed or until 6 months after randomization if the ulcer was unhealed (deferred-intervention group). The primary outcome was the time to ulcer healing. Secondary outcomes were the rate of ulcer healing at 24 weeks, the rate of ulcer recurrence, the length of time free from ulcers (ulcer-free time) during the first year after randomization, and patient-reported health-related quality of life.

RESULTS Patient and clinical characteristics at baseline were similar in the two treatment groups. The time to ulcer healing was shorter in the early-intervention group than in the deferred-intervention group; more patients had healed ulcers with early intervention (hazard ratio for ulcer healing, 1.38; 95% confidence interval [CI], 1.13 to 1.68; P=0.001). The median time to ulcer healing was 56 days (95% CI, 49 to 66) in the early-intervention group and 82 days (95% CI, 69 to 92) in the deferred-intervention group. The rate of ulcer healing at 24 weeks was 85.6% in the early-intervention group and 76.3% in the deferred-intervention group. The median ulcer-free time during the first year after trial enrollment was 306 days (interquartile range, 240 to 328) in the early-intervention group and 278 days (interquartile range, 175 to 324) in the deferred-intervention group (P=0.002). The most common procedural complications of endovenous ablation were pain and deep-vein thrombosis.
CONCLUSIONS  Early endovenous ablation of superficial venous reflux resulted in faster healing of venous leg ulcers and more time free from ulcers than deferred endovenous ablation. (Funded by the National Institute for Health Research Health Technology Assessment Program; EVRA Current Controlled Trials number, ISRCTN02335796.)
Summary

- Perform appropriate wound care:
  - Debridement
  - Moisture-balanced dressing
  - Off-load
- Treat infection if present
- Check ABIs on all ulcers if cannot easily feel distal pulses
- Check venous duplex on venous ulcers
- Appropriate compression for venous ulcers
- Refer when necessary, based on studies
Thank You
References

- Rutherford: Vascular Surgery, 8th edition