Current Treatment of Venous Ulcers

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Disclosures

• None

Outline

• Magnitude of problem
• Current clinical guidelines
• Vascular/endovascular treatment options
• Pharmacotherapy

VS ulcer Characteristics

✓ Irregularly shaped
✓ Granular base
✓ Edema & lymphedema
✓ Hemosiderin staining
✓ Varicosities
✓ Exudate
✓ Stasis Dermatitis
✓ Cellulitis
✓ Sharp or aching pain
✓ Itching
✓ sc fibrosis
Venous Ulcer

- Medial Malleolus
- Shallow
- Irregular borders
- Base with granulation tissue
- Surrounding white scar (atrophie blanche)
- Surrounding hemosiderin deposition
- Surrounding Edema
- 80% of LE ulcers
- $40,000

Venous Ulcer. A. Khachemoune & C. L. Kauffman: Diagnosis Of Leg Ulcers. The Internet Journal of Dermatology. 2002 Volume 1 Number 2

Scope of the problem

- VIU 1-3% population (Kerstein 2003)
- Peak at 60-80 yo (Paquette & Falanga, 2002)
- 6-7 million Americans have LEVD & 1 million of those develop ulcerations (WOCN Society 2005)

Burden of venous leg ulcers

- 2012 patients: Medicare vs private insurers
- Incidence of VLU 2.2%MC vs 0.5% private
- VLU patients used 50% more medical resources than non-VLU
- VLU patients missed more work (30% more)
- Did not look at lost productivity or out of pocket costs

ANNUAL PAYOR BURDEN:
$14.9 BILLION


Costs of Venous Ulcers

- Costs:
  - Lifetime costs of LEVD care est at $40,000/individual
  - Total cost of care of LEVD in US est at $1 billion/year (Simka & Majewski 2003)
- Ulcer Recurrence:
  - 57-97%, which reflects the chronicity of the problem & also failure to effectively address the underlying etiology (Paquette & Falanga 2002)
- Repeat hospitalizations, repeat antibiotics
- Lost productivity (work, hobbies, family care, volunteering)
- Loss of independence (application of compression garments)
- Pain, itching, anxiety, social isolation & reduced ability to carry out usual activities reported to be areas of greatest concern by individuals w/ venous disease (deAraujo et al, 2003)
Diseases Process

Bicuspid valve damage due to DVT or heredity results in **venous HTN** and regurgitation.

White cell trapping theory: venous HTN & increased cap pressure trap leukocytes in cap & become activated, thus damaging cap beds. Increased permeability leads to fibrin cuff formation & hypoxemia, which leads to inflammation & tissue loss.

Compression for venous leg ulcers

- Forty-eight RCTs reporting 59 comparisons were included (4321 participants in total)
- Compression increases ulcer healing rates compared with no compression.
- Multi-component systems are more effective than single-component systems. Multi-component systems containing an elastic bandage appear to be more effective than those composed mainly of inelastic constituents.

Compression for venous leg ulcers

- Two-component bandage systems appear to perform as well as the 4LB. Patients receiving the 4LB heal faster than those allocated the SSB. More patients heal on high-compression stocking systems than with the SSB. Further data are required before the difference between high-compression stockings and the 4LB can be established.
Intermittent Compression Devices and Ulcer Healing

- Cochrane review of the literature  May 2014
- Nine RCTs, 489 patients
- IPC may increase healing compared with no compression. It is unclear whether it can be used instead of compression bandages
- Further trials are required to determine the reliability of current evidence, which patients may benefit from IPC in addition to compression bandages, and the optimum treatment regimen.

Role of Antibiotics and Antiseptics

- Forty-five RCTs reporting 53 comparisons and recruiting a total of 4486 participants were included, Many RCTs were small, and most were at high or unclear risk of bias.
- No evidence is available to support the routine use of systemic antibiotics in promoting healing of venous leg ulcers.
- In terms of topical preparations, some evidence supports the use of cadexomer iodine. Current evidence does not support the routine use of honey- or silver-based products.

Debridement for venous leg ulcers

- 10 RCT’s with 715 participants, all use of enzymatic or autolytic debridement
- No RCTs evaluated surgical, sharp or mechanical methods of debridement, or debridement versus no debridement.
- There is limited evidence to suggest that actively debriding a venous leg ulcer has a clinically significant impact on healing

Surgical treatments of Venous Insufficiency

- Treatments of GSV/SSV insufficiency:
- Endovenous ablation-laser/ RF
- Venaseal
- MOCA/Clarivein
- Varethena
Surgical treatment of venous insufficiency

- Perforator treatments: SEPS/RF/Sclerotherapy
- Deep venous valve repair/tranpsalnt
- Courtesy O. Malleti, MD

ESCHAR Study BMJ 2007

No significant difference in ulcer healing between 4 layer compression and compression + treatment of superficial venous reflux at 3 years. However, recurrence rate was cut in half by the addition of surgery.

ROOM FOR IMPROVEMENT!!!

What is the frequency of iliac vein obstruction in patients with a healed (C5) or an active (C6) venous ulcer?

- Of 78 patients with C5 or C6 ulcers, reviewed with CT and MR
  - 37% had a venous stenosis >50%
  - 23% had a venous stenosis >80%
    » Associated with females, history of DVT, deep venous reflux
    » Interestingly, no limb >80% venous stenosis found to have superficial venous reflux.


Percutaneous Endovenous Stenting

- Seshadri Raju at Univ of Mississippi, Jackson
- Extensive work in femoroiliac venous stenosis and obstruction 1997 – 2005
  - 982 limbs stented
  - 148 limbs stented for ulcer
  - 68% healed at 3 months
  - Cumulative recurrence-free rate 58% at 5 years
  - Once healed, 8% (8/101) recurrence rate
Iliac Vein Stenting

- No FDA approved stents currently available
- Three stents now in clinical trials—Bard Venovo, Veniti (Boston part-owner), Cook Zilver Zena

Compressed vs Normal LCIV: Comparison of IVUS and Venogram

Clinical Outcomes: Symptom Relief
Raju & Neglén Experience:

<table>
<thead>
<tr>
<th>Outcome 2.5 years Following Stenting</th>
<th>NIVL with Reflux</th>
<th>NIVL without Reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pain</td>
<td>82%</td>
<td>77%</td>
</tr>
<tr>
<td>No Swelling</td>
<td>47%</td>
<td>53%</td>
</tr>
<tr>
<td>Ulcer Healed</td>
<td>67%</td>
<td>76%</td>
</tr>
<tr>
<td>Good/Excellent Outcome</td>
<td>75%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Patient Characteristics

<table>
<thead>
<tr>
<th>NIVL with Reflux (n=151)</th>
<th>NIVL without Reflux (n=181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32% Superficial reflux</td>
<td>20% Deep reflux only*</td>
</tr>
<tr>
<td>28% Combined superficial &amp; deep reflux*</td>
<td>*Deep reflux axial in 1/3 of limbs</td>
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AHRQ: Treatment approaches for chronic venous ulcers reviewed

- There is a general lack of conclusive evidence on the benefits and harms of advanced wound dressings, systemic antibiotics, and surgical interventions in the treatment of venous leg ulcers lasting six or more weeks in patients with preexisting venous disease
- Some evidence supports:
  - Antimicrobial dressings (low or evidence)
  - Collagen dressings (low or evidence)
  - Bilayered human skin equivalents (low or evidence)
- Surgical procedures do not improve healing but do decrease recurrence (high or evidence)
**Agency for Healthcare Research and Quality**

**Objectives:**
- To systematically review whether the use of advanced wound dressings, systemic antibiotics, or venous surgery enhanced the healing of venous ulcers over the use of adequate venous compression.

**Data sources:**
- MEDLINE®, Embase®, the Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL®) from January 1980 through July 2012.

**Review methods:**
- We included studies of patients with venous leg ulcers lasting 6 or more weeks coincident with signs of preexisting venous disease. We excluded patients with arterial ulcers, pressure ulcers, postsurgical ulcers, and neuropathic ulcers. To select articles for analysis, teams of two independent investigators reviewed titles, abstracts, and articles. Conflicts between investigators regarding inclusion were negotiated. We found insufficient data for meta-analysis but qualitatively summarized studies not amenable to pooling.

**Results:** 60 studies reviewed:
- ADVANCED WOUND DRESSINGS that regulate moisture, facilitate debridement, include antimicrobial activity, or incorporate putative wound healing accelerants DID NOT demonstrate a statistically higher percentage of wounds healed compared with adequate compression with simple dressings.
- BIOLOGICAL DRESSINGS containing living cells such as the cellular human skin equivalents showed more rapid healing of venous ulcers (moderate strength of evidence).
- No definitive conclusions regarding the effectiveness of advanced wound dressings in terms of intermediate and other final outcomes, including quality of life and pain measures.
- VENOUS SURGERY may not increase the proportion of ulcers healed (low to high strength of evidence), although there was a trend toward greater durability of healing.

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**Pharmacotherapy in Venous Disease**

Pentoxiphylline:
- A xanthine derivative & competitive nonselective phosphodiesterase inhibitor which
  - raises intracellular cAMP
  - activates PKA
  - inhibits TNF and leukotriene synthesis and
  - reduces inflammation and innate immunity.

Adapted from Eberhardt RT, Pubnet. J. Circulation. 2005; 111:2398–2409
Trental Side effects

Cardiac disorders  Arrhythmia, Tachycardia, Angina Pectoris
• Blood and lymphatic system disorders  Thrombocytopenia, Leukopenia/neutropenia
• Nervous system disorders  Dizziness, headache, meningitis aseptic
Gastrointestinal disorders  Gastrointestinal disorder, Epigastric discomfort, Abdominal distension, Nausea, Vomiting, Diarrhoea, Constipation, Hypersalivation
• Skin and subcutaneous tissue disorders  Pruritus, Erythema, Urticaria, Hot flush, Rash
• Vascular disorders  Haemorrhage, Hypotension
• Immune system disorders  Anaphylactic reactions, Anaphylactoid reaction, Angioedema
• Hepatobiliary disorders  Cholestasis
• Psychiatric disorders  Agitation, Sleep disorder
• Respiratory disorders  Bronchospasm

Review of Pentoxifylline

Cochrane Review

• Twelve trials met the inclusion criteria
• –11 trials compared pentoxifylline with placebo (Weitgasser 1983; Schürmann 1986; Arenas 1988; Colgan 1990; Barbarino 1992; Pizarro 1996; Herdy 1997; Dale 1999; Falanga 1999; Belcaro 2002) or no treatment (Nikolovska 2002) and
• –one trial compared pentoxifylline with the anticoagulant defibrotide (Apollonio 1992).
• Compression was a standard treatment in seven studies (Schürmann 1986; Apollonio 1992; Barbarino 1992; Pizarro 1996; Dale 1999; Falanga 1999; Belcaro 2002).

Jull, Cochrane Database of Systematic Reviews 2012
Pentoxifylline Conclusion

Pentoxifylline is more effective than placebo in terms of complete ulcer healing or significant improvement (RR 1.70, 95% CI 1.30 to 2.24).

- Pentoxifylline plus compression is more effective than placebo plus compression (RR 1.56, 95% CI 1.14 to 2.13).
- Pentoxifylline in the absence of compression appears to be more effective than placebo or no treatment (RR 2.25, 95% CI 1.49 to 3.39).
- There is a dose-related response: 800mg tid appears more effective than 400mg tid.

Pentoxifylline Conclusions

- Appears to contribute to cost-savings in the care of these patients with or without compression.
- About 20% of patients reported side effects, but 75% of these were mild GI complaints.

Effect of Pentoxifylline on Healing

- Overall 61% of patients with it healed c/w 37% in placebo group (p=.01) risk ratio 1.7

Micronized Purified Flavonoid Fraction (MPFF)-Pharmacologic Properties

- Inflammation----- Inhibits the initiation of venous inflammatory cascade
- Venous tone------ Increases venous tone
- Venous wall and valves----- Decreases venous wall and valve inflammation
- Capillary leakage---- Increases capillary resistance reduces capillary filtration
- Lymphatic drainage---- Increases lymphatic drainage
- Rheology---- Decreases blood viscosity

2- Barbe, 1992; Savineau, 1994
3- Takase and Schmid-Schönbein, 2006
MFPP and Venous ulcer healing

One meta-analysis - Coleridge-Smith (5 RCT)
• MPFF gives additional benefit to conventional therapy in patients suffering from ulcers between 5 and 10 cm² and for those present for 6 to 12 months. MPFF seems to be more appropriate when the venous leg ulcer disease has been present for less than 5 years.
  • Coleridge-Smith P, Lok C, Ramelet AA. Venous Leg Ulcer: A meta-analysis of adjunctive therapy with Micronized purified flavonoid fraction. Eur J Vasc Endovasc Surg 2005;30:198-208

One veno-active drug review in ulcer healing - Raffetto
• MPFF is the only active veno-active agent effective in venous ulcer healing
  • Raffetto JD Pharmacologic treatment to improve venous leg ulcer healing JVS. V&L.2016:4:371-4

Recommendations of the SVS and AVF
• We suggest using pentoxifylline or micronized purified flavonoid fraction, if available, in combination with compression, to accelerate healing of venous ulcers.
  • Grade 2B
• International guidelines have this as a Grade 1A/B,

• JVS, August 2014: Volume 60, Issue 2, Supplement, Pages 3S–59S
• This is important to adopt because several studies have demonstrated improved ulcer healing, lower recurrence, and ultimately lower cost by following clinical guidelines
• Very few grade 1 recommendations:
  • Assess arterial perfusion with ABI/ pulse and doppler exam
  • Classify venous wound and measure weekly
  • Sharp surgical debridement at evaluation and if slough/bioburder present
  • Compression- multilayer
  • Wound moisture balance with appropriate dressing
  • Pentoxifylline (these are from before FDA approval of MFPP)
• If improvement is less than 30-40% in 4 weeks then consider adjuvant therapies
  • Suggest against STSG, prefer allogenic bilayer cellular therapy (skin substitutes) with appropriate preparation of wound bed prior
  • Do not like negative pressure, ultrasound, or electrical stimulation treatment
  • Surgery really only to prevent ulcer recurrence (evidence is 2C for healing, 1B for recurrence)
Conclusion

- Venous ulceration is a huge economic and quality of life issue in the US and the world
- Must follow clinical guidelines to improve outcomes and control costs in the care of this chronic health problem
- Better trials are needed to allow stronger conclusions to be made about current therapeutic options
- Understanding of the microcirculatory problems may lead to further pharmacotherapy
- Deep venous stenting appears to be a useful adjunctive treatment (FDA approved stents pending)