Medical Management of Venous Ulcers
When a Vascular Consult Isn’t Enough

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“Non-Surgical” Management of Venous Ulcers
When a Vascular Consult Isn’t Enough

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Disclaimer

• Although the information contained in this session is focused on a disease state with details as it pertains to practice in the Department of Veterans Affairs, it is not intended to provide interpretation of VA policy nor specific details about how individual VA Medical Centers operate services within their jurisdiction.

• The contents do not represent the views of the United States Department of Veterans Affairs nor the United States Government.
Outline

• General Philosophy
• Common Ground
• Components of Non-Operative Management
• Food for Thought
• Conclusions
WHO YA GONNA CALL?

GHOSTBUSTERS
**Hydrostatic**
Weight of the column of blood from the right atrium to the foot

**Hydrodynamic**
Related to the pressures generated by contractions of the skeletal muscles of the leg in the capillary network
Incompetent superficial valves

Rest

Contraction

Relaxation

Pathogenesis

- Disrupting of microcirculation
- Increasing permeability
- Leakage of plasma and erythrocytes into the surrounding tissue
- Increased levels of leukocytes in the dependent limbs of patients with chronic venous insufficiency

- Thomas PR, Nash GB, Dormandy JA. White cell accumulation in dependent legs of patients with venous hypertension: a possible mechanism for trophic changes in the skin. BMJ 1988;296:1693–1695
White Cell Trapping

- Localized hypertension → leukocyte trapping/activation
- Releasing free radicals and promotes cell death/tissue damage
- Capillary bed hypertension macromolecules leaking in dermis
- Traps growth factors and cytokines necessary for tissue repair
Fibrin Cuff Theory

- Pericapillary fibrin cuffs that result from venous hypertension
- Extravasation of fibrinogen
- Barriers to the diffusion
- Leading to tissue hypoxia, cell death and ulceration
- However, discontinuous, and ulcers can heal

Clinical Classification

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0</td>
<td>No visible sign of venous disease</td>
</tr>
<tr>
<td>C1</td>
<td>Telangiectases and/or reticular veins</td>
</tr>
<tr>
<td>C2</td>
<td>Varicose veins</td>
</tr>
<tr>
<td>C3</td>
<td>Edema</td>
</tr>
<tr>
<td>C4‡</td>
<td>Changes in skin and subcutaneous tissue</td>
</tr>
<tr>
<td></td>
<td>Pigmentation or eczema</td>
</tr>
<tr>
<td>A</td>
<td>Lipodermatosclerosis or atrophie blanche</td>
</tr>
<tr>
<td>B</td>
<td>Healed ulcer</td>
</tr>
<tr>
<td>C5</td>
<td>Active ulcer</td>
</tr>
<tr>
<td>C6</td>
<td></td>
</tr>
</tbody>
</table>

NON-OPERATIVE MANAGEMENT
NUTRITION

INFECTION CONTROL

WOUND CARE

ACTIVITY

NON-OPERATIVE MANAGEMENT

MEDICAL MANAGEMENT

COMPRESSION
The Effect of Weight

• Obese increases the risk of chronic venous disease and varicose veins
• ☝ reduces pressure on leg veins
• ☟ micro-circulation
• ☟ energy
• ☟ mobility
Diet

• Low fiber diet ~ bowel movement strain

• Straining
  – ⬆ abdominal pressure
  – ⬆ venous pressure
  – ⬇ venous wall strength
  – ⬆ varicose veins

ACTIVITY
How Active is Active?

• Advanced chronic venous disease is associated with overall poor mobility status
• Increased mobility promotes ulcer healing and to be an adjunct to compression therapy
• Aged matched controls (> 60 years) to those with VU
  – walking speed, endurance, and self-perceived exertion were severely impaired
  – ankle plantar flexion and dorsiflexion were significantly reduced if active ulcers were present

Leg Elevation

- 🧼 Venous drainage
- ⚠️ Blood return to the heart
- 💧 Ankle edema
- 🌿 Cutaneous microcirculation
- ☠️ C5 recurrence with
  - compression
  - leg elevation times of 33 minutes per day

- https://www.loungedoctor.com/classroom.html
Ambulatory Venous Pressure
COMPRESSION
Rationale

• Foundation of the treatment
• Attenuate reflux-induced venous hypertension.
• Normal standing resting venous pressure ~ 60 to 80 mmHg
• Compression between 35 - 40 mmHg
• Safe limit ~ 60 mm Hg has been shown to the safe upper limit (ABI > 0.5)
Biochemical Effects

- Capillary density
- Transcutaneous oxygen
- Inflammatory cytokines
- Tumor necrosis factor α
- Endothelial growth factor
- Interleukin 1β
<table>
<thead>
<tr>
<th>Venous Pathophysiology</th>
<th>Primary Treatment</th>
<th>Secondary Treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux</td>
<td>Compression</td>
<td>Ablation, HLS,</td>
</tr>
<tr>
<td>Superficial</td>
<td></td>
<td>sclerotherapy, foam,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>phlebectomy, pharmacologic</td>
</tr>
<tr>
<td>Deep Perforator</td>
<td>Compression</td>
<td>Valve reconstruction</td>
</tr>
<tr>
<td></td>
<td>Compression</td>
<td>Ablation, foam, ligation,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SEPS</td>
</tr>
<tr>
<td>Obstruction (nonacute)</td>
<td>Compression, venous stenting</td>
<td>Venous stenting</td>
</tr>
<tr>
<td>Central</td>
<td>Compression</td>
<td>Valve reconstruction</td>
</tr>
<tr>
<td>Peripheral Muscle pump</td>
<td>Compression</td>
<td>Structured exercise</td>
</tr>
<tr>
<td>dysfunction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Ablation indicates endovenous radiofrequency and laser ablation. HLS indicates high ligation and stripping. Pharmacologic includes the micronized purified flavonoid fraction (Daflon), horse chestnut seed extract. SEPS indicates subfascial endoscopic perforator surgery. Central obstruction indicates vein segments involving the femoroiliac segments, and peripheral vein segments involve the femoropopliteal segments.*
Lets Get Real

- Thrombo-Embolic Deterrent Hose (TED)
- Gradient compression stockings
- Anti-embolism compression stockings
- Knee-high
- Thigh-high length
- 10 to 15 mmHg

Paul Gerson Unna

- 1850 to 1929
- Private Dermatology practice
- Strong interest in venous disease
- “Unna Boot”
What is Unna’s Boot?

- 4 inches wide
- 10 yards long
- Thick creamy mixture
  - zinc oxide
  - calamine
  - acacia
  - glycerin
  - castor oil and white petrolatum
To Treat or Not To Treat

• Complex
• Bacterial colonization
• Superimposed bacterial infections
• Cochrane review of 22 RCTs
  – Systemic antibiotics?
  – Topical antibiotics?
  – Antiseptics?
  – No evidence that routine use of oral antibiotics improves healing

https://www.masterorganicchemistry.com/2015/01/06/my-recent-absence-explained-with-9-molecules/
Bugs Bugs Bugs

- Staphylococcus aureus
- Pseudomonas aeruginosa
- Beta-haemolytic streptococci
- Broad spectrum penicillin
- Macrolide
- Quinolone
- Two-week course
Antibiotics

- Topical antiseptic agent cadexomer iodine - increased healing rate at four to six weeks compared with placebo.
- Oral antibiotics are recommended to treat venous ulcers only in cases of suspected cellulitis.
- Consider IV antibiotics for failed outpatient management

MEDICAL MANAGEMENT
Pentoxifylline

- Competitive nonselective inhibitor of the enzyme adenylate cyclase
  - Intracellular cyclic adenosine monophosphate
  - Protein kinase A
  - Inhibition of tumor necrosis factor
  - Leukotriene synthesis

https://granulomaannulare.wordpress.com/2016/03/29/pentoxifylline/
Pentoxifylline

- Prospective randomized trial
  - 245 C₆ patients
  - Pentoxifylline 1200 mg daily
  - Standard dressings
  - Ulcer healing (62% vs 53%; p= NS)
  - Cox regression analysis model resulted in a clinically marginal significant improvement in ulcer healing in the Pentoxifylline group
Pentoxifylline

- Cochrane review
- 12 trials
- 864 patients
- Pentoxifylline plus compression was found to be more effective than compression alone
- Pentoxifylline therapy alone was more effective than placebo or no treatment

Phlebotropic

- Daflon 500
- 90% micronized Diosmin and 10% Flavonoids
- Anti-inflammatory activity with inhibition of granulocytes and macrophage infiltration in the venous parenchyma.
- Animal model
  - leukocyte adhesion/migration into valvular tissue
  - expression of intercellular adhesion molecule-1 and P-selectin
  - apoptosis of endothelial cells
  - venous valve degeneration was attenuated in the treatment group
Horse Chestnut Seed Extract

- Aesculus hippocastanum
- Traditional herbal remedy
- Swelling and inflammation
- Used extensively in Europe to treat venous disorders.
- RCT is an effective and safe short-term treatment for chronic venous insufficiency
- Extract contains flavonoids

- www.amazon.com/Natures-Life-Chestnut-Extract-capsules/dp/B00014HV0W
Pycnogenol

- French maritime pine bark.
- Chronic venous insufficiency
- Venous ulcer healing
- Reducing extremity edema
- Anti-inflammatory
- Vasodilating
- Anti-thrombotic properties
- May slow progression to chronic venous insufficiency?

- www.ilactr.com/ilac/dafion.html
- www.pycnogenol.com/about/faq/
Centella Asiatica

- Gotu kola
- Southeast Asia tropical plant
- Carotenoids and Vitamins C and B complex
- RCT
  - likely exerts beneficial effects on the signs and symptoms of chronic venous insufficiency
  - significantly improved edema-related symptoms in patients with venous hypertension
  - ankle edema
  - improved the capacity of veins to stretch or dilate


www.ilactr.com/ilac/dafon.html
https://en.wikipedia.org/wiki/Centella Asiatica#media:Thankuni_Herbs.jpg
Sulodexide

- Purified complex of glycosaminoglycans
- Naturally occurs in ulcers
- Anticoagulant
- Anti-inflammatory
- Improves healing
- Used in Europe

**References:**

Oxerutin

- Semisynthetic flavonoids mixture
- Commonly used in Europe
- Clinical trials
  - reduced edema
  - decreased pain
- Reduce excessive venous permeability and improvement in venous micro-circulation
## Others

<table>
<thead>
<tr>
<th>Compound</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>Fat-soluble vitamin and free radical scavenger/anticoagulant</td>
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<tr>
<td>Grape Seed Extract</td>
<td>Proanthocyanidins&lt;br&gt;Inhibit enzymes that degrade collagen and elastin efficacy in enhancing vascular function and circulation.</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Scavenger of free radicals that also contributes to venous dilation. &lt;br&gt;Necessary for the synthesis of collagen &lt;br&gt;Important role in wound healing</td>
</tr>
<tr>
<td>Butcher’s Broom</td>
<td>Ruscus aculeatus &lt;br&gt;Inhibit elastase enzymes - reduces vascular permeability &lt;br&gt;Contributes to edema.</td>
</tr>
<tr>
<td>Red Vine Leaf Extract</td>
<td>Leaves of the wine grape plant (Vitis vinifera) &lt;br&gt;Powerful flavonoid present in many plants. &lt;br&gt;Improves pain and sensation of heaviness and swelling</td>
</tr>
</tbody>
</table>

- Higdon J. Linus Pauling Institute. Micronutrient Information Center: Vitamin E.  
FOOD FOR THOUGHT
Venous Epidemiology

- ~ 1% Western Countries
- ~ 0.3% World Wide
- Active or healed venous ulcer
- Chronic venous disease prevalence with age considered a “dose-related risk factor”


# Prevalence

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Reference</th>
<th>CVI manifestation</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>1958</td>
<td>Arnoldi (23)</td>
<td>Active or healed ulcer</td>
<td>1.9</td>
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<tr>
<td>1966</td>
<td>Bobek et al. (99)</td>
<td>Active or healed ulcer</td>
<td>0.9</td>
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<tr>
<td>1969</td>
<td>Mekky et al. (37)</td>
<td>Hyperpigmentation, ulcer, edema, and eczema</td>
<td>10.0</td>
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<tr>
<td>1973</td>
<td>Coon et al. (54)</td>
<td>Stasis skin change**</td>
<td>3.0</td>
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<tr>
<td></td>
<td></td>
<td>Active or healed ulcer</td>
<td>0.1</td>
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<tr>
<td>1974</td>
<td>DaSilva et al. (56)</td>
<td>Dilated subcutaneous veins</td>
<td>10.0</td>
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<tr>
<td></td>
<td></td>
<td>Hyperpigmentation</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active or healed ulcer</td>
<td>1.1</td>
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<tr>
<td>1978</td>
<td>Widmer (20)</td>
<td>Skin changes*</td>
<td>6.0</td>
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<tr>
<td></td>
<td></td>
<td>Active or healed ulcer</td>
<td>1.0</td>
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<tr>
<td>1986</td>
<td>Maffei et al. (53)</td>
<td>Edema</td>
<td>17.1</td>
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<tr>
<td></td>
<td></td>
<td>Hyperpigmentation</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eczema</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrosis</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active or healed ulcer</td>
<td>2.5</td>
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<tr>
<td>1992</td>
<td>Franks et al. (60)</td>
<td>Active or healed ulcer</td>
<td>4.7</td>
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<tr>
<td>1994</td>
<td>Komsuoglu et al. (42)</td>
<td>Hyperpigmentation</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eczema</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active or healed ulcer</td>
<td>0.6</td>
</tr>
<tr>
<td>1999</td>
<td>Evans et al. (21)</td>
<td>Dilated subcutaneous veins</td>
<td>6.9</td>
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<tr>
<td>2002</td>
<td>Ruckley et al. (32)</td>
<td>Hyperpigmentation</td>
<td>1.3</td>
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<tr>
<td>2003</td>
<td>Criqui et al. (40)</td>
<td>Active or healed ulcer</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trophic changes†</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Edema</td>
<td>7.4</td>
</tr>
</tbody>
</table>

*Excluding varicose veins.
**Hyperpigmentation, fibrosis, induration, atrophy.
†Edinburgh Vein Study (results published in two manuscripts).
††Hyperpigmentation, lipodermatosclerosis, ulcer.
Venous Epidemiology

- Around 400,000 to 600,000 venous ulcers affect the US population

- Rarely fatal and hardly ever progress to amputation frequent hospitalizations

- 37% to 48% recurrence rate of healed venous stasis wounds at 3 years

References:
Percutaneous Valves
## Genes

### Table 1 - Reports of genetic mutations associated with poor healing and progression of venous leg ulcers.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of genetic defect</th>
<th>Phenotypic change</th>
<th>Clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zamboni, 2006 [43]</td>
<td>HFE gene</td>
<td>Increased iron deposition</td>
<td>Exacerbation of venous ulcers</td>
</tr>
<tr>
<td>Sam, 2003 [44]</td>
<td>MTFR gene (SNP C677T)</td>
<td>Reduction in enzyme methylenetetrahydrofolate reductase function</td>
<td>Associated with varicose veins and chronic venous disease (CEAP score 4–6)</td>
</tr>
<tr>
<td>Sverdlova, 1998 [45]</td>
<td>SLC40A1 (SNP 8CG)</td>
<td>Possible increased iron deposition</td>
<td>Increased the risk of chronic venous disease and primary leg ulcer development</td>
</tr>
<tr>
<td>Gemmati, 2009 [46]</td>
<td>MMP-12 (SNP 82AA)</td>
<td>Functional change</td>
<td>Increased risk of ulcer formation</td>
</tr>
<tr>
<td>Gemmati, 2009 [46]</td>
<td>FGFR-2 (SNP 2451 AG)</td>
<td>Possible messenger RNA instability-reduced mitogenesis</td>
<td>Associated with nonhealing ulcers</td>
</tr>
</tbody>
</table>

Adapted from Anwar et al [10], with permission. CEAP, clinical, etiology, anatomy, pathophysiology.
Psychological Impact

- 81% patients with venous stasis ulcers experience decreased mobility
- 57% of patients report severely limited mobility
- 68% with fear, anger, depression and social isolation
CONCLUSIONS
to bind up the nation’s wounds, to care for him who shall have borne the battle and for his widow, and his orphan, to do all which may achieve and cherish a just and lasting peace among ourselves and with all nations.”
References

References


References

References

References

- https://www.heise.de/preisvergleich/novartis-venoruton-gel-a1015855.html
- Higdon J. Linus Pauling Institute. Micronutrient Information Center: Vitamin E.
References


References


• www.ilactr.com/ilac/daflon.html

• https://en.wikipedia.org/wiki/Centellaasiatica#/media/File:Thankuni_Herbs.jpg