Pharmacologic Agents, Wound Care, Compression Therapy
Treatment/Therapy

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Disclosures

No pertinent disclosures

No financial interests

Some pharmacologic discussion will involve compounds which are considered herbal or alternative and are not FDA-approved.

Some wound care products will be discussed using “trade-name”
CVD/VV
Therapy/Treatment

- Pharmacologic Agents
- Wound Care
- Compression Therapy
CVD/VV
Pharmacologic Agents

- **Venoactive drugs (venotonics)**
  - Decrease CVI symptoms
  - Decrease swelling
  - Accelerate wound healing
CVD/VV
Pharmacologic Agents

- **Venoactive drugs (venotonics)**
  - Precise mechanism of action unknown, but
    - Increase venous tone
    - Decrease capillary permeability
  - In the case of flavonoids, . . .
    - Anti-inflammatory effect on endothelium and leukocytes
CVD/VV
Pharmacologic Agents

- **Saponins**
  - horse chestnut seed extract (aescin).

- **Gamma-benzopyrenes (flavonoids)**
  - rutosides, diosmin, and hesperidin;

- **micronized purified flavonoid fraction (MPFF)**
  - 90% micronised diosmin and 10% flavonoids expressed as hesperidin

- **Various plant extracts**
  - French Maritime Pine Bark Extract

- **Synthetic compounds**
  - calcium dobesilate
2005 Cochrane Review: 44 studies

- ↓ edema
- ↓ restless leg syndrome

Diosmin, hesperidin, and MPFF appeared to be most effective venoactive drugs. Calcium dobesilate reduced cramps and restless legs.

Diosmin & hesperidin helped healing of trophic skin changes and were useful in treatment of cramps and swelling.

Rutosides decreased venous edema.

CVD/VV
Pharmacologic Agents

- Horse chestnut seed extract
  - Decreased edema
  - Decreased pain
  - Decreased itching

Pentoxifylline for ulcers

- Falanga compared placebo to pentoxifylline:
- median healing time:
  - 100 days (placebo)
  - 83 days (pentoxifylline 400mg TID)
  - 71 days (pentoxifylline 800mg TID)

400 mg three times daily is suggested to patients with venous ulcers in addition to local care, compression garment, or intermittent compression pump (ICP) in the venous guidelines of the American College of Chest Physicians (2006) (ACCP; GRADE 2B)

CVD/VV
Pharmacologic Agents

MPFF (90% micronised diosmin and 10% hesperidin)

32% improvement in ulcer healing at 6 months compared to conventional treatment alone.¹

SVS/AVF Guideline Committee also suggests that MPFF or pentoxifylline be used for patients with venous ulcers as an adjuvant therapy to compression to accelerate ulcer healing (GRADE 2B)²

² J Vasc Surg 2011;53:2S-48S
4.3 Pharmacologic Treatment of Patients With PTS

4.3. In patients with PTS of the leg, we suggest that venoactive medications (e.g., rutosides, defibrotide, and hidrosmin) not be used (Grade 2C).

- “Patients who value the possibility of response over the risk of side effects may choose to undertake a therapeutic trial.”
### CVD/VV Pharmacologic Agents

#### Table 61.5 Grades of Recommendation of the International Consensus Statement

<table>
<thead>
<tr>
<th>Compound</th>
<th>Recommendation</th>
<th>Number of Influential Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RCTS</td>
</tr>
<tr>
<td>Calcium dobesilate</td>
<td>Grade A</td>
<td>3</td>
</tr>
<tr>
<td>MPFF</td>
<td>Grade A</td>
<td>4</td>
</tr>
<tr>
<td>HR-exerutins</td>
<td>Grade A</td>
<td>5</td>
</tr>
<tr>
<td>HCSE (escin)</td>
<td>Grade B</td>
<td>1</td>
</tr>
<tr>
<td>Ruscus extract</td>
<td>Grade B</td>
<td>2</td>
</tr>
<tr>
<td>Diosmin (synthetic)</td>
<td>Grade C</td>
<td>1</td>
</tr>
<tr>
<td>Troxerutin</td>
<td>Grade C</td>
<td>2</td>
</tr>
<tr>
<td>Gingko biloba</td>
<td>Grade C</td>
<td>2</td>
</tr>
<tr>
<td>Proanthocyanidines</td>
<td>Grade C</td>
<td>2</td>
</tr>
<tr>
<td>Troxerutin + coumarin</td>
<td>Grade C</td>
<td>1</td>
</tr>
<tr>
<td>Centella asiatica</td>
<td>Grade C</td>
<td>1</td>
</tr>
<tr>
<td>Naftazone</td>
<td>Grade C</td>
<td>1</td>
</tr>
</tbody>
</table>

RCTs: randomized clinical trials
(From Reference 34)

2005 International consensus
## Table 61.7 SUMMARY OF TENTATIVE RECOMMENDATIONS, ACCORDING TO THE PRINCIPLES OF THE GRADE SYSTEM

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>VENO-ACTIVE DRUG</th>
<th>RECOMMENDATION FOR USE</th>
<th>QUALITY OF EVIDENCE</th>
<th>CODE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relief of symptoms associated with CVD in patients C0s to C6s and with CVD-related edema</td>
<td>Micronized purified flavonoid fraction (MPFF)</td>
<td>Strong</td>
<td>Moderate</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td>Nonmicronized dionsins or synthetic dionsins</td>
<td>Weak</td>
<td>Poor</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td>Rutosides (O-betahydroxyethyl)</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Calcium dobesilate</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>HCSE</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Ruscus extracts</td>
<td>Weak</td>
<td>Moderate</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Gingko biloba</td>
<td>Weak</td>
<td>Poor</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td>Other VADs</td>
<td>Weak</td>
<td>Poor</td>
<td>2C</td>
</tr>
<tr>
<td>Healing of large or long-standing venous ulcer, as an adjunct to compressive and local therapy (Reference 86)</td>
<td>Micronized purified flavonoid fraction (MPFF)</td>
<td>Strong</td>
<td>Moderate</td>
<td>1B</td>
</tr>
</tbody>
</table>

HCSE: horse chestnut seed extract; VADs, venoactive drugs
(From Reference 86)
Wound Care
Wound Care

Venous Ulcers

- Many take > 9 months to heal
- Up to 66% last > 5 years
- Affect 1% general population w/ annual healthcare cost of $1 billion (US)

October; 20(4): 363–366
Venous ulceration

- Superficial venous disease present in >50%
- Initial Rx includes graduated compression and routine wound care
- All pts deserve Duplex evaluation
- Rx venous disease for long-term control

Ulcers

Features:

Elevated:

- Inflammatory cytokines
- Collagenolytic activity
- Matrix metalloproteinases (MMPs)
- Serine proteases
- Degradation of Fibronectin, Vtironectin, Tenascin
- Presence of senescent cells
Ulcers

- Decreased:
  - Tissue inhibitors of MMPs
  - $\alpha_1$ – protease inhibitor
  - $\alpha_2$ – macroglobulin
  - Mitotic activity
  - Growth factor activity
Ulcers

What you see:
- Necrotic & unhealthy tissue
- Surrounding skin/tissue damage from drainage
- Lack of adequate blood supply (arterial)
- Lack of healthy granulation tissue
- Lack of reepithelization
- Recurrent wound breakdown due to “superficial bridging”
Ulcers

- Vascular
- Neurotrophic
- Vasculitis
- Infectious
- Metabolic Disorders
- Miscellaneous (factitial, trauma, post-surgical)

- Tumors
- Drugs
- Hematologic Disorders
Differential Dx

Necrobiosis Lipoidica, NL (formerly NLD)
Ulcers

- Most common? Vascular
  - Venous
  - Arterial
  - Lymphatic
Ulcer Approach

- History, History, History!
  - First appearance
  - Inciting event. What started it?
  - Family history
  - Painful?
  - Drugs?
  - Any systemic illnesses
Ulcer Approach

- **Exam**
  - Location of the ulcer
  - Condition of surrounding skin
  - Signs of systemic illnesses
  - Color of the base
  - Presence of pulses
  - Overall hygiene, skin condition
Ulcer Approach

Diagnostic tests

- Routine
  - CBC, CMET, UA
  - Bacterial culture? Where?
- ABI’s
Ulcer Approach

Special Testing

- Serologic testing for syphilis
- CXR
- ANA, anti-DNA
- Serum complement levels, cryoglobulins
- X-rays of affected area (SQ gas, osteo, f.b.)
- Bone scans, 3-phase, WBC labeled
- ESR, CRP, RA, sickle cell prep, hypercoagulable profile
- Skin biopsy
Wounds

- Bounding (3+) DP and PT pulses
- Long-standing VV w/ posterolateral thigh perforating vein reflux
Ulcers – Useful clues

Venous

- Gaiter region (mid to lower calf)
  - Medial – think GSV distribution
  - Lateral - think SSV
- Hyperpigmentation
- Surrounding induration or lipodermatosclerosis
- “Stasis” dermatitis
- May or may not be painful
- Presence of varicose veins or spider veins (corona)
Ulcers- Useful Clues

Neuropathic

- History of DM
- Loss of sensation, monofilament test
- Surrounding callus (often start as a callus!)
- Usually painless or less pain than expected
- Base usually necrotic or purulent
- Extension to bone or tendon very common
- Always suspect osteomyelitis
Wound Care - Arterial
Venous vs. Arterial Ulcers

- Venous ulcers are significantly more common
- Venous ulcers are behind malleoli; arterial ulcers are in areas of chronic pressure or trauma (bony prominences)
- Arterial ulcers usually have a more necrotic base and are more painful
- Look for evidence of CVI (pigmentation, etc.) or ischemia (absent pulses, hair loss, etc.)

Photo courtesy of John Bergan, MD
Ulcer Management

Arterial

- Based on testing, increase inflow! Consult.
- Watch for pressure (heels, other bony prominences)
- Elevate head of bed
- Stop smoking
- Avoid adhesive tape
- Exercise caution with nail care
Ulcer Management--Venous

Controlling edema paramount (↓ ambulatory venous HTN)

Elastic compression- graduated stockings.

NO TED HOSE

Start with class I and titrate up.

Knee high are most common

Make sure arterial supply adequate

Non-elastic compression

CircAid leggings, short-stretch bandaging, UNNA boots, Duke boots, multi-layer compression
Ulcer Management

Venous

- Dermatitis: topical steroids, topical doxepin,
- Treat surrounding skin (moisturizing lotions, etc.)
- Ulcers rarely “infected”, but usually colonized.
- Type of dressing depends upon amount of drainage
  - Hydrocolloids
  - Absorbent foams
  - Saline wet-to-dry
Ulcer Management

Venous

- Ulcer debridement
  - Usually enzymatic (but also use mechanical, etc.)
  - Will occur just with bio-occlusive dressings

- “Advanced Wound Care”
  - Skin grafting, “skin substitutes”
Ulcer Management

Venous

- Antibiotics?
  - Obvious: Fever, lymphadenopathy, leukocytosis, purulent drainage.
  - Less obvious: Ulcer pain, erythema, increased drainage, friable granulation tissue, drainage changes color
Ulcer Management

Skin substitutes

Acellular
- LaserSkin®
- Transcyte®
- Integra®
- Alloderm®
- Biobrane®
- Grafix®
- Oasis Wound Matrix®
- Epifix

Cellular (Living)
- Dermagraft®
- Apligraf®/Graftskin®
Ulcer Management
Apligraf

Cultured from human foreskin-derived fibroblasts
1998- FDA-approved for VLU

Best patient?

- VLU that has failed to respond to 3-4 weeks of “standard treatment”, or the presence of NEGATIVE markers
  - Duration > 6 mo.
  - Size > 5cm
  - LDS located below malleolus
  - Failure of previous tx’s coexisting site infection
Ulcer Management

Apligraf

Wound healed @ 6 mos.

63% Apligraf (up to 5 applications) + compression

49% Conventional therapy (compression)

Sub-group analysis: better in duration > 6 mo.

Size > 10cm²

5 studies from 2000-2003 showed ↓ costs w/ Apligraf compared to conventional therapy.


Ulcer Management

Miscellaneous

**Pain:**

- Ischemia
- Infection
- Inflammation

Tissue damage (infection, repeated trauma, etc.)
Wound Care

- ESCHAR Trial:
  - 500 patients w/ CEAP 5 or 6
  - randomized to superficial vein surgery (saphenous vein ligation & stripping) and compression vs compression alone.
  - At 24 weeks, healing rates of 65% in each group
  - 12 month recurrence rate was 12% vs 28% favoring surgery

- Take home message:
  - Probably translate that to ablation procedures
  - Venous surgery is NOT routine or first-line therapy for VLU, BUT will
  - Lower recurrence

Lymphedema

Wounds

Lymphedema patients CAN get ulcers. Usually from neglect (uncontrolled weeping resulting in maceration) or trauma.
Compression Therapy
Compression Therapy

- Elastic compression
  - Graduated compression hosiery

- Inelastic compression
  - Unna’s boot (paste)
  - Multi-layered compression

- Dynamic compression
  - Sequential pneumatic pumping
Compression Therapy

- **Actions:**
  - Increased venous flow—especially deep veins
  - Decreased reflux with ambulation
  - Increased ejection fraction with ambulation (calf pump)

- **Clinical results:**
  - Decreased edema
  - Decreased pain
  - Improved wound healing
Compression Therapy
Sub-groups

- Varicose veins (CEAP class C2):
  - Strength of compression controversial
  - Improves symptoms but may not halt progression (high non-compliance)
  - SVS/AVF Guideline Committee suggests graded prescription stockings with an ankle pressure of 20 to 30 mm Hg (GRADE 2C)
Compression Therapy
Sub-groups

Varicose veins (CEAP class C₂):

- **REACTIV trial (246 patients):**
  - Conservative therapy (incl. stockings vs surgery)
  - Better QoL measures in first 2 years in surgery group
  - More cost-effective in surgery group¹

- “Trial of conservative therapy” including stockings?
  - SVS/AVF Guideline Committee recommends **against** compression therapy being considered the primary treatment of symptomatic varicose veins (class C₂) in those patients who are candidates for saphenous vein ablation (GRADE 1B)

Compression Therapy

Sub-groups

- **CVI (CEAP classes C3-C6):**
  - Less controversial and use is “gold standard”
  - Type of compression is less important than **COMPLIANCE**
    - Improved ulcer healing (and more rapid) w/ stockings
    - Ulcer recurrence: 16% in compliant patients
      - 100% in noncompliant patients

- **Studies differ on which type of compression is best**
  - Recent meta-analysis suggested stockings better tolerated than compression bandages w/ faster healing.
  - Conflicts with SVS/AVF recommendations

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Compression Therapy
Sub-groups

- CVI (CEAP classes C3-C6):
  - Compression pumps (not just for lymphedema)
    - Recommended as adjunctive therapy in recalcitrant ulcers

Compression Therapy

- Provides a gradient of pressure, highest at the ankle, decreasing as it moves up the leg
- Reduces reflux of blood
- Improves venous outflow
- Increases velocity of blood flow to reduce the risk of blood clots

Photo courtesy of Juzo
Inelastic compression

- Most physiologic in its effect
- Available as bandage, which requires significant skill in applying.
- “Velcro wraps are “user friendly,””
- Good choice for elderly, diabetics, patients with arterial disease (lower resting pressure), obese, arthritics, etc.
Conclusions

- **Pharmacologic?**
  - Be familiar w/ pentoxifylline, venotonics

- **Wound Care?**
  - Difference between arterial & venous
  - Compression therapy same as surgery for initial tx.

- **Compression?**
  - Since compliance most important, type must be individualized.
  - Know actions
Pharmacologic Agents, Wound Care, Compression Therapy
Treatment/Therapy

Thank you.