

## Update on pharmacological treatment for venous ulcers

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## Disclosure

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### Guidelines in Venous Ulcers

**Wound healing society 2015 update on guidelines for venous ulcers**

*Guideline #7c.1: Pentoxifylline used in conjunction with compression therapy improves healing of venous ulcers (Level I).*

*Guideline #7c.3: Oral treatment with micronized purified flavonoid fraction (MPFF) may be a useful adjunct to conventional compression therapy in the treatment of leg ulcers (Level I).*

**Management of venous leg ulcers: Clinical practice guidelines of the Society for Vascular Surgery<sup>®</sup> and the American Venous Forum**

*Guideline 7.1: Nutrition Assessment and Management*  
 We recommend that nutrition assessment be performed in any patient with a venous leg ulcer who has evidence of malnutrition and that **nutritional supplementation** be provided if malnutrition is identified. (BEST PRACTICE)

*Guideline 7.2: Systemic Drug Therapy*  
 For long-standing or large venous leg ulcer, we recommend treatment with either **pentoxifylline or micronized purified flavonoid fraction** used in combination with compression therapy. (GRADE = LEVEL OF EVIDENCE = B)

\*Xanthine derivative, prescribed in the arterial disease

### Impact of oral nutritional supplement composition on healing of different chronic wounds: A systematic review

**9 studies, 741 patients**

- Evidence supporting nutritional supplementation (high calorie and protein diet and antioxidant micronutrients, zinc, vitamins A, E, C)

### Nutrients with Antioxidant Properties and Their Effects on Lower-Limb Ulcers: A Systematic Review

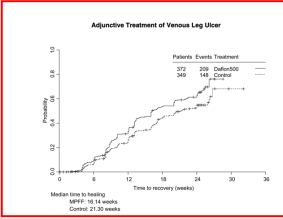
- 14 studies
- Omega-3 fatty acids, magnesium, zinc, vitamins A, C, D, and resveratrol along with probiotics positively improved the ulcer healing
- Importance of adequate nutritional status

### MPFF meta-analysis in chronic venous disease

- 30 studies (15 RCTs, 15 non-RCTs)
- 24,000 patients
- Rate of ulcer healing improved in 73.4% of patients and a complete healing was observed in 48.9% (P<0.001)
- MPFF effective in venous ulcers

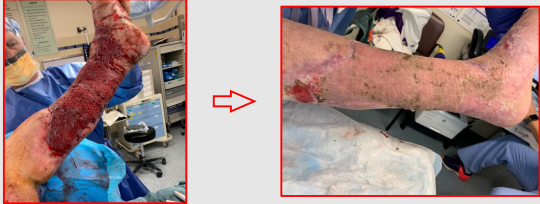
### A Meta-analysis of Adjunctive Therapy with Micronized Purified Flavonoid Fraction (MPFF)

- Healing rates at 6 months: 61.3% in the MPFF group versus 47.7% in the control group.
- Reduced the median time to healing (16.1 weeks for MPFF and 21.3 weeks in control group)
- The relative hazard of healing for MPFF group 38% (CI, 11-70) better than control



Coleridge-Smith P et al. Venous leg ulcer: a meta-analysis of adjunctive therapy with micronized purified flavonoid fraction. Eur J Vasc Endovasc Surg 2005;30:198-208

### Patient treated with wound care, compression and MPFF



4 months later

Photos: courtesy of Dr. M. Melin


### Cost-effectiveness of MPFF adjuvant venous ulcers' treatment

Cost-effectiveness =  $\frac{\text{Total cost per patient} \times n \text{ of patients in the treatment group}}{n \text{ of ulcers healed}}$

- MPFF adjuvant therapy improved the cost-effectiveness ratio by 45%
- MPFF treatment effective and cost-saving

Simka M, Majewski E. The social and economic burden of venous leg ulcers: focus on the role of micronized purified flavonoid fraction adjuvant therapy. Am J Clin Dermatol 2003;4:573 - 81

### Adjunctive Therapy with Pentoxifylline\*



- 13 RCTs, 921 patients
- Pentoxifylline vs placebo significantly improved the ulcer healing rate (RR = 1.59, P < .001), ↓ mean duration of healing (P = .007), ↓ ulcer size (P = .02).
- ↑ incidence of gastrointestinal disturbances (RR = 2.29, P = .04)
- Moderate-certainty evidence

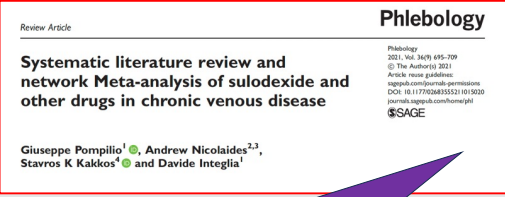
\*Xanthine derivative

### Phlebology

Review Article


#### Systematic literature review and network Meta-analysis of sulodexide and other drugs in chronic venous disease

Giuseppe Pompilio<sup>1</sup>, Andrew Nicolaides<sup>2,3</sup>, Stavros K Kakkos<sup>4</sup> and Davide Integlia<sup>1</sup>



Sulodexide, pentoxifylline and MPFF are effective in improving the rate of ulcer healing in patients with CVD

### Adjunctive Therapy with Sulodexide\* in Venous Ulcers



- Healing of ulcers increased
- 4 RCTs, only 3 full papers available
- 1 RCT vs placebo
- 30-90 days treatment
- In one study inclusion of PTS patients

\* Mixture of glycosaminoglycans composed of low molecular weight heparin (80%) and dermatan sulfate (20%)

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 DOI: 10.1111/wrr.12987

**BRIEF COMMUNICATION**

**Statin and venous leg ulcer healing: Secondary analysis of data from a cohort of three randomised controlled trials**

Andrew Jull RN PhD<sup>1,2</sup> | Han Lu BSc<sup>3</sup> | Yannan Jiang PhD<sup>2,3</sup>

**Modest but significant improvement in the statins group when adjusted for confounders (age, diabetes, first ever ulcer, ulcer area and ulcer duration)**

**European Society for Vascular Surgery 2022 CVD Guidelines**

ARTICLE IN PRESS

European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs

**6.6. Pharmacotherapy**

**Recommendation 82** Unchanged

For patients with active venous leg ulceration, micronised purified flavonoid fraction, hydroxyethylrutosides, pentoxifylline, or sulodexide should be considered, as an adjunct to compression and local wound care to improve ulcer healing.

Class	Level	References	ToU
IIa	A	Cokeridge-Smith et al. (2005), <sup>102</sup> Jull et al. (2012), <sup>103</sup> Scallion et al. (2013), <sup>104</sup> Wu et al. (2016) <sup>105</sup>	

**Nutrition and Venoactive Compounds in Venous Ulcers**

**HANDBOOK OF VENOUS AND LYMPHATIC DISORDERS**  
 FIFTH EDITION  
 Guidelines of the American Venous Forum

34.6	We recommend nutrition assessment and if needed nutritional supplementation addressing nutritional deficiencies in patients with venous leg ulcers.	1 (strong)	B (moderate)
34.7	We recommend in venous leg ulcers either micronised purified flavonoid fraction, or pentoxifylline, as adjunctive treatment with compression, early intervention and wound local care.	1 (strong)	A (high)
34.8	We recommend sulodexide as adjunctive treatment with compression, early intervention and wound local care.	1 (strong)	B (moderate)
34.9	We suggest in venous leg ulcers hydroxyethylrutosides as adjunctive treatment with compression, early intervention and wound local care.	2 (weak)	C (low to very low)

Gloviczki ML and Raffetto JD. Drug treatment for chronic venous disease. Handbook of Venous and Lymphatic Disorders, 5<sup>th</sup> Ed.

**Conclusions**

- Nutritional supplements are indicated for patients with venous ulcers and vitamins/minerals deficiencies.
- Several academic societies, including the SVS/ESVS/AVF/Wound Healing Society, recommend for venous leg ulcer, in addition to standard wound care and compression therapy, an adjunctive treatment with MPFF, pentoxifylline, hydroxyethylrutosides, or sulodexide.

