

به نام خداوند جان و خرد



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MANAGEMENT OF CUTANEOUS VASCULITIS

interdisciplinary collaboration

Therapeutic decisions dependent upon:

- o **Vasculitis itself**

(Severity, complications, chronicity, recurrence)

- o **Underlying disease**

infection (15–20%), inflammatory disease (15–20%), drug intake (10–15%), malignancy (5%)

Disease severity & potential drug efficacy
carefully balanced
possible toxicities

Micheletti RG. Cutaneous vasculitis in rheumatologic disease: Current concepts of skin and systemic manifestations.
Clin Dermatol. 2018 Jul - Aug;36(4):561-566.

Table 2. Dermatological Addendum to the 2012 International Chapel Hill Consensus Conference Nomenclature of Vasculitides

CHCC 2012 Name	Systemic vasculitis skin component	Skin-restricted or skin-dominant variant
Large-vessel vasculitis		
Takayasu arteritis	No	No
Giant cell arteritis	Rare	No
Medium-vessel vasculitis		
Polyarteritis nodosa	Yes	Yes
Kawasaki disease	No	No
Small-vessel vasculitis		
Microscopic polyangiitis	Yes	Yes
Granulomatosis with polyangiitis	Yes	Yes
Eosinophilic granulomatosis with polyangiitis	Yes	Yes
Antiglomerular basement membrane disease	No	No
Cryoglobulinemic vasculitis	Yes	Yes
IgA vasculitis (Henoch-Schönlein)	Yes	Yes
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)	Yes	Yes
Normocomplementemic urticarial vasculitis	Rare	Yes
Variable-vessel vasculitis		
Behçet's disease	Yes	Yes
Cogan's syndrome	Rare	No
Vasculitis associated with systemic disease		
For example, LE, rheumatoid arthritis, sarcoidosis, etc.	Yes	Yes
Vasculitis associated with probable cause		
For example, drugs, infections, sepsis, autoimmune diseases, etc.	Yes	Yes
Cutaneous single-organ vasculitis		
IgM/IgG vasculitis	No	Yes
Nodular vasculitis (erythema induratum of Bazin)	No	Yes
Erythema elevatum et diutinum	No	Yes
Hypergammaglobulinemic macular vasculitis	No	Yes

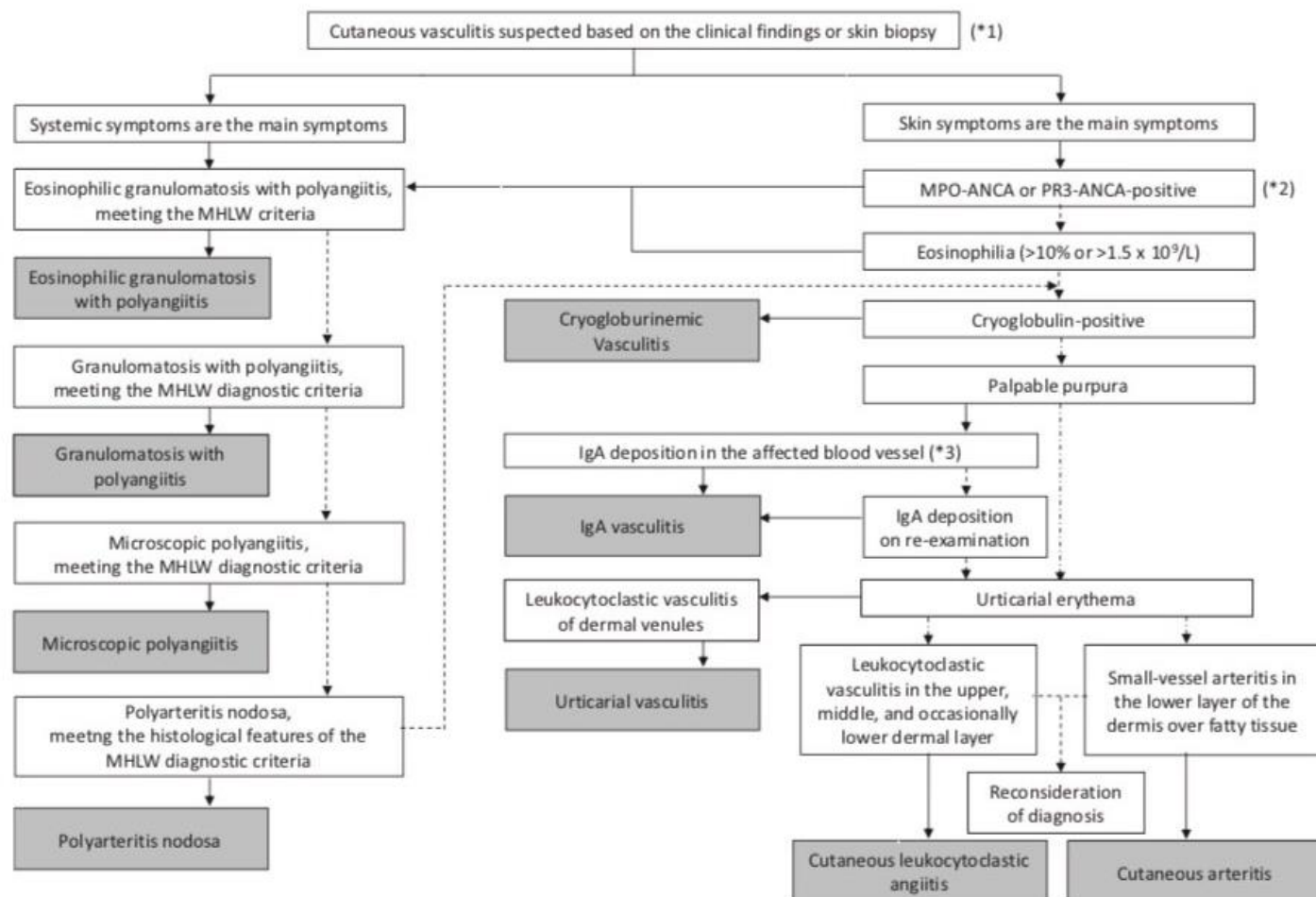
Sunderko" tter CH, Zelger B, Chen KR, et al. Nomenclature of cutaneous vasculitis: dermatologic addendum to the 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheumatol 2018; 70:171–184.

**whether the skin or systemic symptoms is the
main symptom**

Differentiation of systemic vasculitis

Takaharu IKEDA, Fukumi FURUKAWA, Tamihiko KAWAKAMI

Journal of Dermatolog **Outline of guidelines for the management of vasculitis and vascular disorders in Japan, 2016 revised edition** 2018; 45: 122–127



Cutaneous idiopathic small vessel vasculitis (CSVV)

Cutaneous Single organ vasculitis (IgM/IgG V)

Therapeutic ladder

data from case reports and small case series precludes definitive conclusions on the efficacy of any specific therapy.

Micheletti RG. Cutaneous vasculitis in rheumatologic disease: Current concepts of skin and systemic manifestations.
Clin Dermatol. 2018 Jul - Aug;36(4):561-566.

Acute and uncomplicated single episode

- Spontaneous resolution
- Rest, leg elevation, and compression stockings
- Nonsteroidal antiinflammatory drugs (NSAIDs)
- Oral antihistamines
- Short taper of prednisolone (40-60mg 4-6 weeks) followed by
- Colchicine or dapsone until new lesion formation ceases

Topical corticosteroids has not been beneficial

Continuation of long-term monotherapy with glucocorticoids
is not recommended

Complicated or chronic idiopathic CSVV

First-line therapy

Colchicine (0.6 mg twice to three times daily)

Data conflict on the efficacy of colchicine

Dapsone (50-200 mg per day) (For Erythema Elevatum Diutinum with Niacinamid)

pentoxifylline (400 mg three times daily) + dapsone (100 mg per day)

Colchicine+dapsone

Megan R. Goeser , Valerie Lariosz , David A. Wetter A
Practical Approach to the Diagnosis, Evaluation, and Management of
Cutaneous Small-Vessel Vasculitis. Am J Clin Dermatol april 2014

Second-line therapy

Azathioprine, (doses of 0.5 to 2.5 mg/kg per day)

Methotrexate, (10 to 25 mg per week)

Mycophenolate mofetil (1 to 1.5 g twice daily)

Immunoglobulin A vasculitis or urticarial vasculitis

Refractory disease (unresponsive to second line drugs)

Hydroxychloroquine (**400 mg daily only for Urticarial Vasculitis**)

Intravenous immune globulin (2 gr/kg) monthly-divided over 2-4 days)

Cyclosporine (2.5-5 mg/kg per day) short-term use

Rituximab (1gr on day 1 & 15)

Cyclophosphamide, is not typically prescribed for CSVV

●Duration of therapy

discontinue therapy once existing lesions have healed and no new lesions have developed for two to three months.
If lesions recur, treatment is reinitiated.

HOW TO TREAT HEPATITIS C VIRUS RELATED MIXED CRYOGLOBULINEMIA VASCULITIS?

Anne C. Desbois, Cloe Comarmond, David Saadoun, Patrice Cacoub
Cryoglobulinemia vasculitis: how to handle
Curr Opin Rheumatol 2017, 29:343–347

- **Multidisciplinary consensus and evidence-based recommendations :**
- HCV-CryoVas manifestations improve or disappear when a sustained clearance of HCV is achieved
- Patients who relapsed for HCV infection usually relapsed for the vasculitis

Ferri C, Ramos-Casals M, Zignego AL, et al.
International diagnostic guidelines for patients with HCV-related extrahepatic manifestations. A multidisciplinary expert statement. Autoimmun Rev 2016; 15:1145–1160

Direct-Acting Antivirals (DAA) as first line lead to high cure rates with a very good safety profile

Immunosuppressive treatments
(rituximab, glucocorticosteroids, cyclophosphamide)
and plasmapheresis in severe form of HCV-cryo-Vas,
failure or contradiction to antiviral treatments

Emery J, Kuczynski M, La D, et al. Treatment of hepatitis C associated mixed cryoglobulinemia with direct acting antivirals.
J Hepatol 2016; 64:S779

- During the decade 2002–2012, Pegylated interferon (PegIFN) and ribavirin for 12 months led to sustained virologic response (SVR) in 50–60% of HCV-CryoVas patients

Gragnani L, Visentini M, Fognani E, et al. Prospective study of guideline-tailored therapy with direct-acting antivirals for hepatitis C virus-associated mixed cryoglobulinemia. *Hepatology* 2016; 64:1473–1482

Kondili LA, Weimer LE, Mallano A, et al. HCV-related mixed cryoglobulinemia: data from PITER, a nationwide Italian HCV cohort study. *J Hepatol* 2016; 64:S618.

- The use of triple HCV therapy combining **PegIFN, ribavirin** and a **direct-acting antiviral** (DAA) (NS3/4A protease inhibitor, i.e. boceprevir or telaprevir) led to improved SVR rates (65–70%) in HCV-CryoVas patients

Such combination should be given for a long period (48 weeks)
serious adverse events occurred in up to 47%

- Other **second-generation DAAs** are now approved. The NS3/4A inhibitor **simeprevir** and NS5B inhibitor **sofosbuvir** allow shortened courses of IFN-free therapy, which are associated with high (>95%) SVR rates and relatively few toxicities.

- Gragnani et al. have recently reported :

cohort of 44 patients with HCV-CryoVas.

Patients were treated with:

-sofosbuvir-based treatments associated with ribavirin

-simeprevir , ledipasvir or daclatasvir and ribavirin.

Two patients with severe vasculitis received reduced dose of rituximab.

All patients had negative HCV viremia at week 12 and at week 24,
all had clinical response of vasculitis.

Gragnani L, Visentini M, Fognani E, et al. Prospective study of Guideline-tailored therapy with direct-acting antivirals for hepatitis C virus-associated mixed cryoglobulinemia. Hepatology 2016; 64:1473–1482.

In a nationwide Italian study, Kondili et al. reported the disappearance or improvement of more than 50% of CryoVas symptoms in 31 out of 37 (84%) of patients after DAA.

Kondili LA, Weimer LE, Mallano A, et al. HCV-related mixed cryoglobulinemia: data from PITER, a nationwide Italian HCV cohort study. J Hepatol 2016; 64:S618.

In urgent/life threatening HCV-CryoVas the combination of IFN-free DAA and nonetiologic therapy (glucocorticoids, rituximab, cyclophosphamide and plasmapheresis) can be allowed.

Rituximab has shown a better efficacy than conventional immunosuppressive, plasmapheresis or placebo.

Medium-vessel vasculitis (MVV)

Polyarteritis nodosa (cPAN)

- Exclusion of systemic involvement
(classic PAN 49.9% skin involvement)

The most important differential diagnosis of cPAN is systemic PAN

[Karadag O, Jayne DJ](#) Polyarteritis nodosa revisited: a review of historical approaches, subphenotypes and a research agenda. [Clin Exp Rheumatol](#). 2018 Mar-Apr;36 Suppl 111(2):135-142.

Definition of polyarteritis nodosa-subphenotypes / O. Karadag & D. Jayne

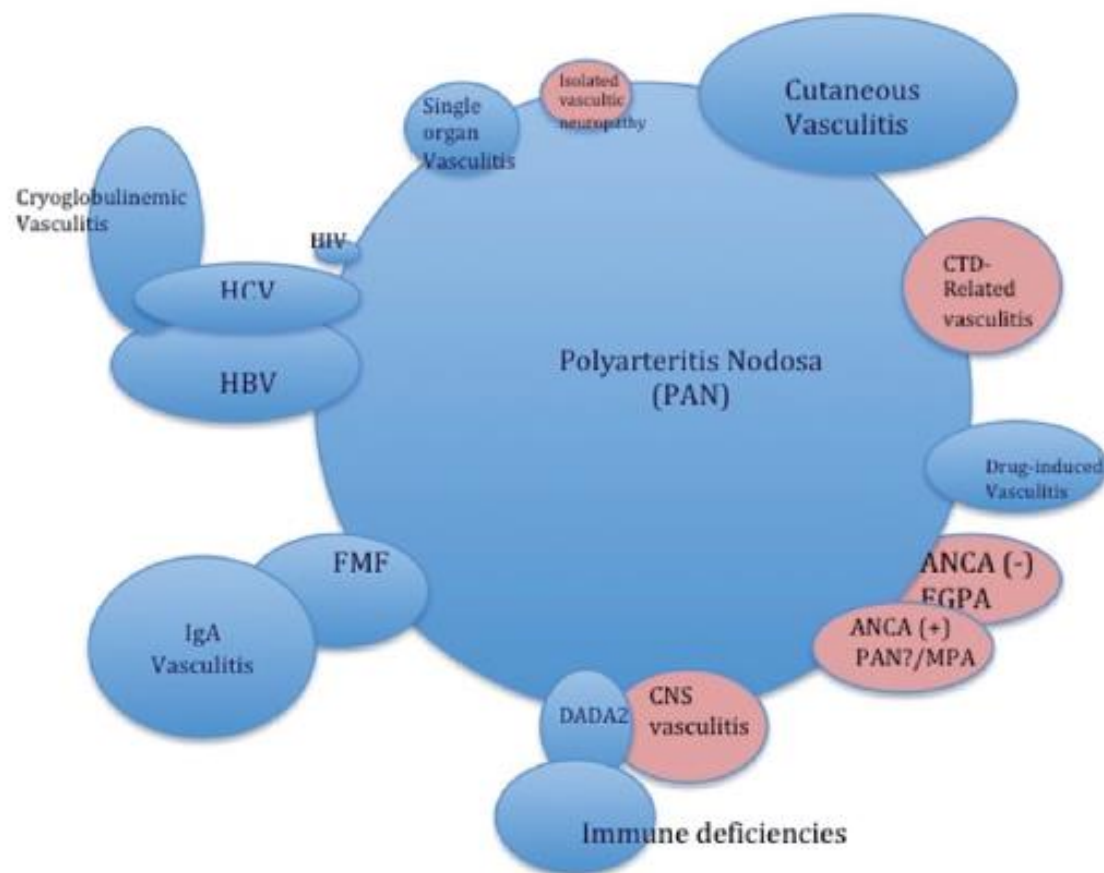


Fig. 1. Schema representing etiologic/genetic factors and subgroups of polyarteritis nodosa (PAN). Less studied/related subgroups are shown in purple.

Karadag O, Jayne DJ Polyarteritis nodosa revisited: a review of historical approaches, subphenotypes and a research agenda. *Clin Exp Rheumatol*. 2018 Mar-Apr;36 Suppl 111(2):135-142.

NATURAL HISTORY cPAN

complete remission in 57% (median f-up 11 yrs)
usually follows a chronic, relapsing - remitting course

progression to systemic disease is rare 10%
long-term follow-up is essential at least every six months even if the patient is otherwise asymptomatic

ALIBAZ-ONER F, KOSTER MJ, CROWSON CS *et al.*: The clinical spectrum of medium-sized vessel vasculitis. *Arthritis Care Res*, 2017; 69: 884-91.

[Ross K](#), [Contreras J](#), [Aung-Din D](#), [Lien M](#)

Asymptomatic cutaneous polyarteritis nodosa: treatment options and therapeutic guidelines. [Cutis](#). 2017 Aug;100(2):125-128

Management of cPAN

Absent high-quality data

Suggestions are based upon case reports, small case series, and expert opinion

Management of cPAN

Treatment depends on the severity of the disease and the frequency of relapses, clinician experience, patient preference or co morbidities

Mild cPAN

(Superficial lesions, nodules and livedo reticularis)

NSAIDs, rest, elevation of the affected limb

Colchicine (0.6 mg twice daily)

Dapsone (50 to 150 mg per day)

+_ NSAIDs for several weeks

Potent topical Corticosteroids (eg, clobetasol propionate)
twice daily over four weeks

Kate Ross, Jessika Contreras, David Aung-Din, Mary Lien, Asymptomatic Cutaneous Polyarteritis Nodosa: Treatment Options and Therapeutic Guidelines Cutis. 2017;100:125-128

Acute flares

pain, ulceration, digital ischemia or extra cutaneous symptoms
systemic glucocorticoids + Glucocorticoid-sparing agents
two to several months

Remission

glucocorticoid taper & glucocorticoid-sparing agent continued

Non-immunosuppressive glucocorticoid-sparing agents

colchicine, dapsone, sulfapyridine, hydroxychloroquine, pentoxifylline

routine use of prophylactic antibiotic therapy not recommend

Severe or refractory cPAN

glucocorticoids + immunosuppressive glucocorticoid-sparing agent
azathioprine, methotrexate, mycophenolate, cyclophosphamide

intravenous immunoglobulins

Criado PR, Marques GF, Morita TC, de Carvalho JF
Epidemiological, clinical and laboratory profiles of
cutaneous polyarteritis nodosa patients: Report of 22
cases and literature review.
Autoimmun Rev. 2016 Jun;15(6):558-63

PAN-associated ADA2 mutations:

Anti-TNF

PAN-associated HBV:

glucocorticoid, plasma exchange, antiviral therapy

sustained control of vasculitis in 90-100% of patients with virological response (HBe seroconversion)

PAN-associated FMF:

strict control of subclinical inflammation with adequate doses of colchicine, anti-IL-1 in resistant cases

PAN-associated IBD: ...

PAN-associated immunodeficiency: ...

Ozen, S. & Bilginer, Y. A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin. *Nat. Rev. Rheumatol.* **10**, 135–147 (2014).

MORGAN AJ, SCHWARTZ RA: Cutaneous polyarteritis nodosa: a comprehensive review. *Int J Dermatol* 2010; 49: 750-6.

Vasculitic Ulcers

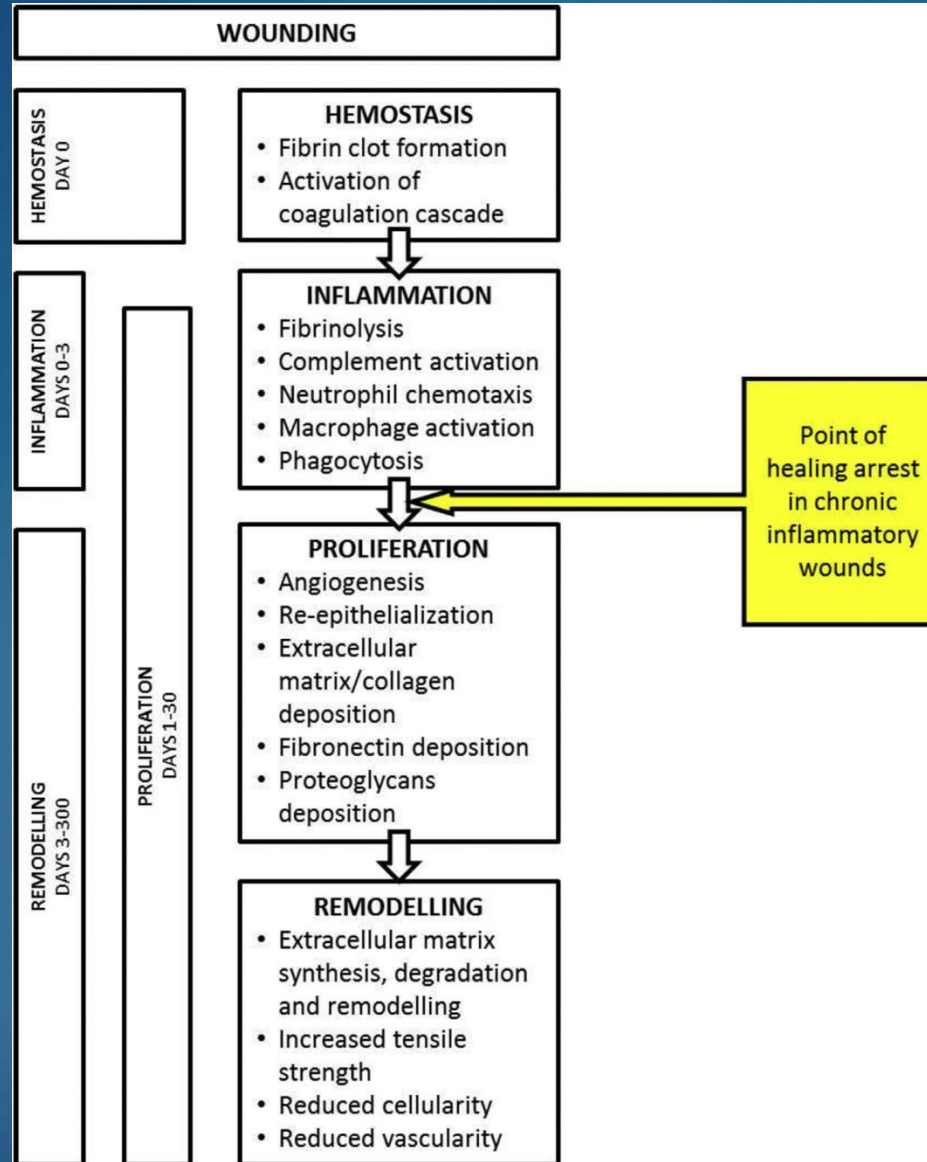
Do all the CVs present the same risk of causing chronic skin ulcers?

- anatomical site, typology, and size of the vessel
- the patient's basic circulatory disturbances
- presence of hypercoagulable disorders & fibrosis
- cryoprotein-related vasculitis and PAN are at higher "risk of ulcer formation."



Massimo Papi, MD, Claudia Papi. Vasculitic Ulcers
The International Journal of Lower Extremity Wounds
2016, Vol. 15(1) 6–16

Four phases of normal wound healing



Vasculitic and autoimmune wounds
 Victoria K. Shanmugam, Divya Angra, Hamza Rahimi, Sean McNish
 Journal of Vascular Surgery: Venous and Lymphatic Disorders,
 Volume 5, Number 2, March 2017

Vasculitic Ulcers

Principles of Therapy

The patient improved with antibiotic, oral corticosteroids, colchicine and local care.

corticosteroid combined with cytotoxic drugs, most commonly cyclophosphamide.

Rituximab has been used with very good results



Vasculitic Ulcers

Principles of Therapy

Local therapy:
corticosteroids, zinc oxide creams, and diluted
antiseptics in case of exudative areas.

treated with tacrolimus ointment 0.1% twice a
day.

Vasculitic Ulcers

Principles of Therapy

Compression therapy with bandage or elastic stockings is advisable, when the macrocirculatory conditions allow it.

Vasculitic Ulcers

Principles of Therapy

- surgical debridement must be performed with great attention in active phase of the vasculitis, due to the risk of “pathergy phenomenon” that usually consists in the formation of severe necrotic or undermined lesions.

Victoria K. Shanmugam, Divya Angra, Hamza Rahimi, Sean McNish, Vasculitic and autoimmune wounds
Journal of Vascular Surgery: Venous and Lymphatic Disorders,
Volume 5, Number 2, March 2017

Patients with autoimmune disease have a significantly high rate of skin graft failure (50% compared to 97% in patients without autoimmune disease P .0002)

Victoria K. Shanmugam, Divya Angra, Hamza Rahimi, Sean McNish, Vasculitic and autoimmune wounds
Journal of Vascular Surgery: Venous and Lymphatic Disorders,
Volume 5, Number 2, March 2017

RA-associated leg ulcers

Surgical revascularization

The overall 1-year rates of amputation-free survival and freedom from reintervention were 89% and 91%



Obara H, Matsubara K, Fujimura N, Sekimoto Y, Kitagawa Y. Preliminary report of endovascular treatment for critical limb ischemia patients with connective tissue disease: cases series and review of the literature. *Int J Angiol* 2015;24:137-42.

RA-associated leg ulcers

Prior use of steroids or immunosuppressive drugs in the 100 days before surgery was not a risk factor for postoperative wound dehiscence

If limb vascularization has been adequately addressed, we strongly recommend referral to a rheumatologist

Vasculitic Ulcers

Principles of Therapy

Autologous epidermal cells
Platelet-derived Growth Factors
Non cultured Autologous Cell Suspension

. PRP contains a concentration of platelets , fibrin and high concentrations of growth factors, PRP is known to promote wound healing



Maria Trapasso,
Regenerative Surgery for the Definitive Repair of a Vasculitic Nonhealing Ulcer Using
Platelet-derived Growth Factors and Noncultured Autologous Cell Suspension.
American Society of Plastic Surgeons. PRS GO • 2013

Yotsu RR, Hagiwara S, Okochi H, Tamaki T
Case series of patients with chronic foot ulcers treated with autologous platelet-
rich plasma. J Dermatol. 2015 Mar;42(3):288-95

Vasculitic Ulcers

Principles of Therapy

Intravenous treatment with **iloprost** can be useful in non healing vasculitic ulcers.

Massimo Papi, MD, Claudia Papi. Vasculitic Ulcers
The International Journal of Lower Extremity Wounds
2016, Vol. 15(1) 6–16

Multicentre studies are needed to further define appropriate & more-specific treatment of cutaneous VAS and provide a high level of evidence.

Marzia Capronia and Alice Verdellib
An update on the nomenclature for
cutaneous vasculitis
Curr Opin Rheumatol 2019, 31:46–52



از توجه شما متشکرم.