Vasculitis

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Disclosures

None

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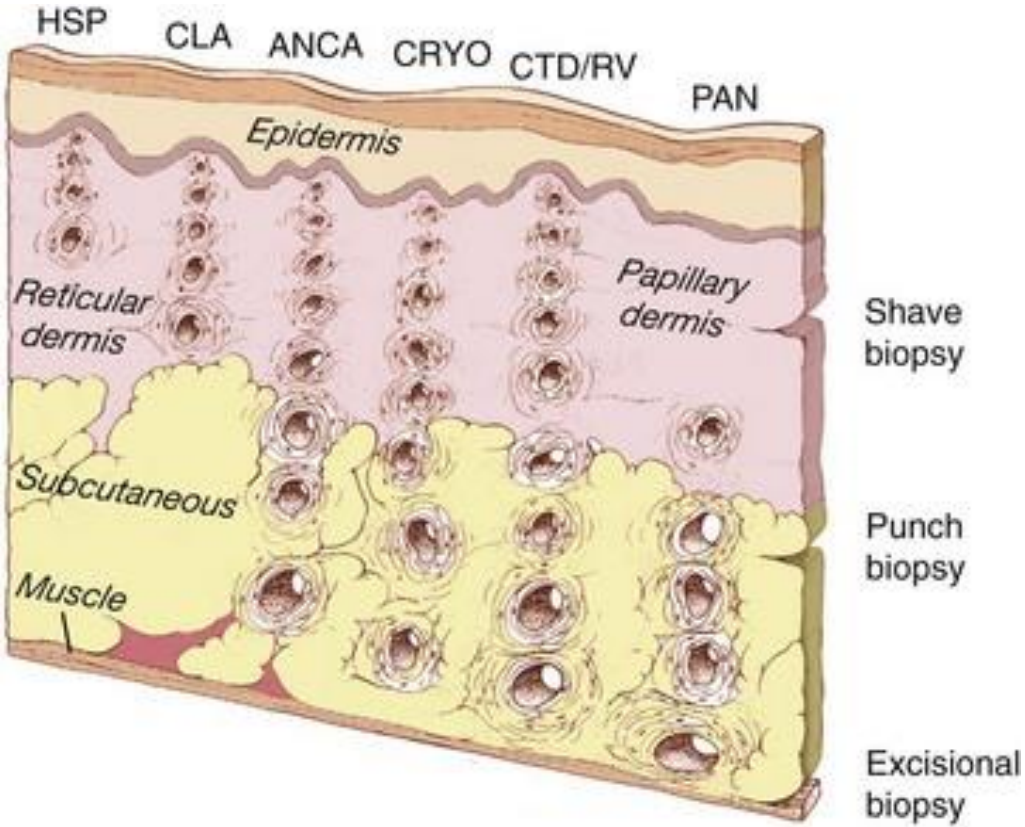

The location and size of blood vessels involved in various types of cutaneous vasculitis, illustrates the types of blood vessels affected by several forms of IC-mediated disease.

A blood vessel's size correlates closely with its depth in the skin layers: The larger the vessel, the deeper its location.

Although telltale signs of vasculitis may be evident on inspection of the skin's surface, the epidermis is avascular.

Therefore **the pathologic findings in cutaneous vasculitides lie within the dermis and subcutaneous tissues.**

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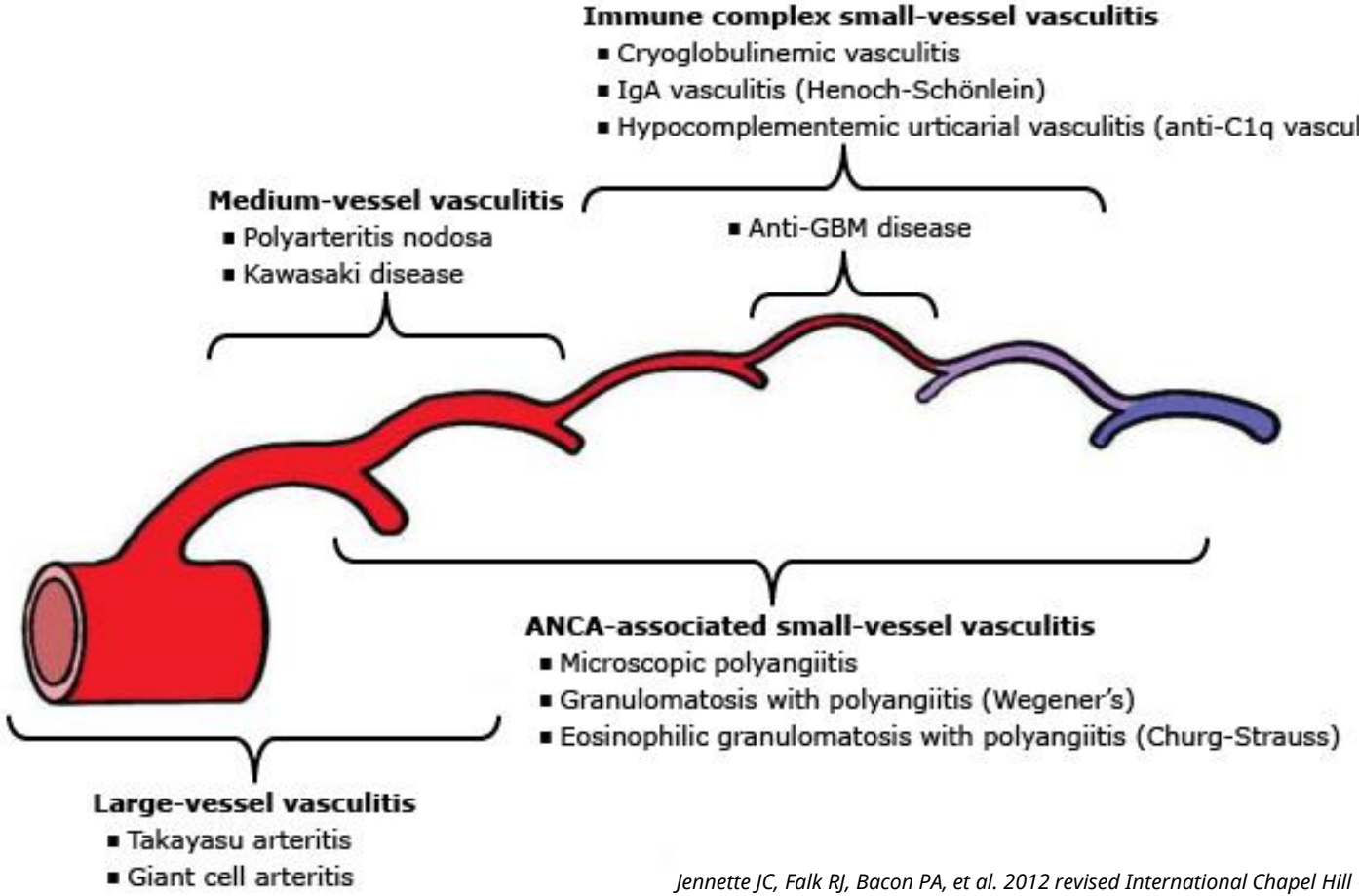
https://musculoskeletalkey.com/immune-complex-mediated-small-vessel-vasculitis/



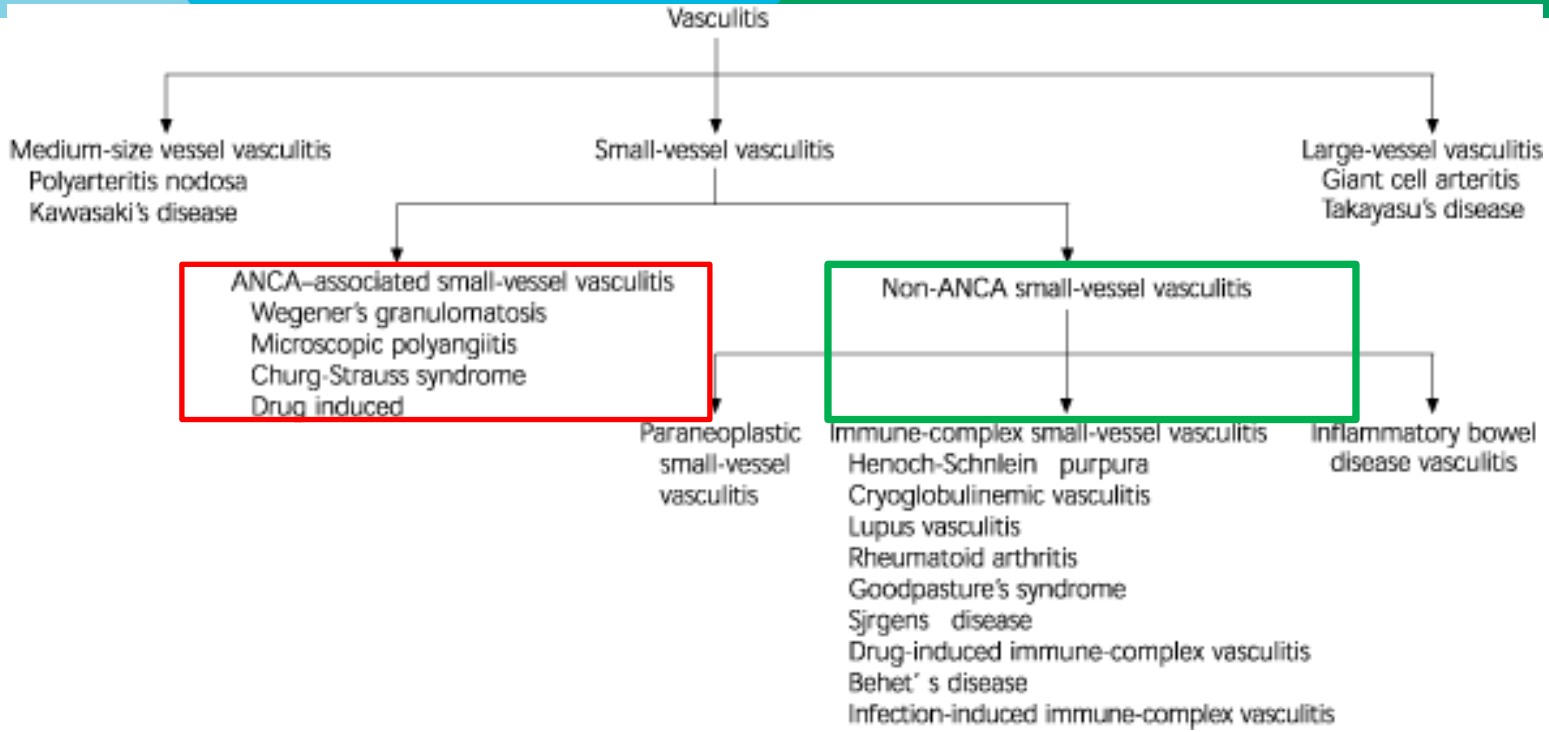
Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013; 65:1. Reproduced with permission from John Wiley & Sons, Inc. Copyright © 2013 by the American College of Rheumatology.

Table 4. Classification of Vasculitis.*

Type of Vasculitis	Size of Vessels Affected	Most Common Site of Involvement	Results of Test for ANCA	Other Features or Associated Conditions
Large-vessel vasculitis				
Giant-cell (temporal) arteritis	M, L	Aorta, temporal arteries	Negative	Age >50 yr, polymyalgia rheumatica
Takayasu's arteritis	M, L	Aorta and arch vessels	Negative	Age <50 yr
Medium-sized–vessel vasculitis				
Polyarteritis nodosa	M	Visceral arteries	Negative	Idiopathic, hepatitis B
Kawasaki's disease	M	Coronary arteries	Negative	Age <5 yr
Pauci-immune small-vessel vasculitis				
Wegener's granulomatosis	S, M	Lungs, kidneys	Positive	Granulomatous inflammation
Churg–Strauss syndrome	S, M	Lungs	Positive	Asthma, eosinophilia
Microscopic polyangiitis	S, M	Kidneys	Positive	
Immune-complex small-vessel vasculitis				
Henoch–Schönlein purpura	S, M	Skin, musculoskeletal	Negative	IgA immune complexes
Cryoglobulinemic vasculitis	S, M	Skin, musculoskeletal	Negative	Circulating cryoglobulins
Drug-induced vasculitis	S, M	Skin	Negative	Occasionally systemic

* M denotes medium-sized vessels, which are small-to-medium-sized arteries; L large vessels, which are the aorta and proximal branches to the head and extremities; S small vessels, which can be arterioles, capillaries, and venules; and ANCA antineutrophil cytoplasmic antibodies.

July 10, 2003N Engl J Med 2003; 349:160-169
DOI: 10.1056/NEJMra022694



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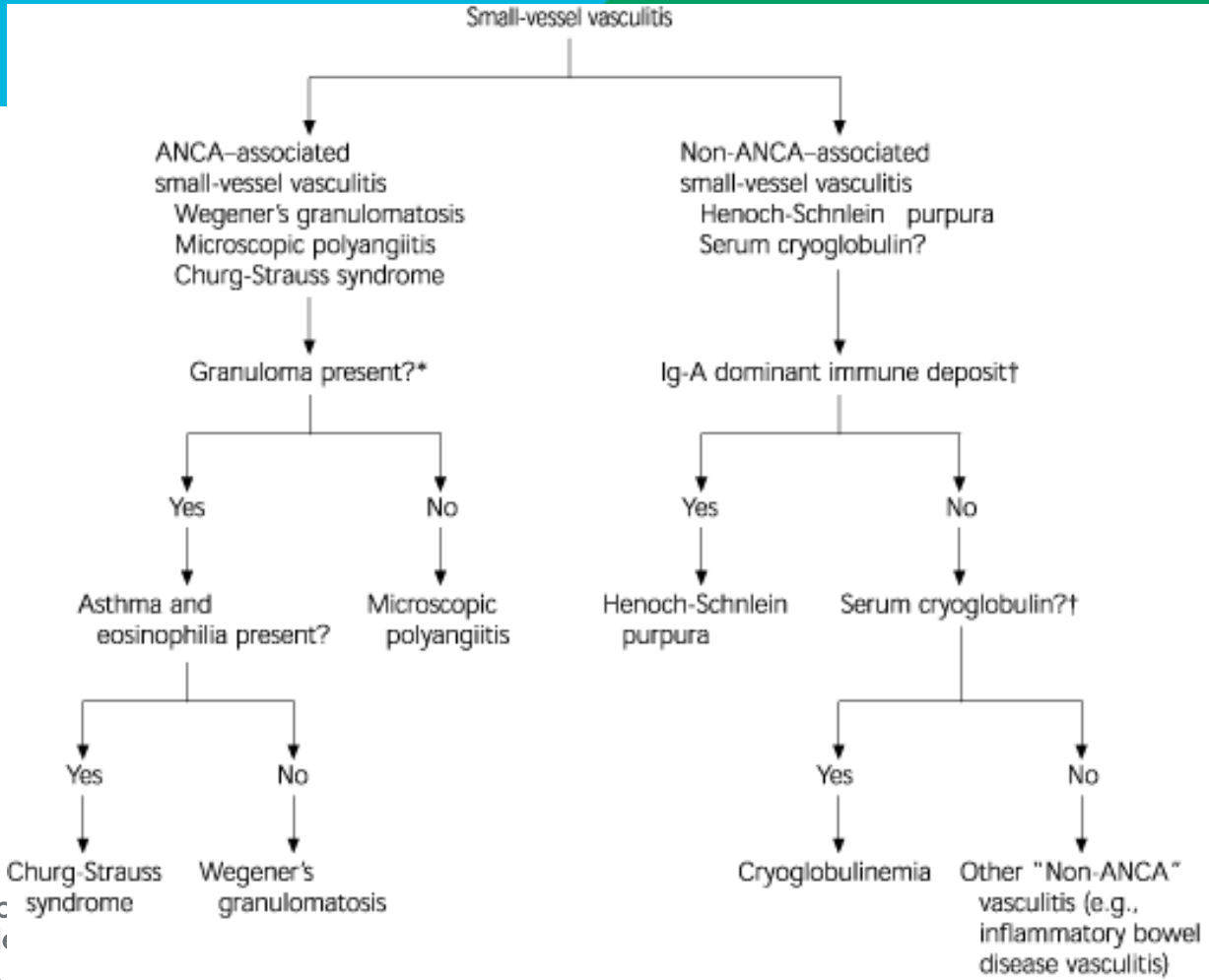

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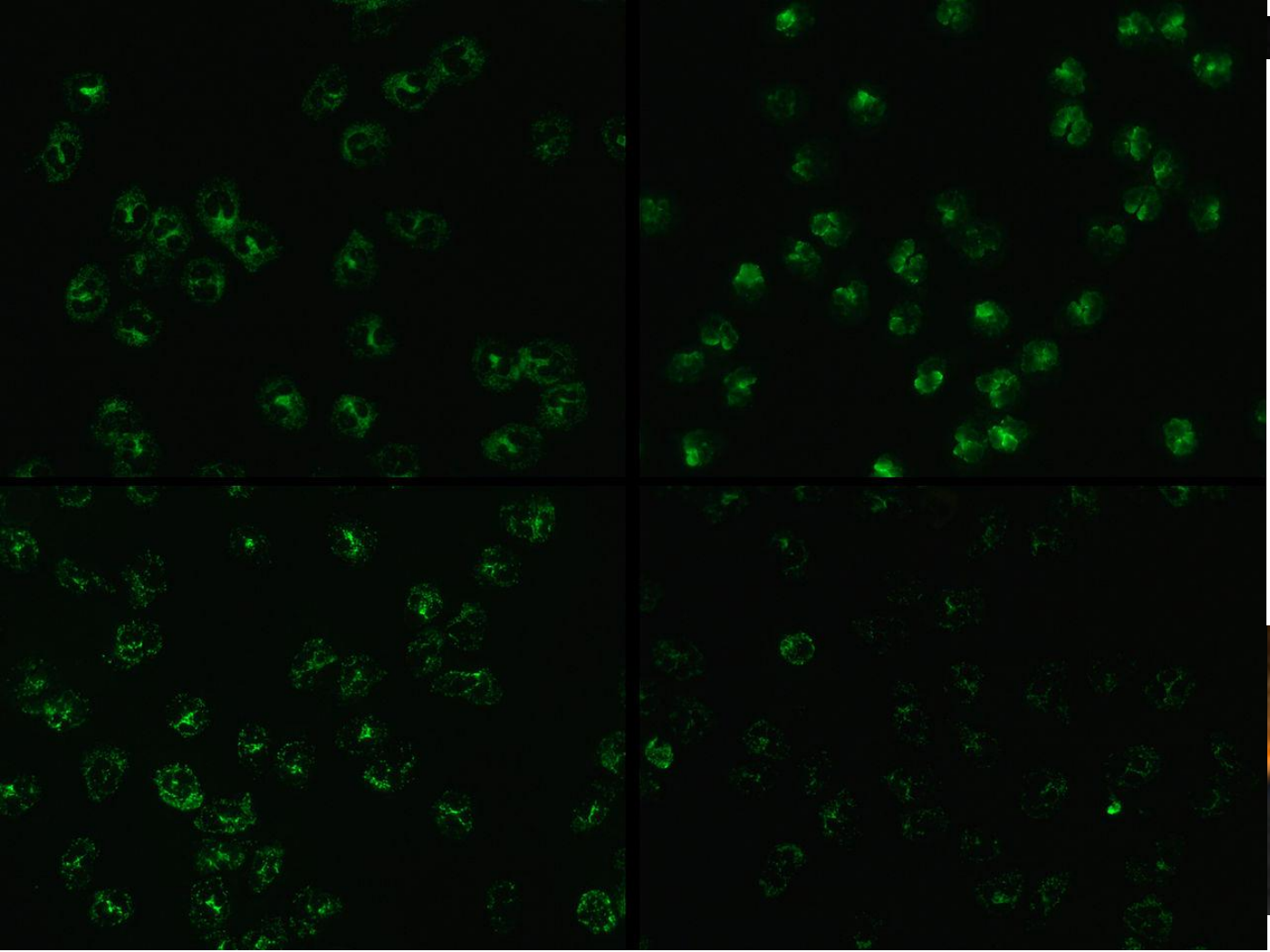

Immunofluorescence staining pattern of ANCA:

Top left - PR3 antibodies on ethanol-fixed neutrophils (c-ANCA pattern).

Bottom left - PR3 antibodies on formalin-fixed neutrophils(c-ANCA pattern).

Top right - MPO antibodies on ethanol-fixed neutrophils (p-ANCA pattern).

Bottom right - MPO antibodies on formalin-fixed neutrophils (c-ANCA pattern).

Table 2. Vessel Involvement and ANCA Association With Myeloperoxidase (MPO) or Proteinase 3 (PR3) in Small-Vessel Vasculitides Compared With a Medium-Vessel Vasculitis.[a]

	EGPA	MPA	GPA	PAN
Vessel size	Small	Small	Small	Medium
ANCA status	Positive (70%)	Positive (80%)	Positive (90%)	Negative
ANCA type (by ELISA)	MPO	MPO	PR3	N/A
Neutrophil staining pattern	Perinuclear	Perinuclear	Cytoplasmic	N/A

[a] This table is based on information in references 1, 3, and 10 in the citation list.

Abbreviations: EGPA, eosinophilic granulomatosis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa.

c-ANCA (atypical) is present
- 80% of cystic
- IBD
- RA

p-ANCA is present:
- IBD
- RA
- Drug-induced vasculitis
- Autoimmune liver disease
- Parasitic infections

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Case 1

A 42-year-old woman presents with shortness of breath, fatigue, mild fevers, and a 12-lb weight loss over the past 8 weeks.

Lost sensation in her right arm approximately 2 weeks ago as well as in her left arm approximately 2 months ago

PMHx: asthma, atopic dermatitis and eczema

Exam: notable for wheezing

Labs: Hemoglobin level of 14 g/dL

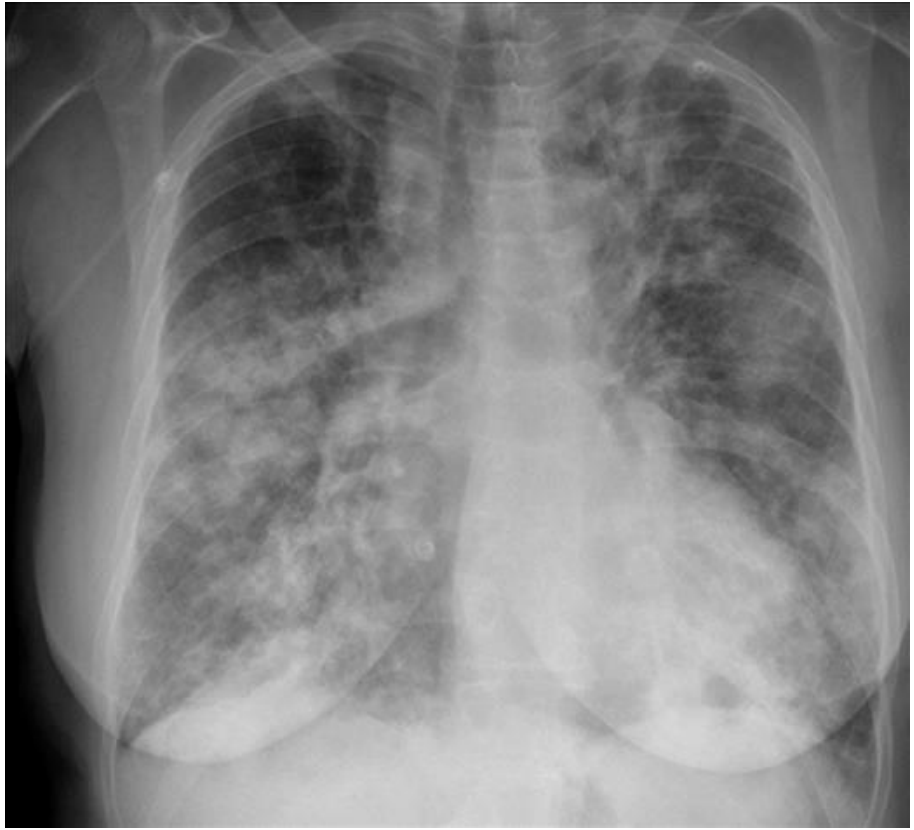
White blood cell count of 98,000 cells/µL, with a differential of 28% neutrophils, 7% lymphocytes, **24% eosinophils**, and 1% basophils

BUN of 12 mg/dL; **creatinine level of 1.4**

ESR is 65, C-reactive protein is 3.2

P-ANCA staining is positive

Urinalysis shows numerous white and red blood cells. Urine cultures are negative.



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Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Rare

The age of onset varies from 15 to 70 years and is rare in men

Three phases:

1. Allergic rhinitis and asthma
2. Eosinophilic infiltrative disease resembling pneumonia
3. Systemic small vessel vasculitis with granulomatous inflammation

Coronary arteritis and myocarditis are the principal causes of morbidity and mortality

Often ANCA negative

Tx: high dosed steroids

- Asthma (wheezing, expiratory rhonchi)
- Eosinophilia of more than 10% in peripheral blood
- Paranasal sinusitis
- Pulmonary infiltrates (may be transient)
- Histological proof of vasculitis with extravascular eosinophils
- Mononeuritis multiplex or polyneuropathy

4 or more of the above to meet criteria

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ORIGINAL ARTICLE

Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

M.E. Wechsler, P. Akuthota, D. Jayne, P. Khoury, A. Klion, C.A. Langford, P.A. Merkel, F. Moosig, U. Specks, M.C. Cid, R. Luqmani, J. Brown, S. Mallett, R. Philipson, S.W. Yancey, J. Steinfeld, P.F. Weller, and G.J. Gleich, for the EGPA Mepolizumab Study Team*

May 18, 2017
N Engl J Med 2017; 376:1921-1932
DOI: 10.1056/NEJMoa1702079

ABSTRACT

BACKGROUND

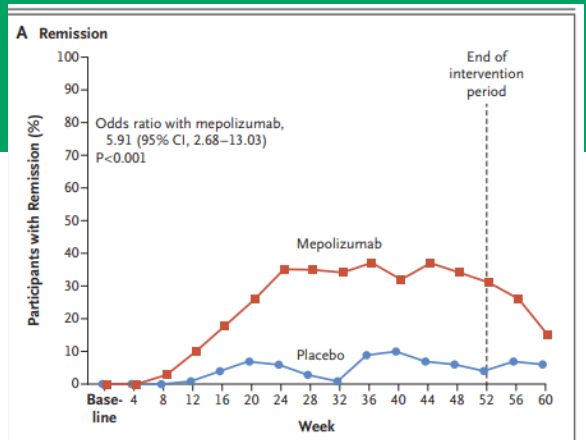
Eosinophilic granulomatosis with polyangiitis is an eosinophilic vasculitis. Mepolizumab, an anti–interleukin-5 monoclonal antibody, reduces blood eosinophil counts and may have value in the treatment of eosinophilic granulomatosis with polyangiitis.

METHODS

In this multicenter, double-blind, parallel-group, phase 3 trial, we randomly assigned participants with relapsing or refractory eosinophilic granulomatosis with polyangiitis who had received treatment for at least 4 weeks and were taking a stable prednisolone or prednisone dose to receive 300 mg of mepolizumab or placebo, administered subcutaneously every 4 weeks, plus standard care, for 52 weeks. The two primary end points were the accrued weeks of remission over a 52-week period, according to categorical quantification, and the proportion of participants in remission at both week 36 and week 48. Secondary end points included the time to first relapse and the average daily glucocorticoid dose (during weeks 48 through 52). The annualized relapse rate and safety were assessed.

RESULTS

A total of 136 participants underwent randomization, with 68 participants assigned



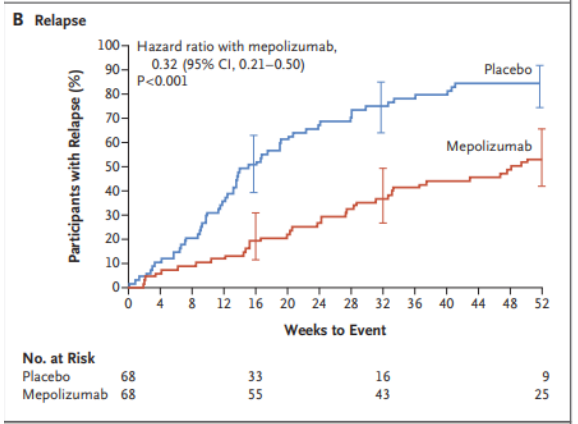


Figure 2. Remission and First Relapse of Eosinophilic Granulomatosis with Polyangiitis in the Intention-to-Treat Population.

Remission was defined as a Birmingham Vasculitis Activity Score of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity) and receipt of a prednisolone or prednisone dose of 4.0 mg or less per day (Panel A). Data on relapse were censored at week 52 per the statistical analysis plan (Panel B). I bars at weeks 16, 32, and 52 indicate 95% confidence intervals.

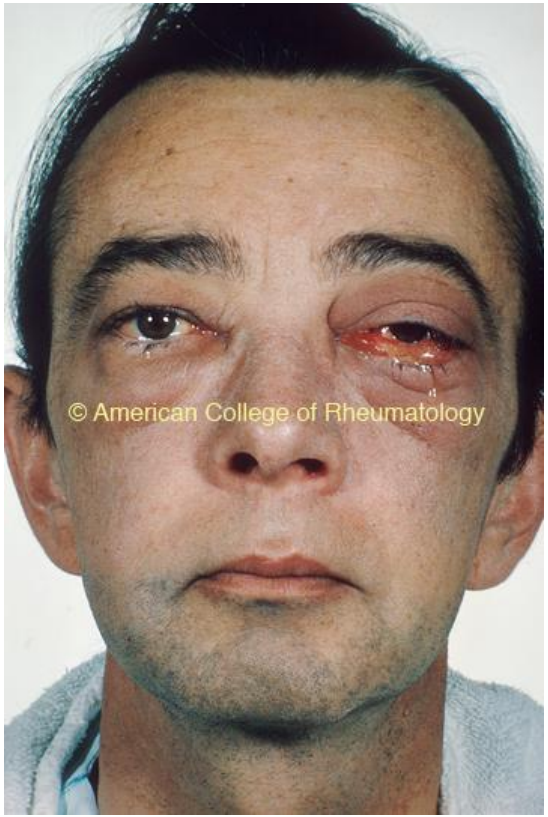
Case 2

67 yo M presents with fevers, fatigue and eye irritation

PMHx: chronic sinusitis, hypertension, hearing loss

Labs:
Hemoglobin 13, platelets of 497
Cr of 2.2, UA with 2+ blood, 2+ protein
ESR: 52, CRP: 5
C-ANCA/PR3 positive

Kidney Bx: extensive glomerular crescent formation



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Granulomatosis with Polyangiitis (Wegener Granulomatosis)

The ACR criteria for GPA include the following:

Nasal or oral inflammation (painful or painless oral ulcers, or purulent or bloody nasal discharge)

Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities

Abnormal urinary sediment (microscopic hematuria with or without red cell casts)

Granulomatous inflammation on biopsy of an artery or perivascular area

The presence of two or more of these four criteria yielded a sensitivity of 88 percent and a specificity of 92 percent

MPA is distinguished from GPA and EGPA by the absence of granuloma formation and the presence of a necrotizing vasculitis

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Granulomatosis with Polyangiitis (Wegener Granulomatosis)

Ophthalmic manifestations
- Conjunctivitis
- Episcleritis
- Uveitis
- Optic nerve vasculitis
- Retinal artery occlusion
- Nasolacrimal duct occlusion
- Proptosis

Ear, nose, and throat manifestations: occurring in 67% of cases
- Epistaxis (11%)
- Rhinitis (22%)
- Collapse of nasal support, resulting in saddle nose deformity (common)
- Serous otitis media and hearing loss
- So-called strawberry gingival hyperplasia
- Stridor, possibly leading to respiratory compromise, from tracheal or subglottic granulomatous masses

*Pulmonary: ca*n be asymptomatic, insidious in onset, or severe and fulminant:
- Pulmonary infiltrates (71%)
- Cough (34%)
- Hemoptysis (18%)
- Chest discomfort (8%)
- Dyspnea (7%)
- Diffuse alveolar hemorrhage due to alveolar capillaritis (5%-45%)
- Atelectasis, with dullness on percussion, decreased breath sounds, and crackles on auscultation

Cutaneous manifestations
- Palpable purpura or skin ulcers (45%)
- Petechiae, vesicles, pustules, hemorrhagic bullae
- livedo reticularis, digital necrosis,
- subungual splinter hemorrhages
- genital ulcers resembling squamous cell carcinoma have been reported

Musculoskeletal manifestations
- Myalgias
- Arthralgias, usually polyarticular and symmetrical, affecting small and medium joints
- Arthritis, typically affecting large joints, but rarely deforming

Renal manifestations

Crescentic necrotizing glomerulonephritis characterized by urinary sediment with more than 5 RBCs per HPF or erythrocyte casts
- Renal disease is present in 17% of patients at initial diagnosis and is usually asymptomatic
- Renal failure occurs in 11% at presentation

Nervous system manifestations: may occur in as many as 67% of patients, typically later in the disease course:
- Mononeuritis multiplex
- Sensorimotor polyneuropathy
- Cranial nerve palsies

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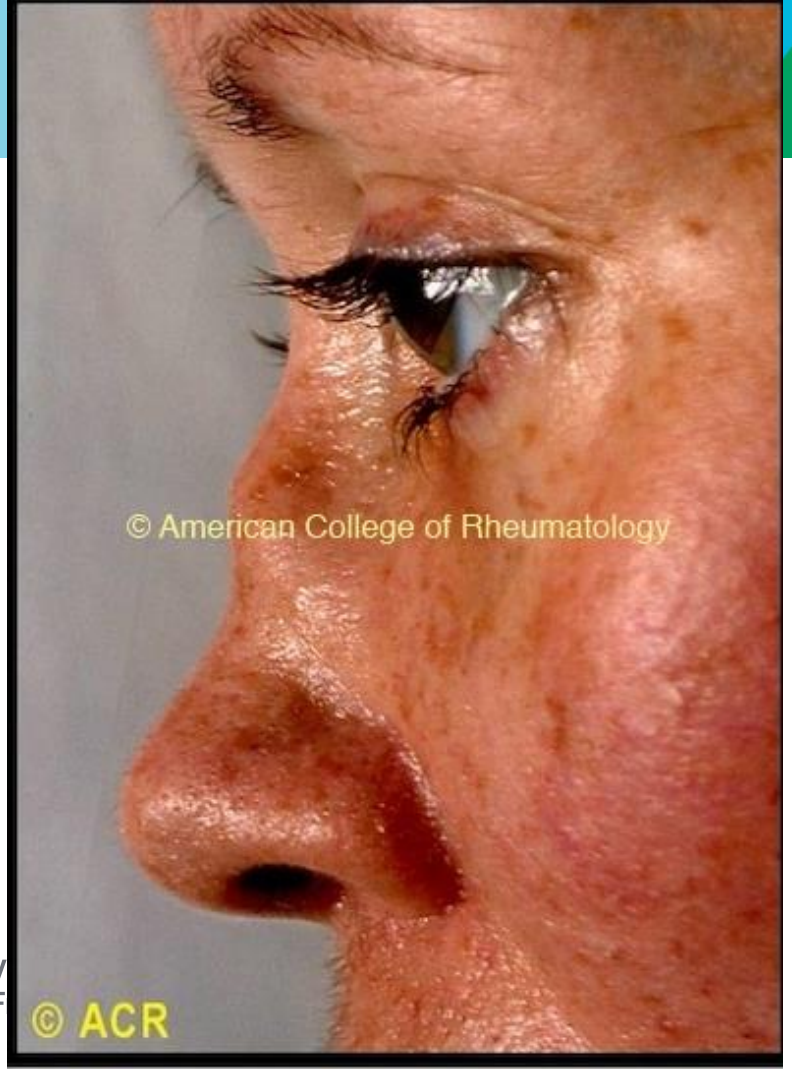
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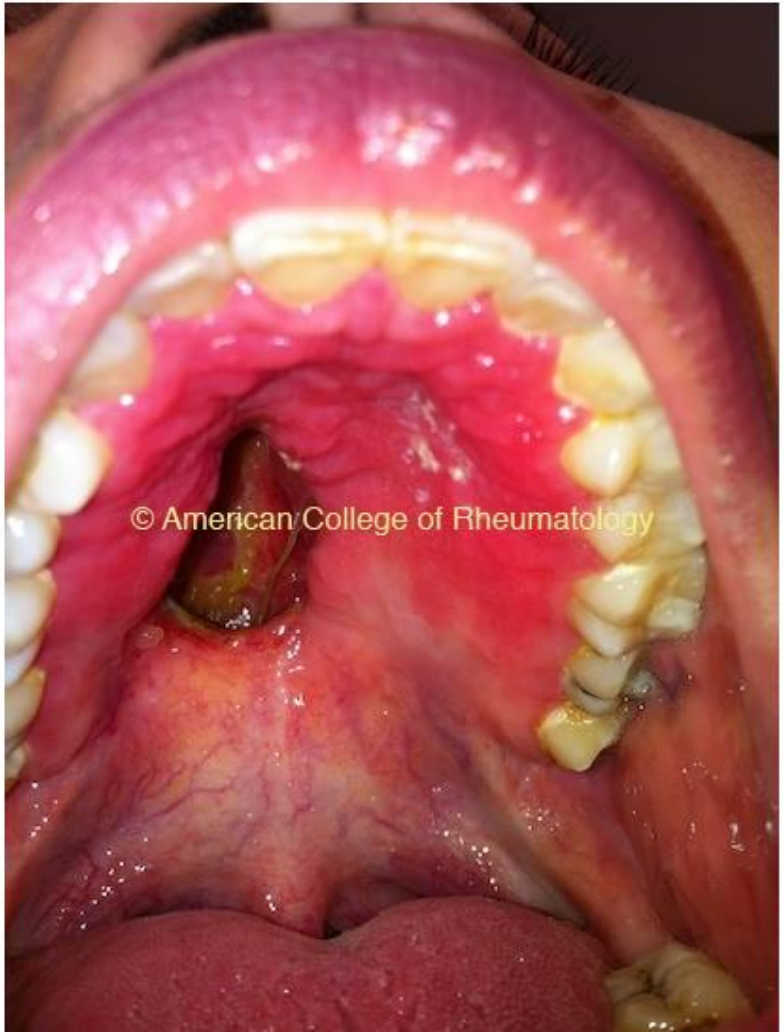
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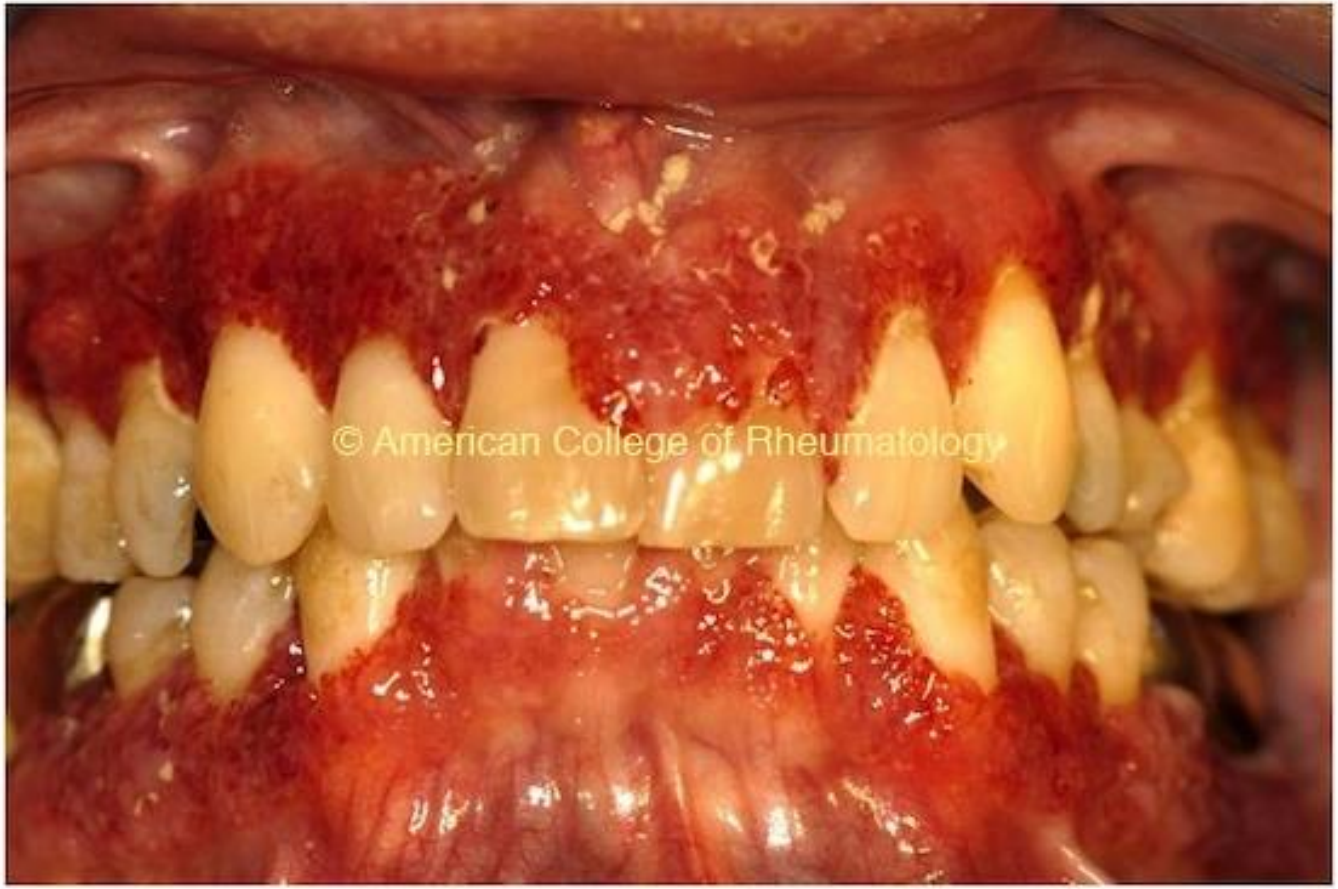

Wegener's Granulomatosis: Gingiva, Strawberry Gums

This variant of hyperplastic gingivitis can present as a part of Wegener's Granulomatosis. Note the swollen, erythematous gingiva involving the pre-molar regions. The granular appearance with yellow flecks has been likened to over-ripe strawberries. Histopathologic changes of gingival Wegener's include pseudoepitheliomatous hyperplasia, microabscesses, and multi-nucleated giant cells.

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RESEARCH SUMMARY

Avacopan for the Treatment of ANCA-Associated Vasculitis

Jayne DRW et al. DOI: 10.1056/NEJMoa2023386

CLINICAL PROBLEM

Patients with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis may have serious complications, decreased quality of life, and side effects from medications (e.g., glucocorticoids) used to treat the condition. Avacopan is an oral small-molecule C5a receptor antagonist that offers a potential treatment option for ANCA-associated vasculitis.

CLINICAL TRIAL

Design: A phase 3 international, double-blind, randomized, controlled trial compared oral avacopan with oral prednisone in patients with ANCA-associated vasculitis concurrently being treated with immunosuppressive drugs.

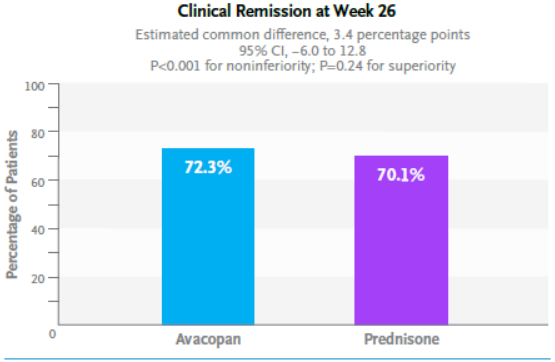
Intervention: 331 patients were assigned to receive either avacopan (30 mg twice daily) plus prednisone-matching placebo or prednisone (60 mg daily tapered to discontinuation by week 21) plus avacopan-matching placebo. All patients also received cyclophosphamide (followed by azathioprine) or rituximab. The two primary efficacy end points — clinical remission at week 26 and sustained remission at both week 26 and week 52 — were tested for noninferiority (noninferiority margin, 20 percentage points) and superiority.

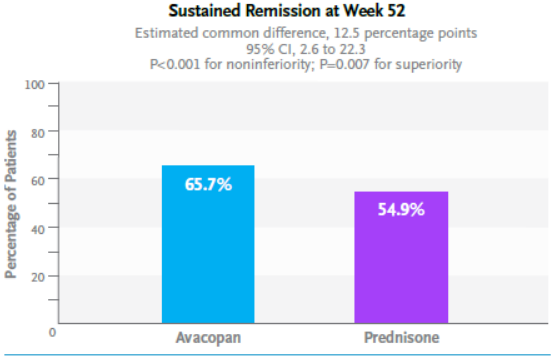
RESULTS

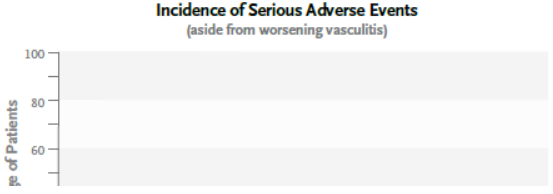
Efficacy: Avocapan was noninferior to prednisone with respect to clinical remission at week 26 and was both noninferior and superior to prednisone with respect to sustained remission at week 52.

Safety: The percentage of patients who had serious adverse events (excluding worsening vasculitis) was similar in the two groups.

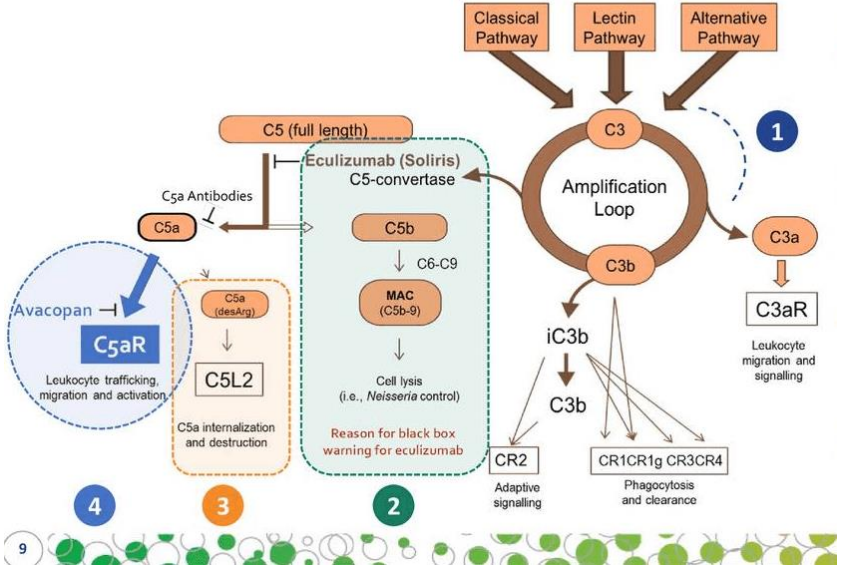
LIMITATIONS AND REMAINING QUESTIONS







Avacopan: Unique Orally Administere



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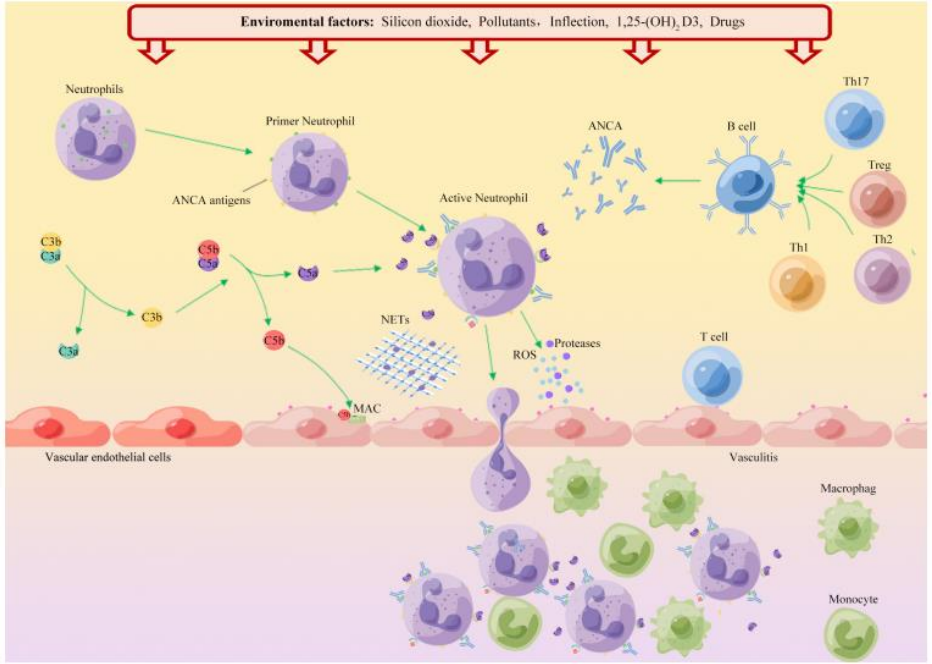

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Environmental factors influencing the risk of ANCA-associated vasculitis

Wen-Man Zhao, Zhi-Juan Wang, Rui Shi, Yu-Yu Zhu, Sen Zhang, Rui-Feng Wang and De-Guang Wang*

Department of Nephrology, The Second Hospital of Anhui Medical University, Hefei, China

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (A/
group of diseases characterized by inflammation and destruction of sn
medium-sized blood vessels. Clinical disease phenotypes include micr

- Continuous exposure to silica increases the risk of positive ANCA
- Incidence of AAV varies significantly with latitude (low Vit D)
- Microbial infection is considered to be an important risk factor for the development of AAV
- Intranasal staphylococcus aureus (S. aureus) infection is most closely associated with AAV
- Peak incidence during winter. AAV is prone to relapse during autumn, accompanied by increased titers of ANCA-related immune markers.

complement replacement pathways may exacerbate vascular inflammation.

LCV

Collagen-vascular disorders (10-15%)

- Urticarial Vasculitis
- SLE, RA, Sjogrens, Bechets related
- HSP
- Cryos

Paraproteinemas

Infections

- Strep
- HIV
- Bacterial endocarditis

Malignancies

- Hairy cell leukemia

IBD related

Idiopathic causes account for up to 50% of cases

Medication-induced: 10% to 20%

Antibiotics, especially beta-lactamases
Diuretics
Nonsteroidal anti-inflammatory drugs
MTX, SSZ, azathioprine, etanercept, cyclosporine, allopurinol, gold salts
Antithyroid agents
Anticonvulsants
Antiarrhythmics

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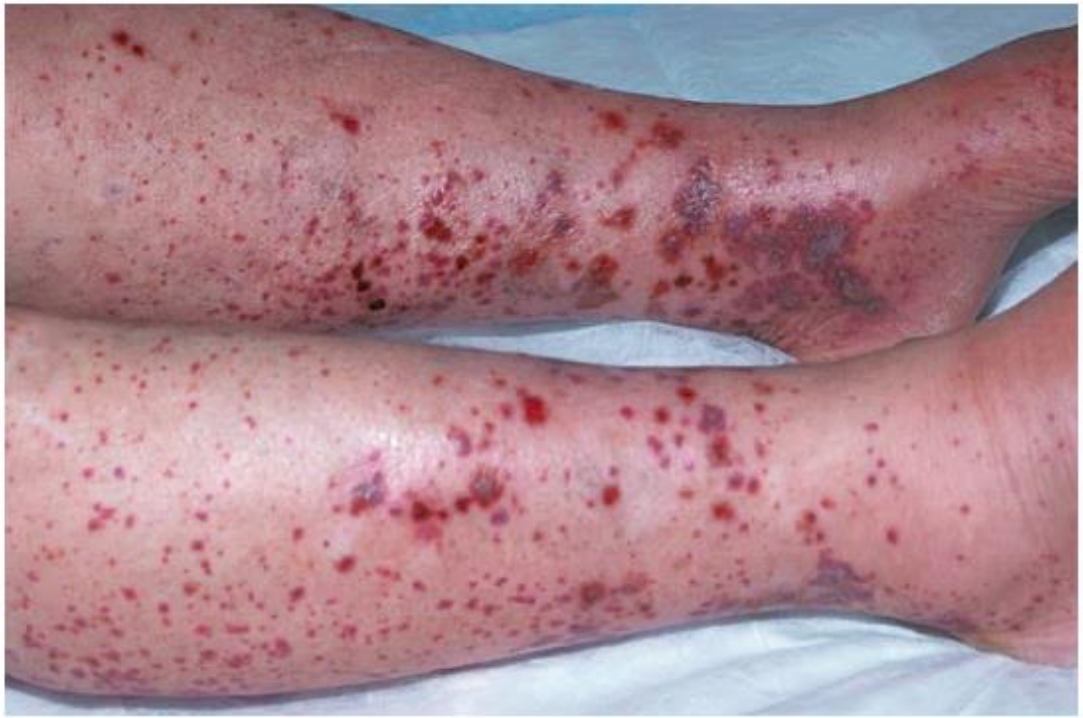
Case 3

50 yo M with hx of Hep C, diabetes, gout, hypertension presenting with LE rash x 2 weeks, joint pain, malaise

Meds: allopurinol, metformin, lisinopril

Skin Bx: “leukocytoclastic vasculitis”



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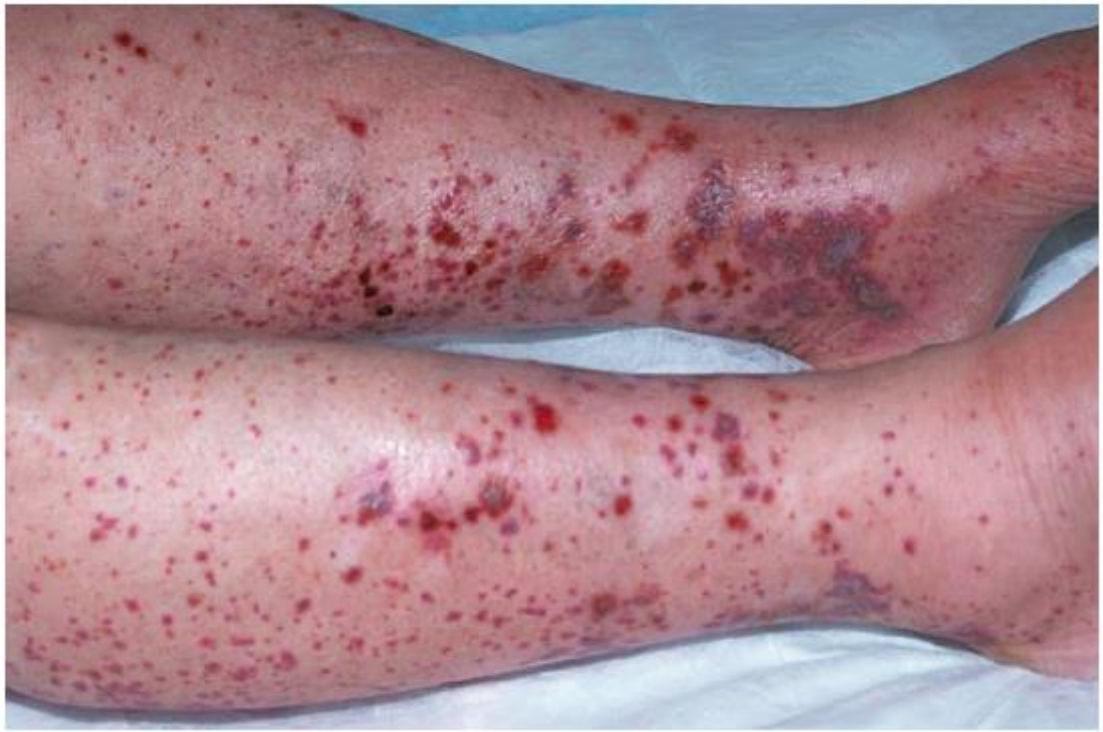
Work up?

CBC: wnl including differential
RF: positive
ANA: negative
C3: 152 (normal)
C4: 3 (low)
Cryos: in process

Hep B: negative
Hep C: reactive
HIV: negative
Blood cultures: negative



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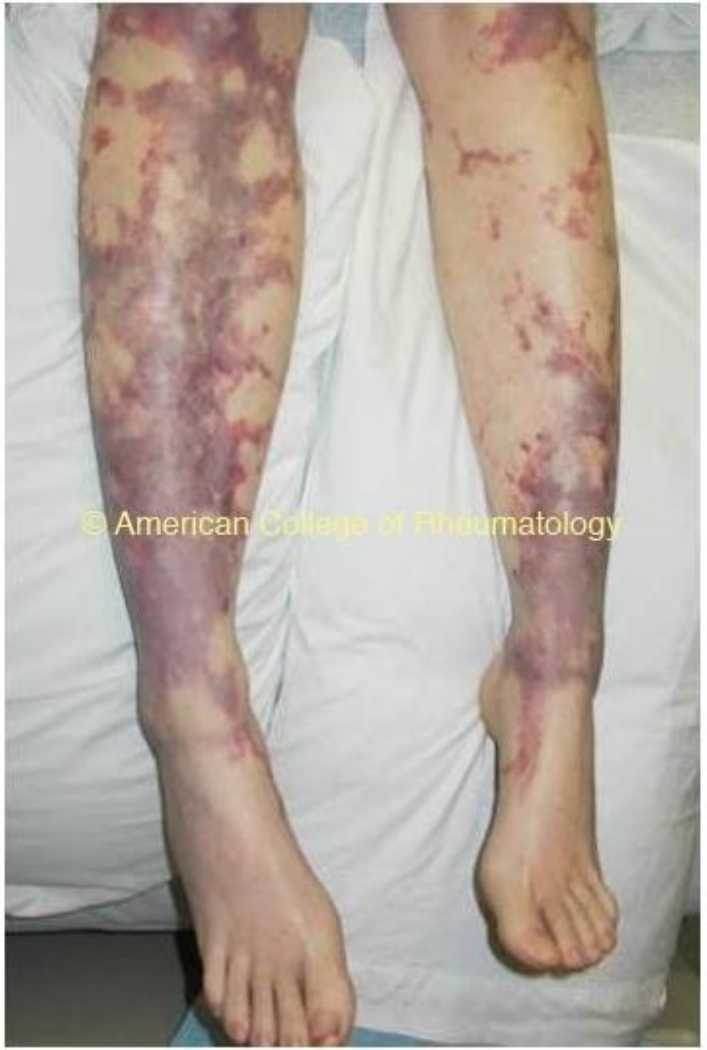
Day 0 7 centrifugatic

+4°C

Contrasting features of types of cryoglobulinemia

	Type I	Type II	Type III
Associated diseases	LPD >>>	HCV >>	HCV >>
	MGUS >	> CTD	CTD >>
	Idiopathic	> Idiopathic	Idiopathic
		> LPD > other infections	> Other infections
Symptoms and signs			
Purpura	+	+++	+++
Gangrene/acrocyanosis	+++	+ to ++	±
Athralgias >> arthritis	+	++	+++
Renal	+	++	+
Neurologic	+	++	++
Liver	±	++	+++

Type I: monoclonal immunoglobulin (Ig); Type II: mixed monoclonal Ig and polyclonal Ig; Type III: mixed polyclonal Ig.
Idiopathic: cases of symptomatic cryoglobulinemia that are not associated with a clear-cut CTD, LPD, or infection (also called 'essential' mixed cryoglobulinemia).
+ and > indicate relative increasing frequency of occurrence.
Prior to the discovery of HCV in 1989, the HCV-associated cases were considered idiopathic or "essential."



Cryoglobulinemia:
Ulcer, Dorsum of Foot

Note the ulcer within an area of retiform purpura. This lacy, non-blanching eruption is due to small-vessel vasculitis within the deeper dermis.

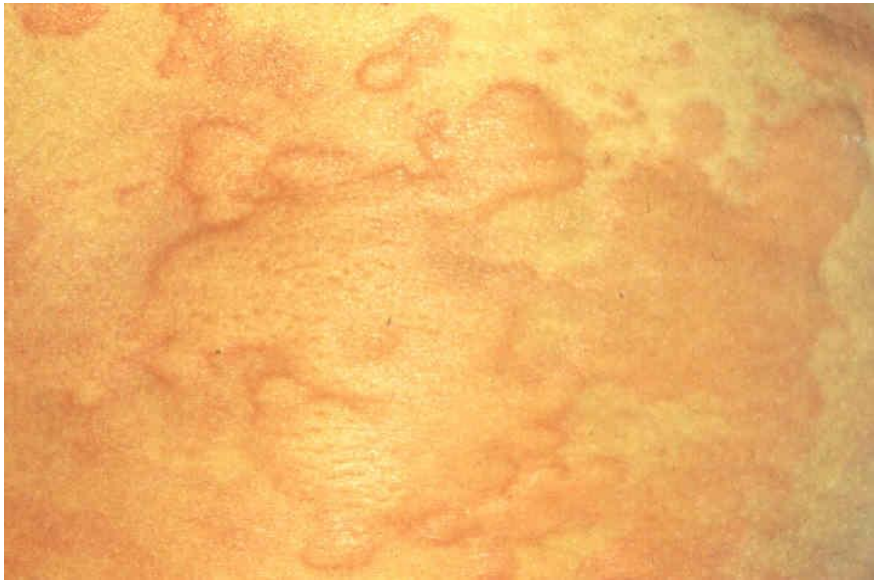
Hypocomplementemia Urticarial Vasculitis: Thigh

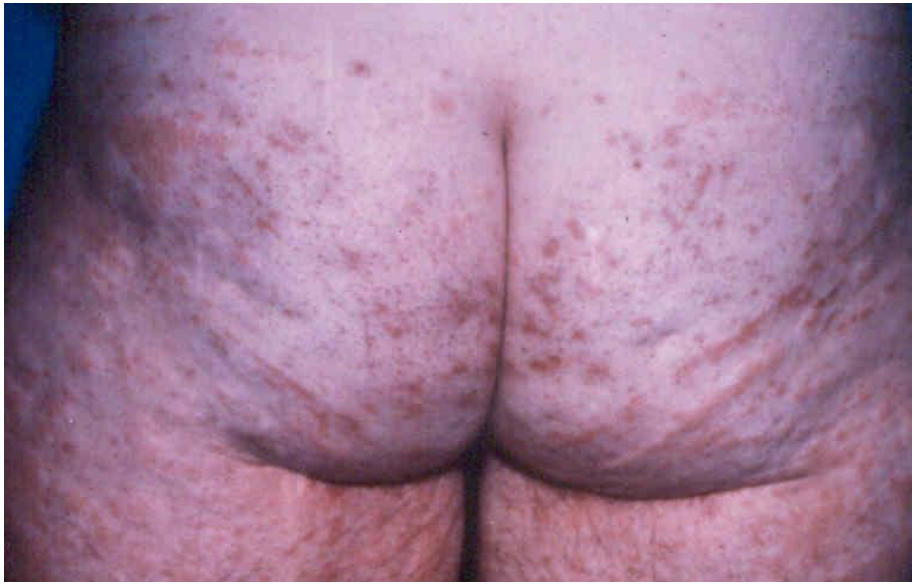
This 50 year-old woman presented with painful erythematous plaques resembling urticaria.

However, the lesions lasted for more than 48 hours and did not blanch completely with pressure, indicating cutaneous hemorrhage.

These two features help differentiate simple urticaria from urticarial vasculitis. She also had arthritis, episcleritis, and low serum concentrations of C1q, C3, and C4.

Leukocytoclastic Angiitis – Urticarial vasculitis





Low C1q, normal C1-inhibitor. 75% isolated; 25% lupus or SS
Musculoskeletal and ocular symptoms. Responds to HCQ
ACR 2014

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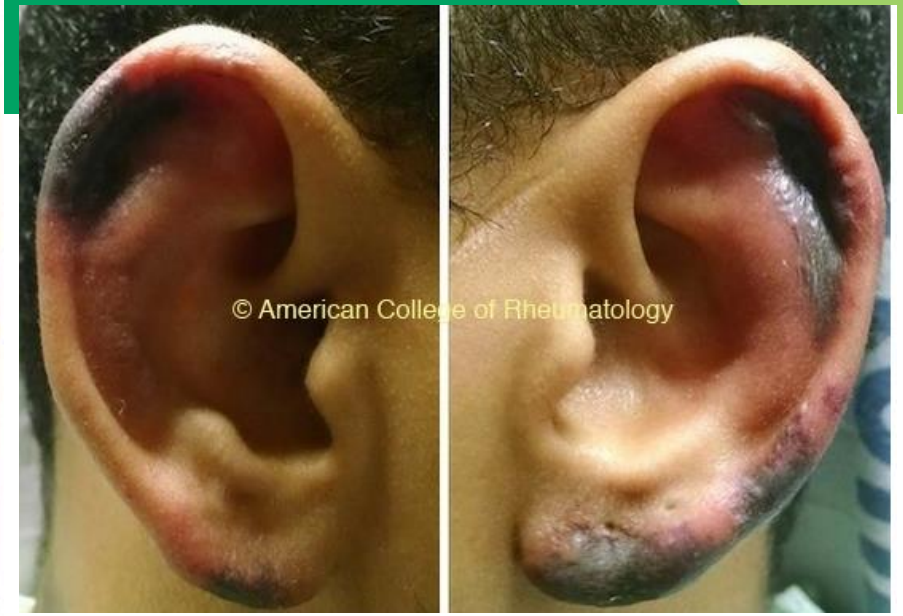

This 24 year-old man developed necrotizing lesions on his ears and tip of his nose along with a purpuric rash over his feet consistent with lavamisole-induced vasculitis . Laboratory testing showed a positive p-ANCA and cocaine in his urine toxicology screen. Levamisole is an antihelminthic frequently added to cocaine to increase volume and potentiate the psychotropic effects. Exposure to levamisole may induce leukopenia and a necrotizing vasculitis affecting the extremities, trunk, nasal tip, digits, cheeks and ear.

It is most frequently associated with p-ANCA antibodies, but c-ANCA antibodies also occur.

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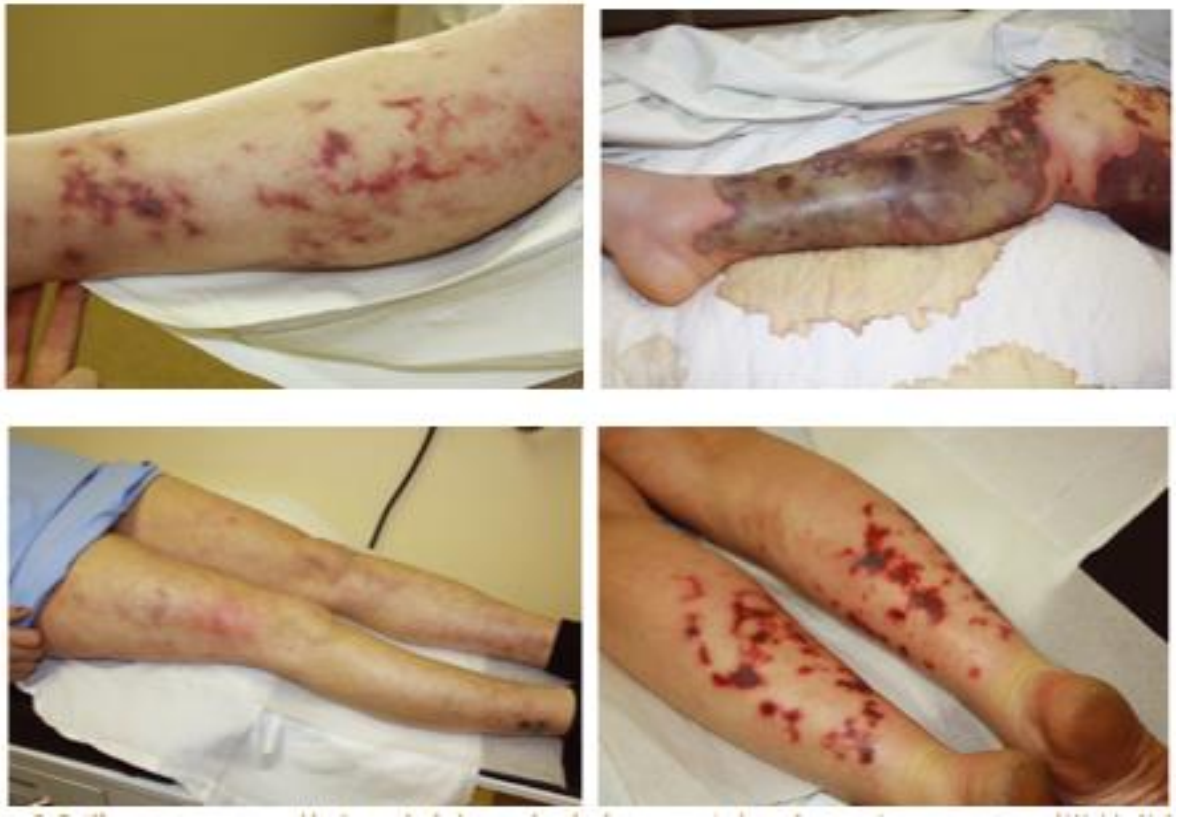
Cocaine- Levamisole Vasculitis: retiform purpura



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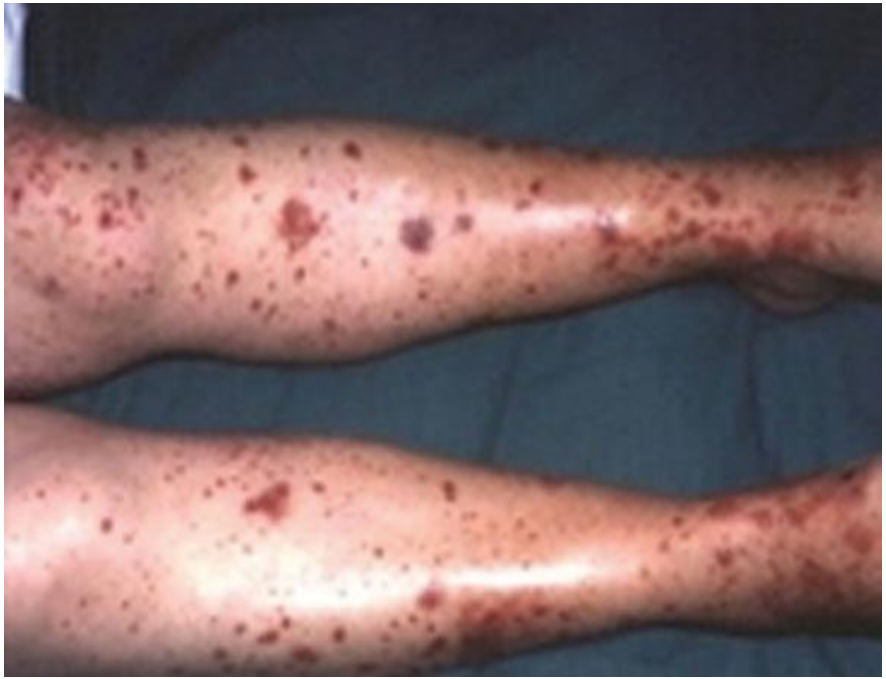
Case 4

24 yo M, smoker presenting with 1 week of rash on legs, diffuse joint pain and abdominal pain, bloody stools.

Labs:
ESR: 75, CRP: 30
Hgb: 10.5
ANCA: negative
C3/C4: wnl
RF: negative
Cryos: negative
Hep B/C: negative
ANA: negative
UA: 2+ protein, 2+ blood



Next step?

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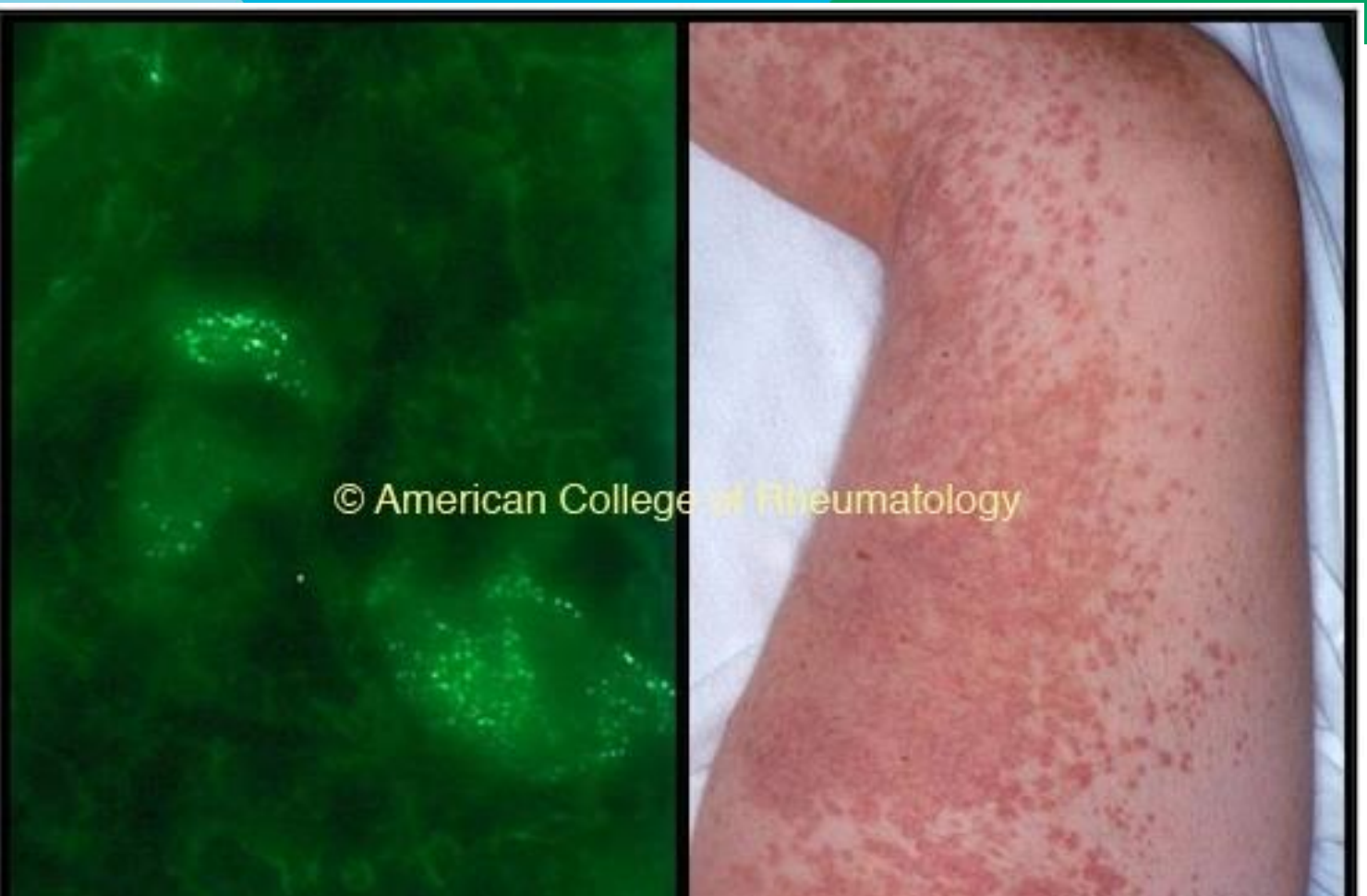

Diffuse erythematous palpable purpuric lesions are seen on the legs

The patient's skin biopsy shows immunoflourescent staining positive for IgA deposition in the walls of cutaneous vessels. Immunofluoresence for IgA, IgG, and C3 were negative.

A renal biopsy showed mesangial glomerulopathy by IgA deposits.

HSP

In adults (as opposed to children), renal involvement and the possibility of progression to kidney failure are greater.

The prevalence is greater in males

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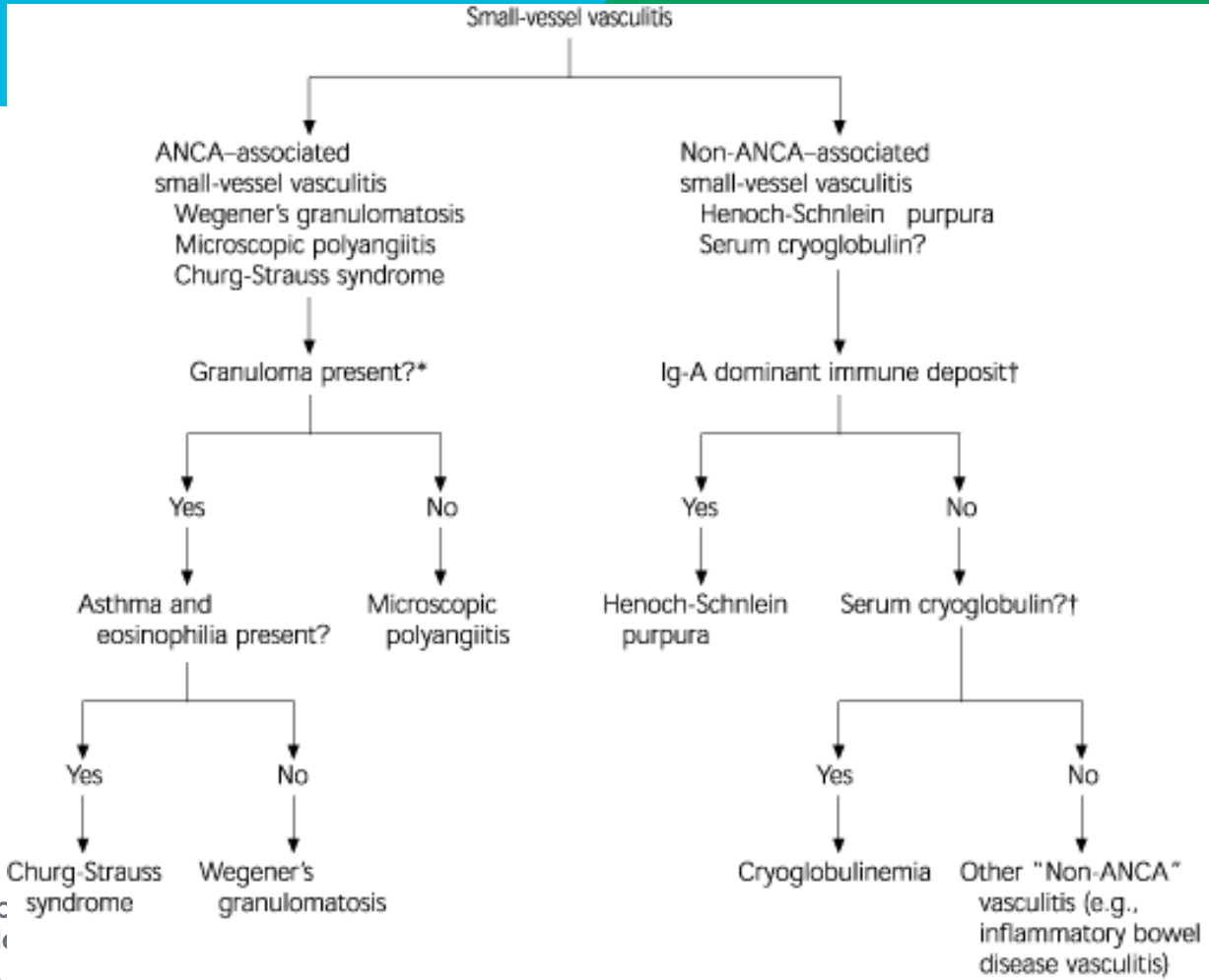

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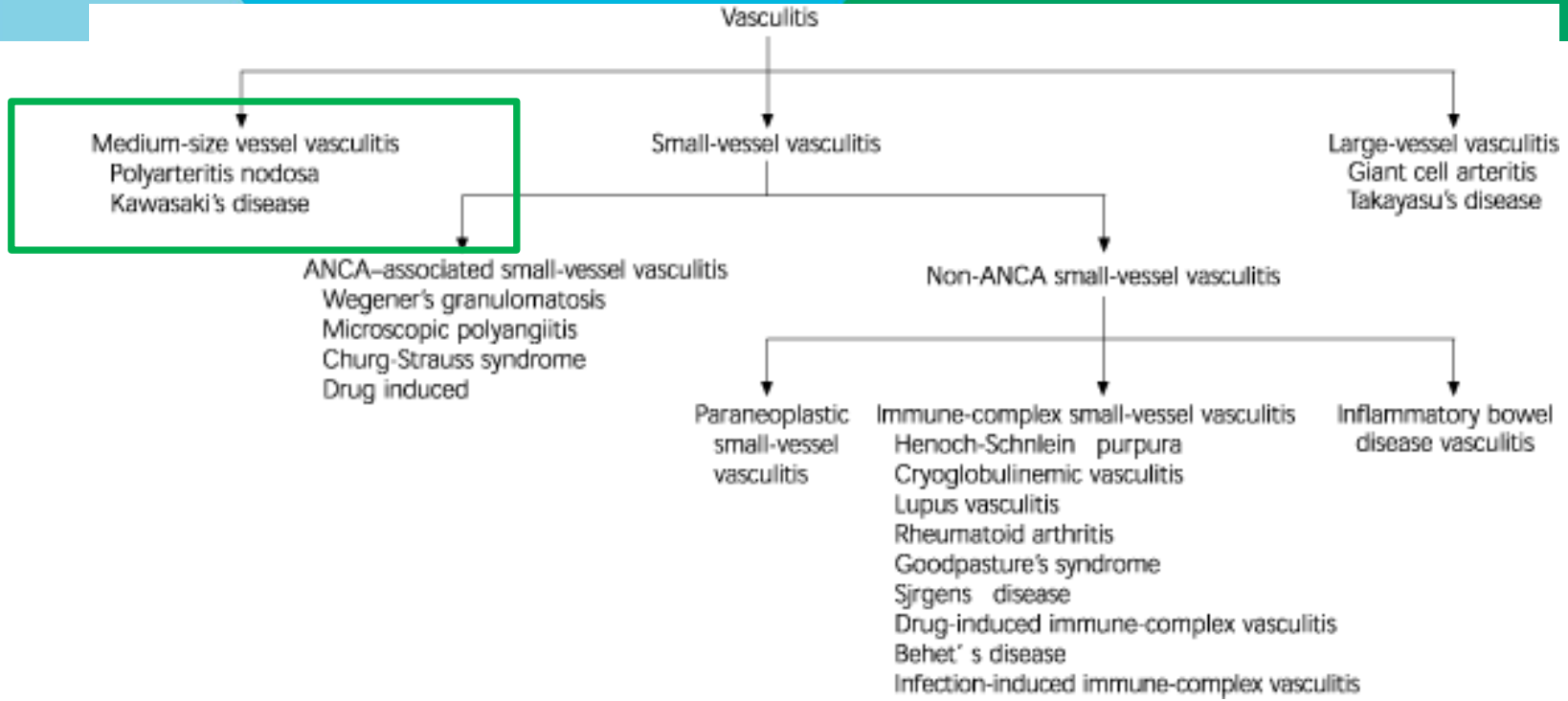

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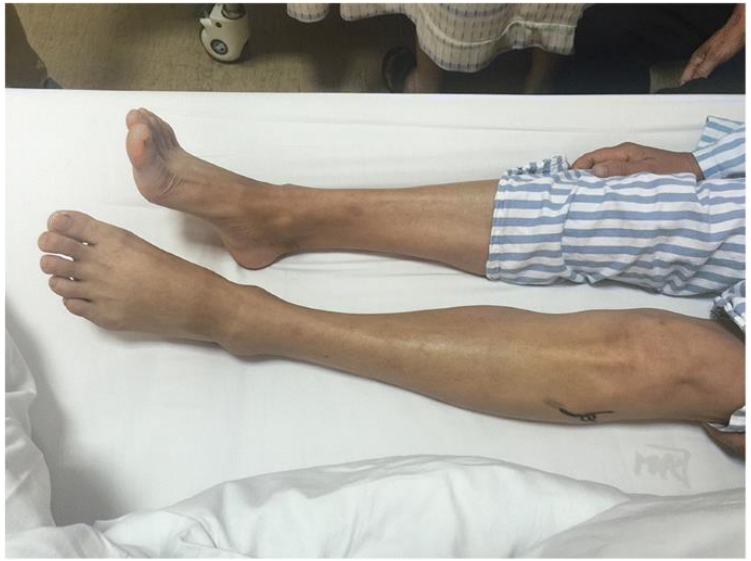
Case 5

55 yo M presenting with 2 weeks of fevers, severe flank pain, weight loss, rash and weakness in the left foot.



Labs:

ESR: 75, CRP: 30

Hgb: 10.5

ANCA: negative

C3/C4: wnl

RF: negative

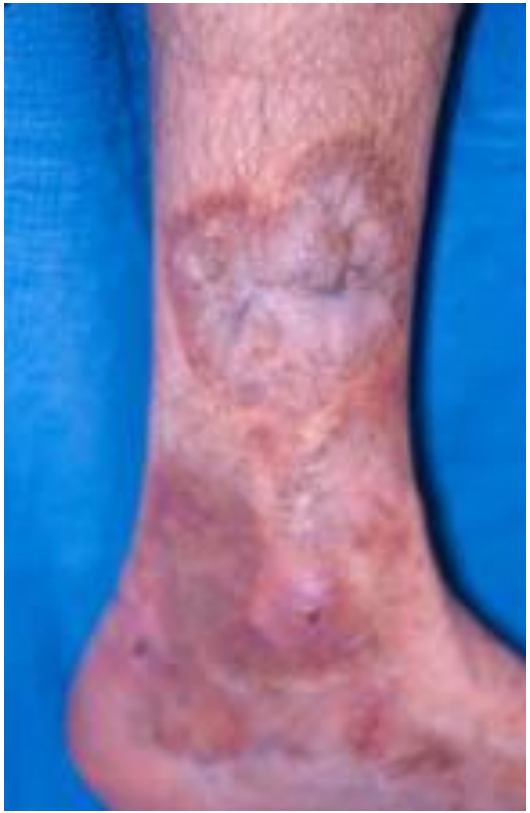
Cryos: negative

ANA: negative

UA: 2+ protein, 2+ blood

Hep B: HBsAg+, anti-Hbc +, IgM anti HepBc: negative, anti-HBs: negative

Hep C: negative



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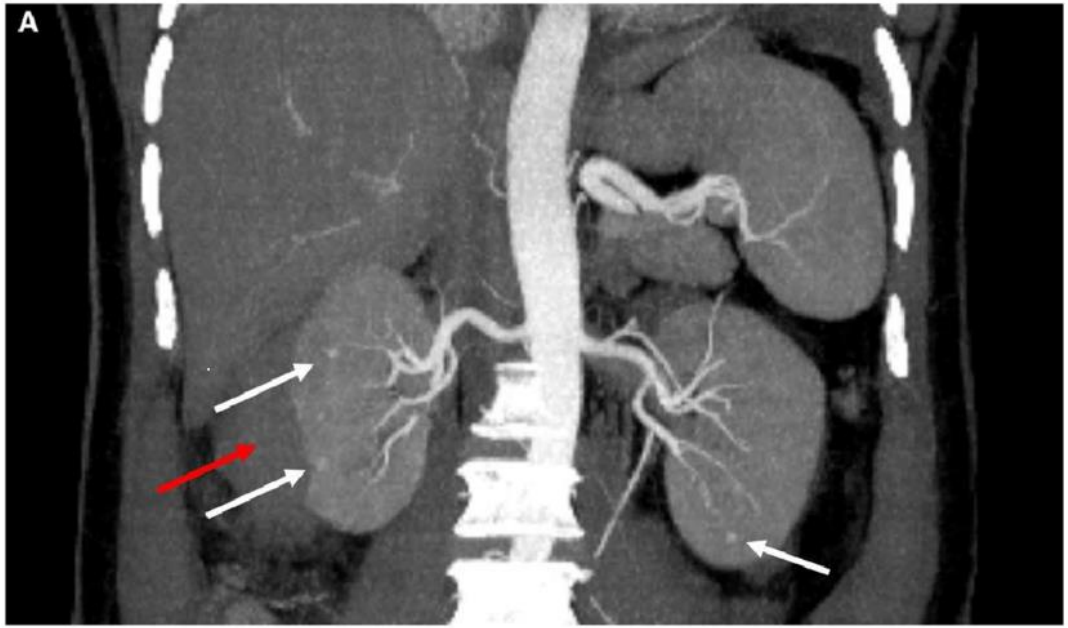

Computed tomography angiography (CTA) in polyarteritis nodosa. A, Coronal maximum intensity projection CTA demonstrating bilateral intrarenal microaneurysms (**white arrows**) and a large right subcapsular perinephric hematoma (red arrow).

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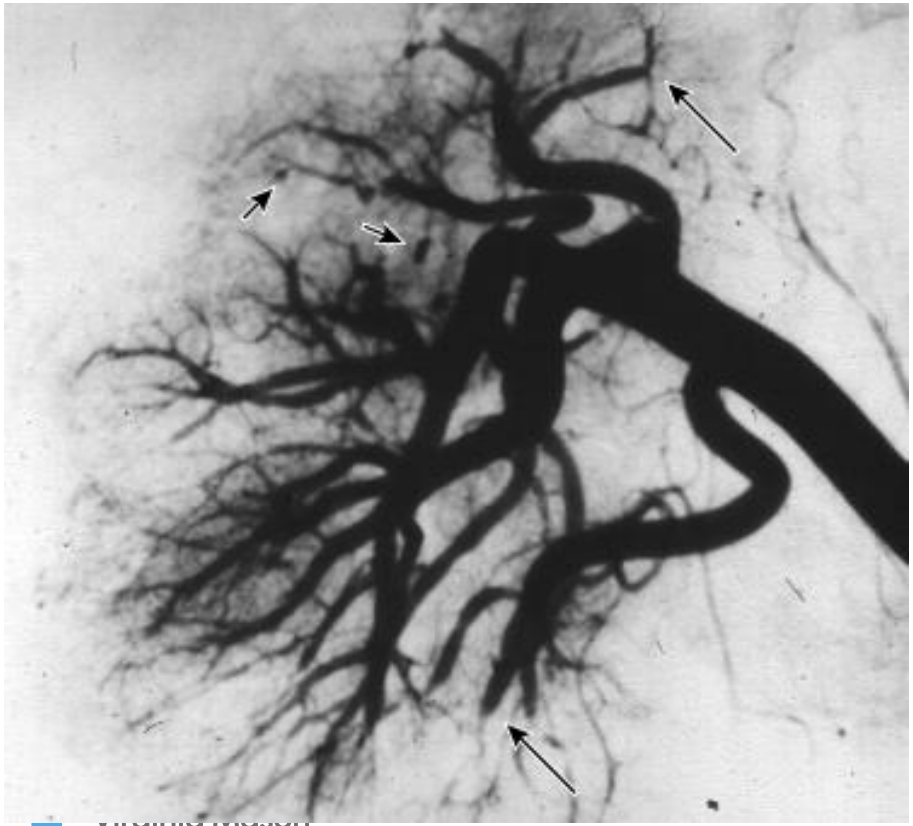


Renal arteriogram in polyarteritis nodosa showing characteristic microaneurysms (small arrows) and abrupt cutoffs of small arteries (large arrows).

Rose BD. Pathophysiology of Renal Disease, 2d ed, McGraw-Hill, New York, 1987.

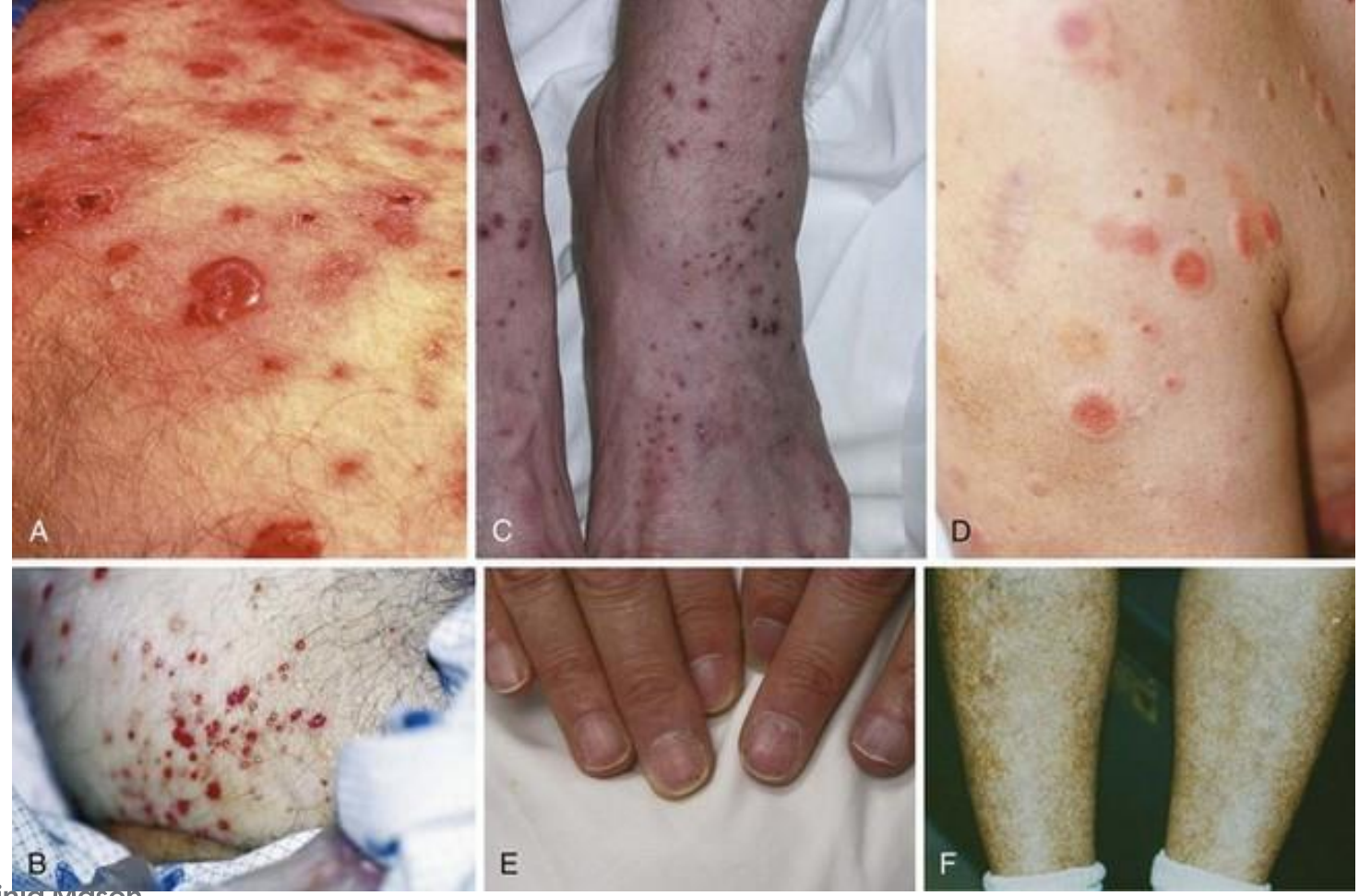
PAN

Peripheral neuropathies are very common (50 to 70%). This includes tingling, numbness and/or pain in the hands, arms, feet, and legs.

Most cases of polyarteritis nodosa (PAN) are idiopathic, although **hepatitis B virus** (HBV) infection, hepatitis C virus (HCV) infection, and hairy cell leukemia are important in the pathogenesis of some cases

The **kidneys** are the most commonly involved organ. Renal involvement frequently leads to variable degrees of renal insufficiency and hypertension. In addition, rupture of renal arterial aneurysms can cause perirenal hematomas.

Orchitis with testicular tenderness and pain occurs in more than 10 percent of patients, and testicular biopsy in patients with these symptoms can often be diagnostic of PAN



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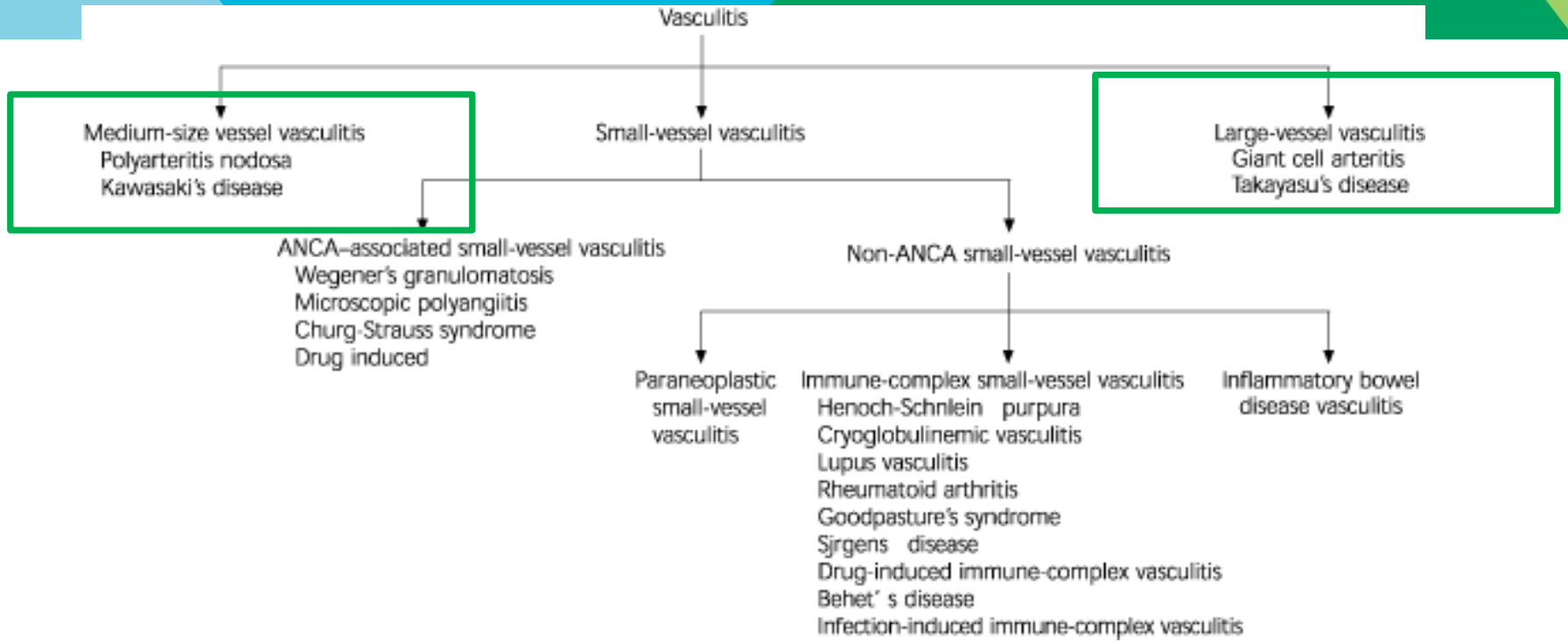
Cutaneous findings of immune complex–mediated small vessel vasculitis. **A,** Vesicles. **B,** Pustules. **C,** Superficial ulcerations. **D,** Urticaria. **E,** Splinter hemorrhages. **F,** Hyperpigmentation.=



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Ms. B is a 77 year old with well controlled diabetes, hyperlipidemia and hypertension who was diagnosed with PMR about 1 month ago by her primary care physician. She started on prednisone 10 mg daily with initial improvement in her symptoms.

She ran out of prednisone 2 weeks ago and is now in Rheumatology clinic with return of hip and shoulder girdle symptoms. Newer severe headaches primarily over the right temple with some tingling over the whole scalp.

Laboratory Testing:

ESR: 78 mm/hr
CRP: 55 mg/L
CBC: normal WBCs, mild normocytic anemia, thrombocytosis
CMP: normal renal function, liver enzymes and calcium
Glucose of 290 mg/dL
CPK: 150 mg/dL
RF/CCP: negative

Giant Cell Arteritis

PMR occurs in approximately 50 percent of patients with GCA

About **10-20 percent of PMR patients** will experience GCA at some point. PMR can precede, accompany, or follow GCA

Only 4 percent of patients with GCA have both the ESR and CRP in the normal range

GCA should be suspected in a patient age ≥50 years with a high ESR and/or CRP* plus one or more of the following¶:

- New headache or change in characteristics of preexisting headache
- Abrupt onset of visual disturbances, especially transient/permanent monocular visual loss
- Jaw claudication
- Unexplained fever or other constitutional symptoms and signs
- Signs/symptoms of vascular abnormalities (eg, limb claudication; asymmetric blood pressures; vascular bruits; temporal artery abnormalities such as tenderness to palpation, decreased pulse amplitude, and presence of nodules)

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Ms. B is a 77 year old with well controlled diabetes, hyperlipidemia and hypertension who was diagnosed with PMR about 1 month ago by her primary care physician. She started on prednisone 10 mg daily with initial improvement in her symptoms.

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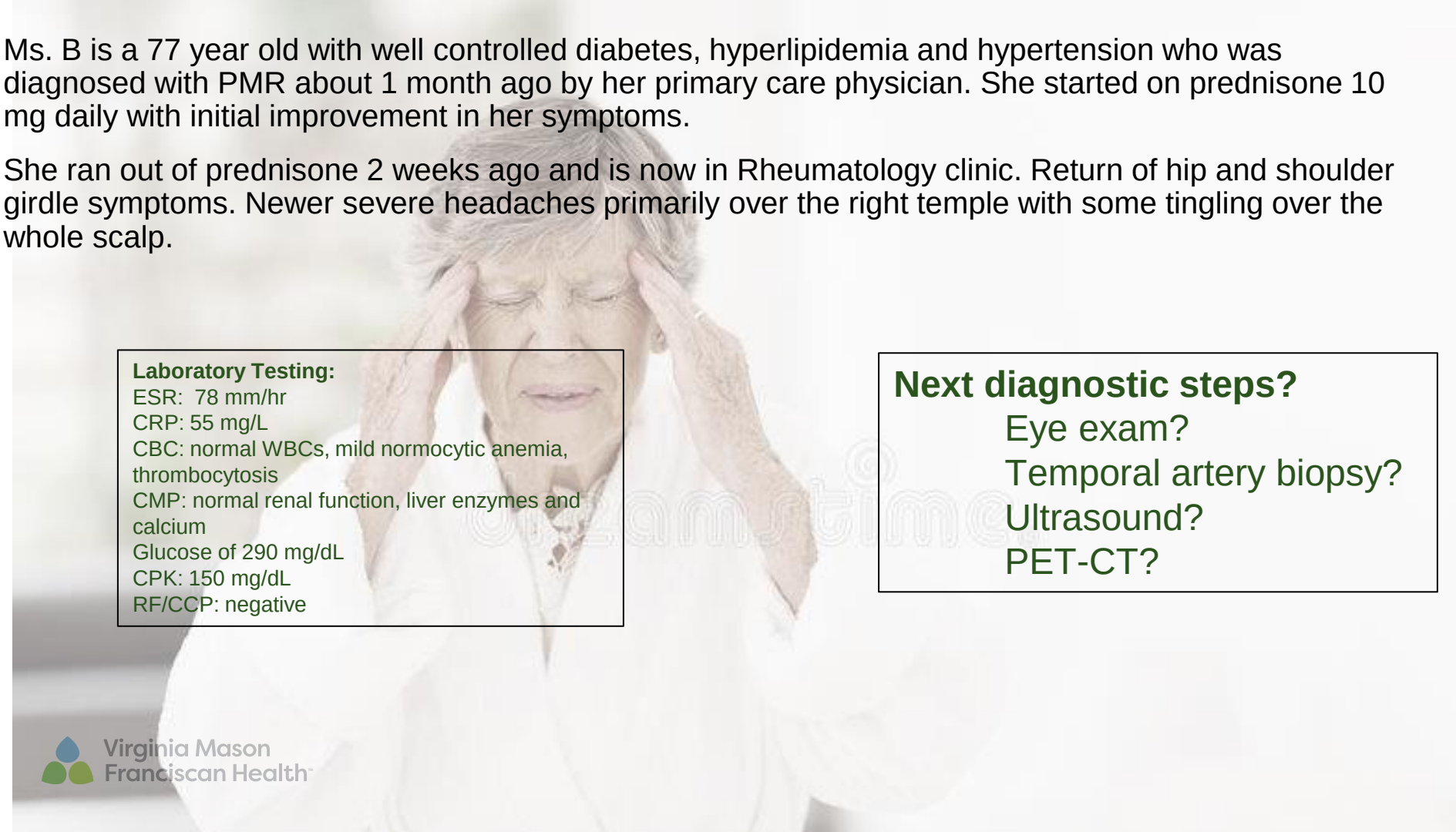

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CBC: normal WBCs, mild normocytic anemia, thrombocytosis
CMP: normal renal function, liver enzymes and calcium
Glucose of 290 mg/dL
CPK: 150 mg/dL
RF/CCP: negative

Next diagnostic steps?

- Eye exam?
- Temporal artery biopsy?
- Ultrasound?
- PET-CT?

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2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis

Cristina Ponte ,[1,2] Peter C Grayson ,[3] Joanna C Robson,[4,5] Ravi Suppiah,[6] Katherine Bates Gribbons,[3] Andrew Judge ,[7,8,9] Anthea Craven ,[7] Sara Khalid,[7] Andrew Hutchings ,[10] Richard A Watts ,[7,11] Peter A Merkel ,[12] Raashid A Luqmani ,[7] For the DCVAS Study Group

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ard-2022-223480).

For numbered affiliations see end of article.

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ABSTRACT

Objective To develop and validate updated classification criteria for giant cell arteritis (GCA).

Methods Patients with vasculitis or comparator diseases were recruited into an international cohort. The study proceeded in six phases: (1) identification of candidate items, (2) prospective collection of candidate items present at the time of diagnosis, (3) expert panel review of cases, (4) data-driven reduction of candidate items, (5) derivation of a points-based risk classification score in a development data set and (6) validation in an independent data set.

Results The development data set consisted of 518 cases of GCA and 536 comparators. The validation data set consisted of 238 cases of GCA and 213 comparators. Age ≥50 years at diagnosis was an absolute requirement for classification. The final criteria items and weights were as follows: positive temporal artery biopsy or temporal artery halo sign on ultrasound (+5); erythrocyte sedimentation rate ≥50 mm/hour or C reactive protein ≥10 mg/L (+3); sudden visual loss (+3); morning stiffness

widespread use of non-invasive and advanced vascular imaging modalities, which have become increasingly incorporated in the clinical assessment of GCA. Vascular ultrasound can be used to diagnose GCA, and depending on the clinical setting, a non-compressible 'halo' sign of a temporal±axillary artery may replace the need for temporal artery biopsy (TAB).[5–8] Moreover, vascular imaging has demonstrated that arterial involvement in GCA is not exclusively confined to the cranial arteries[9 10] and can commonly affect the aorta and primary branches in a pattern similar to Takayasu arteritis (TAK).[11 12]

The limitations of the ACR 1990 criteria for GCA have become more apparent in the conduct of recent clinical trials and other research studies, in which investigators typically modify the 1990 ACR criteria to reflect modern practice.[6 13 14] Notably, the 1990 ACR criteria focus mostly on cranial features of GCA and do not perform well in classifying patients with disease predominantly affecting

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EULAR

CLASSIFICATION CRITERIA FOR **GIANT CELL ARTERITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify the patient as having giant cell arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

ABSOLUTE REQUIREMENT

Age ≥ 50 years at time of diagnosis	

ADDITIONAL CLINICAL CRITERIA

Morning stiffness in shoulders/neck	+2
Sudden visual loss	+3
Jaw or tongue claudication	+2
New temporal headache	+2
Scalp tenderness	+2
Abnormal examination of the temporal artery[1]	+2

LABORATORY, IMAGING, AND BIOPSY CRITERIA

Maximum ESR ≥ 50 mm/hour or maximum CRP ≥ 10 mg/liter[2]	+3
Positive temporal artery biopsy or halo sign on temporal artery ultrasound[3]	+5
Bilateral axillary involvement[4]	+2
FDG-PET activity throughout aorta[5]	+2

Sum the scores for 10 items, if present. A score of ≥ 6 points is needed for the classification of GIANT CELL ARTERITIS.

Temporal Artery Biopsy

Within two to four weeks of starting treatment

Initial unilateral biopsy of at least 1 cm

Sensitivity of the temporal artery biopsy ranges from **50 to 95%** In a large meta-analysis including 3092 patients, the diagnostic sensitivity of the temporal artery biopsy was found to be **77%**

The increased yield of contralateral biopsy for the diagnosis ~5%

Rarely, temporal artery biopsy will disclose pathology other than GCA, such as systemic necrotizing vasculitis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, polyarteritis nodosa, amyloidosis, or lymphoma

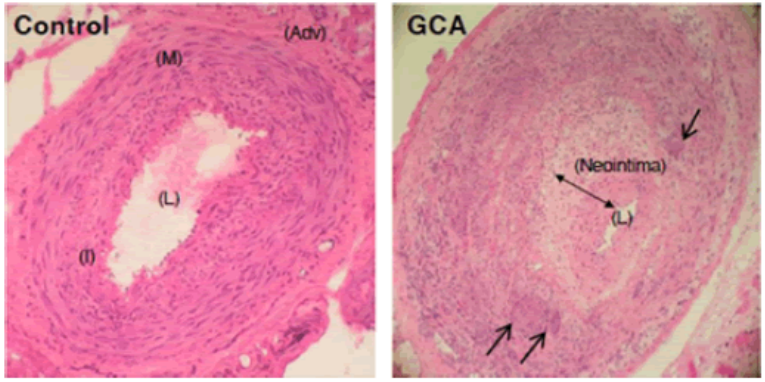
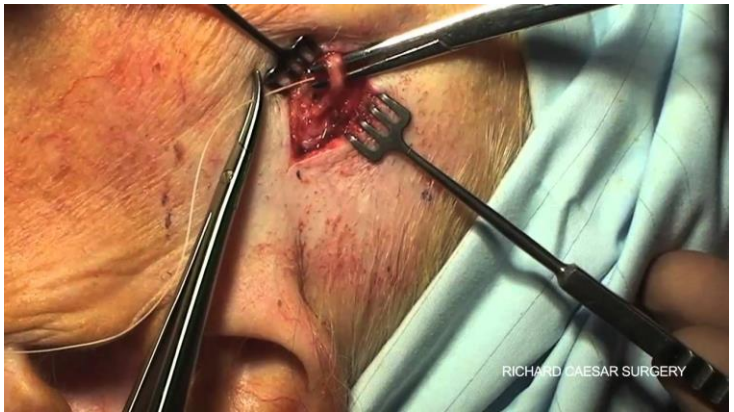


Figure 1: Normal temporal artery biopsy (left) as opposed to a temporal artery biopsy from a patient with giant-cell arteritis (right) disclosing typical transmural mononuclear cell infiltration, internal elastic lamina breakdown and intimal hyperplasia. Double head arrow remarks the thickened intima and single head arrows indicate the presence of giant-cells. Haematoxylin-eosin staining. L: lumen; I: intima; M: media; Adv: adventitia.



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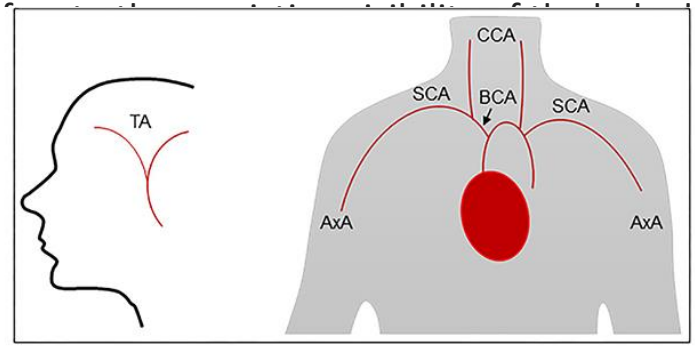
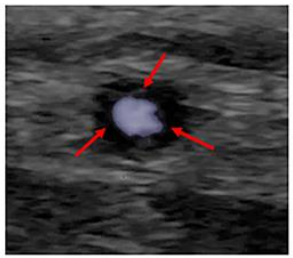
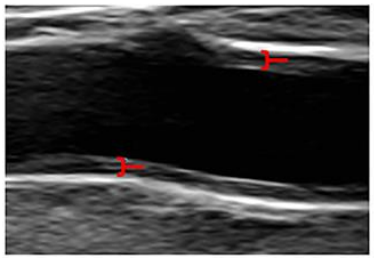
Ultrasound in GCA

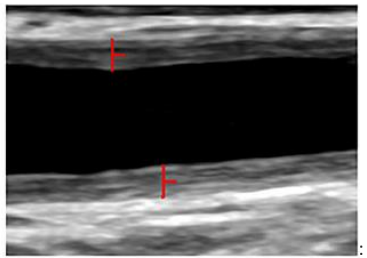
Must be done within <u>one week</u>

“Halo sign”- 0.3 to 2.0 mm hypoechogenic, is highly specific for GCA. The **"compression sign"** also has high specificity for the









Skoog J, Svensson C, Eriksson P, Sjöwall C and Zachrisson H (2022) The Diagnostic Performance of an Extended Ultrasound Protocol in Patients With Clinically Suspected Giant Cell Arteritis. Front. Med. 8:807996

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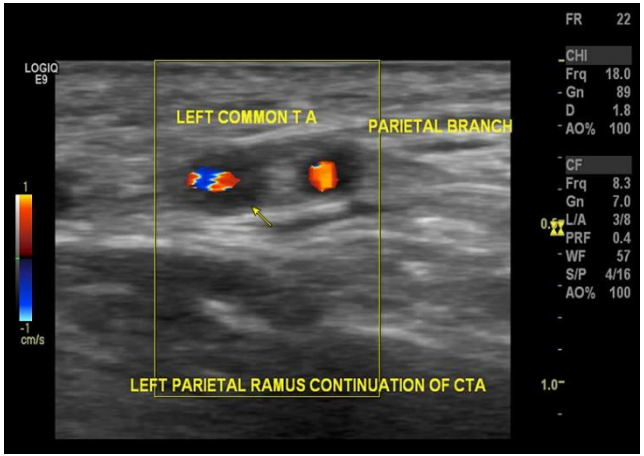

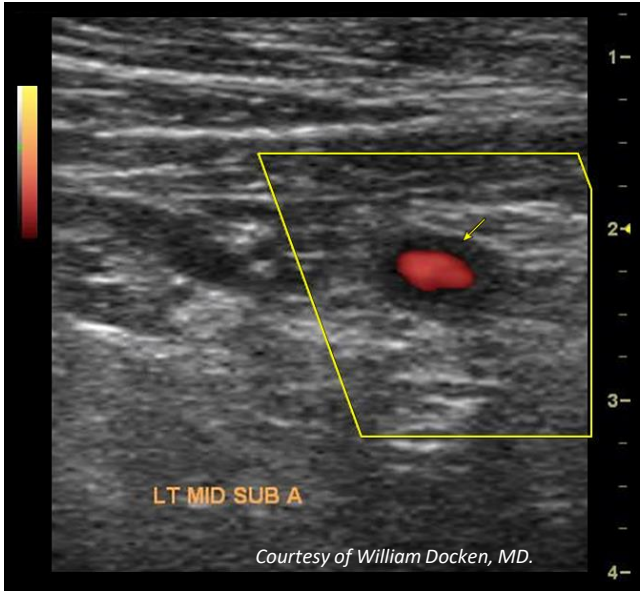

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Treatment of GCA

IV pulse GCs: IV methylprednisolone 500–1,000 mg/day equivalent for 3–5 days

High-dose oral GCs: Prednisone 1 mg/kg/day up to 80 mg or equivalent

Moderate-dose oral GCs Prednisone 0.5 mg/kg/day (generally 10–40 mg/day in adults) or equivalent

Low-dose oral GCs Prednisone ≤10 mg/day or equivalent

Non-GC nonbiologic immunosuppressive therapy
Azathioprine, leflunomide, methotrexate, mycophenolate mofetil, cyclophosphamide

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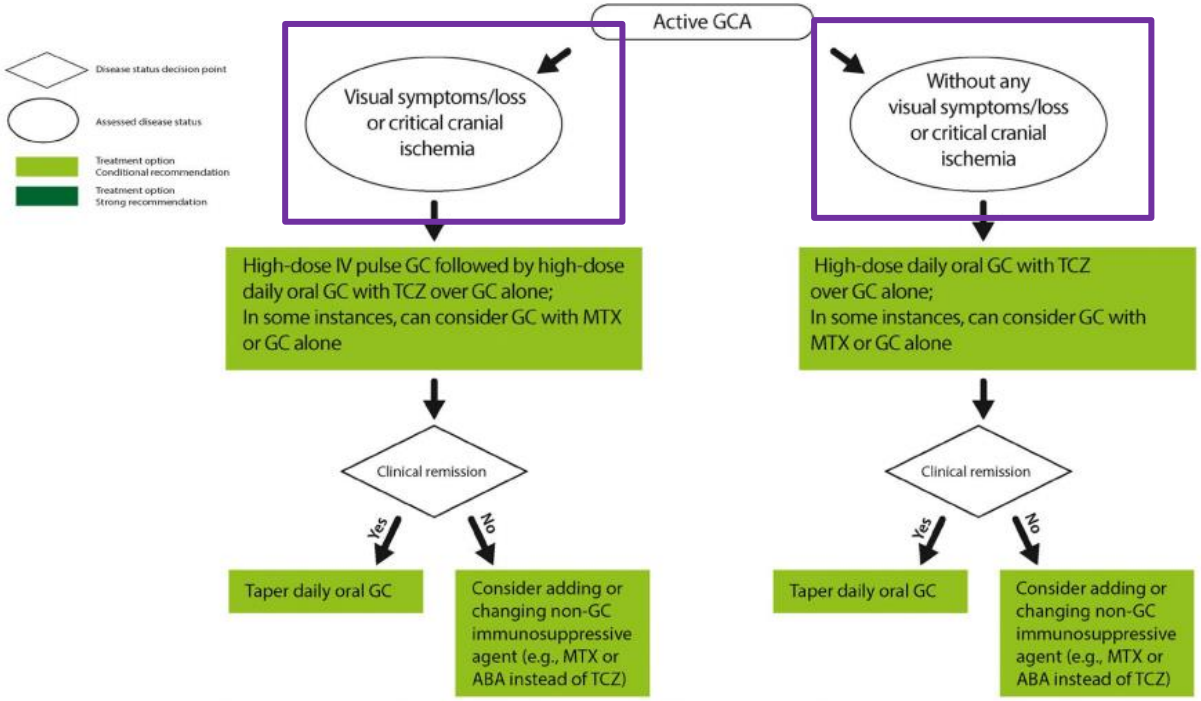
DOI 10.1002/acr.24632

American College of Rheumatology
Empowering Rheumatology Professionals

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis

Mehrdad Maz,[1] Sharon A. Chung,[2] Andy Abril,[3] Carol A. Langford,[4] Mark Gorelik,[5] Gordon Guyatt,[6]

Overview of treatment of giant cell arteritis (GCA)



ABA = abatacept, AZA = azathioprine, GC = glucocorticoids, IV = intravenous, MTX = methotrexate, TCZ = tocilizumab

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FDA NEWS RELEASE

FDA approves first drug to specifically treat giant cell arteritis

More Press Announcements

For Immediate Release: May 22, 2017

Español

The U.S. Food and Drug Administration today expanded the approved use of subcutaneous Actemra (tocilizumab) to treat adults with giant cell arteritis. This new indication provides the first FDA-approved therapy, specific to this type of vasculitis.

"We expedited the development and review of this application because this drug fulfills a critical need for patients with this serious disease who had limited treatment options," said Badrul Chowdhury, M.D., Ph.D., director of the Division of Pulmonary, Allergy, and Rheumatology Products in the FDA's Center for Drug Evaluation and Research.

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The NEW ENGLAND JOURNAL of MEDICINE

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Trial of Tocilizumab in Giant-Cell Arteritis

J.H. Stone, K. Tuckwell, S. Dimonaco, M. Klearman, M. Aringer, D. Blockmans, E. Brouwer, M.C. Cid, B. Dasgupta, J. Rech, C. Salvarani, G. Schett, H. Schulze-Koops, R. Spiera, S.H. Unizony, and N. Collinson

ABSTRACT

BACKGROUND

Giant-cell arteritis commonly relapses when glucocorticoids are tapered, and the prolonged use of glucocorticoids is associated with side effects. The effect of the interleukin-6 receptor alpha inhibitor tocilizumab on the rates of relapse during glucocorticoid tapering was studied in patients with giant-cell arteritis.

METHODS

In this 1-year trial, we randomly assigned 251 patients, in a 2:1:1:1 ratio, to receive subcutaneous tocilizumab (at a dose of 162 mg) weekly or every other week, combined with a 26-week prednisone taper, or placebo combined with a prednisone taper over a period of either 26 weeks or 52 weeks. The primary outcome was the rate of sustained glucocorticoid-free remission at week 52 in each tocilizumab group as compared with the rate in the placebo group that underwent the 26-week prednisone taper. The key secondary outcome was the rate of remission in each tocilizumab group as compared with the placebo group that underwent the 52-week prednisone taper. Dosing of prednisone and safety were also assessed.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Stone at Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114, or at jhstone@mgh.harvard.edu.

N Engl J Med 2017;377:317-28.
DOI: 10.1056/NEJMoa1613849

Table 3. Safety over the 52-Week Trial Period.*

Variable	Tocilizumab Weekly (N=100)	Tocilizumab Every Other Week (N=49)	Placebo +26-Wk Taper (N=50)	Placebo +52-Wk Taper (N=51)
Duration in trial — patient-yr	92.9	45.6	47.4	48.1
Patients with ≥1 adverse event — no. (%)	98 (98)	47 (96)	48 (96)	47 (92)
Adverse events				
No. of events	810	432	470	486
Rate per 100 patient-yr (95% CI)	872.0 (813.0–934.2)	948.0 (860.7–1041.7)	990.8 (903.2–1084.5)	1011.2 (923.3–1105.3)
Patients with ≥1 infection — no. (%)				
Any	75 (75)	36 (73)	38 (76)	33 (65)
Serious	7 (7)	2 (4)	2 (4)	6 (12)
Patients who withdrew from the trial because of adverse events — no. (%)†	6 (6)	3 (6)	2 (4)	0
Patients with injection-site reaction — no. (%)	7 (7)	7 (14)	5 (10)	1 (2)
Flare of giant-cell arteritis reported as serious adverse event — no. (%)‡	1 (1)	1 (2)§	1 (2)	1 (2)
Patients with ≥1 serious adverse event — no. (%)				
Any	15 (15)	7 (14)	11 (22)	13 (25)
According to system organ class¶				
Infection or infestation	7 (7)	2 (4)	2 (4)	6 (12)
Vascular disorder	4 (4)	2 (4)	2 (4)	1 (2)
Respiratory, thoracic, or mediastinal disorder	2 (2)	1 (2)	2 (4)	2 (4)
Injury, poisoning, or procedural complication	3 (3)	1 (2)	1 (2)	0
Nervous system disorder	1 (1)	1 (2)	2 (4)	1 (2)
Cardiac disorder	2 (2)	0	0	2 (4)
Musculoskeletal or connective-tissue disorder	1 (1)	0	1 (2)	2 (4)
Gastrointestinal disorder	1 (1)	0	2 (4)	0
Cancer	0	0‖	1 (2)	1 (2)

* No gastrointestinal perforations were reported, and no patients died.
† Values are reported for the entire trial population; that is, values were included for 50 patients in the group that received tocilizumab every other week (i.e., including the patient who did not receive tocilizumab).
‡ Values are for flares of giant-cell arteritis that met the protocol-defined criteria for being reported as a serious adverse event.
§ This patient had anterior ischemic optic neuropathy after randomization.
¶ Values were those reported in at least 1% of the patients overall. Patients may have had more than one class of serious adverse event.
‖ One patient in the group that received tocilizumab every other week had a benign ovarian adenoma.

Tocilizumab Monitoring:

CBC, LFTs prior , 4 to 8 weeks after start of therapy, and every 3 months thereafter

Lipid panel prior to and 4 to 8 weeks following initiation of therapy

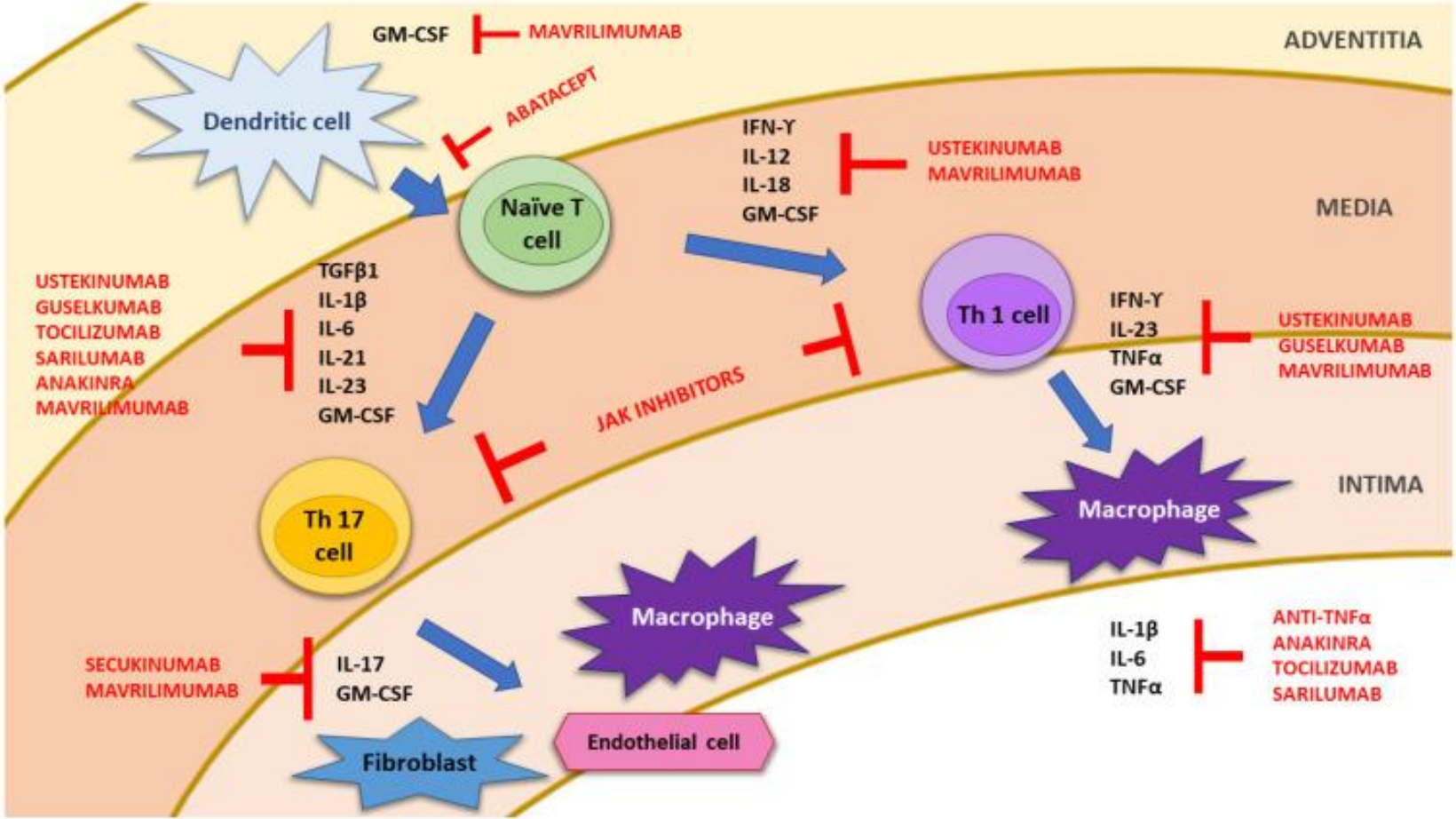
Infection

Signs and symptoms of CNS demyelinating disorder

New onset abdominal symptoms (GI perforation)

Future GCA Treatments?

J Clin Med. 2022 Mar; 11(6): 1588.
Published online 2022 Mar 13. doi: 10.3390/jcm11061588



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2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Recommend risk stratifying patients via FRAX score

For all adults initiating or continuing **GC therapy ≥ 2.5mg/day for > 3 months**, who have never had fracture risk assessment or been treated with OP therapy, initial clinical fracture risk assessment is strongly recommended

Clinical fracture risk factor assessment includes the dose, duration, and pattern of GC use, alcohol use, smoking history, hypogonadism, history of prior fractures, low body weight, significant weight loss, parental history of hip fracture, fall history, thyroid disease, hyperparathyroidism, rheumatoid arthritis, malabsorption, chronic liver disease, inflammatory bowel disease, and height loss.

If available**, BMD testing is recommended within 6 months of starting GC therapy for adults and every 1-2 years thereafter while continuing GC therapy.**

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Table 2. Recommendations for initial treatment for prevention of GIOP in adults beginn GC therapy

Recommendations for patients taking prednisone ≥ 2.5mg/day for > 3months	Certainty of evidence	PICO evidence report basis
For adults and children beginning or continuing chronic GC treatment at low, moderate, or high risk of fracture, optimizing dietary and supplemental calcium and vitamin D in addition to lifestyle modifications (CAL/VIT D/LM) is **conditionally** recommended. All additional recommendations are in addition to CAL/VIT D/LM).	Low or Very Low	1.1a,b,c-1.3a,b,c, 2.1-2.3, 7.16-7.26
In adults ≥ 40 years		
With ***LOW*** fracture risk, adding any OP medications to CAL/VIT D /LM based on known harms with no evidence of benefit is **strongly** recommended ***against***.	Very Low	1.4a-1.28a
With ***MODERATE*** fracture risk, oral or IV BP, PTH/PTHrP, or DEN over no OP therapy is **conditionally** recommended.	Moderate to Very Low	1.4b-1.28b
With ***MODERATE*** fracture risk, using ROM or SERM is **conditionally** recommended *against* except for in patients intolerant of other agents, due to risk of life-threatening harms.	Very Low	1.12b, 1.16b,1.17b,1.21 b-1.25b, 1.28b
With ***HIGH*** fracture risk, oral BP over not giving OP therapy is **strongly** recommended[#]. IV BP, PTH/PTHrP, or DEN over no OP therapy is **conditionally** recommended[$].	Low or Very Low	1.5c-1.28c
With ***HIGH*** fracture risk, using ROM or SERM is **conditionally** recommended ***against*** except for patients intolerant of other agents due to risk of life- threatening harms	Very Low	1.16c, 1.21c, 1.28c

Questions?

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