



# **Granulomatosis with polyangiitis (GPA)**

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# Case report

43 old man with recurrent sinusitis from several years, was admitted to Emergency Unit because of persistent, productive cough. Physical findings: painfulness of infraorbital region, moist rales in the lungs' bottom, infinitesimal, symmetrical oedema of lower legs. Rtg of the chest: shadiness of the costophrenic angle and both top f the lungs. Laboratory findings: creatinine 3.0 mg/dl, urea 120 mg/ml, urine: s.g. 1.020, protein 100 mg/dl, sediment - dysmorphic erythrocytes 10-12, serum: anty-GBM Ab negative, cANCA present. What diagnosis is more plausible?

- A. Acute tubulointerstitial nephritis
- B. Goodpasture Syndrome
- C. IgA Nephropathy
- D. Acute poststreptococcal glomerulonephritis
- E. Granulomatosis with polyagiitis

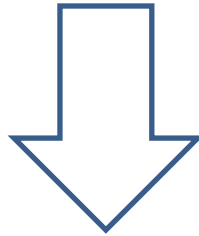
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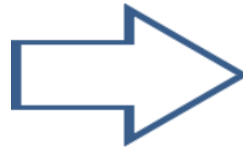
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**American College of Rheumatology (ACR)**  
**American Society of Nephrology (ASN)**  
**European League Against Rheumatism (EULAR)**  
*Januar 2011*



**Wegener's granulomatosis**



**Granulomatosis with polyangiitis**

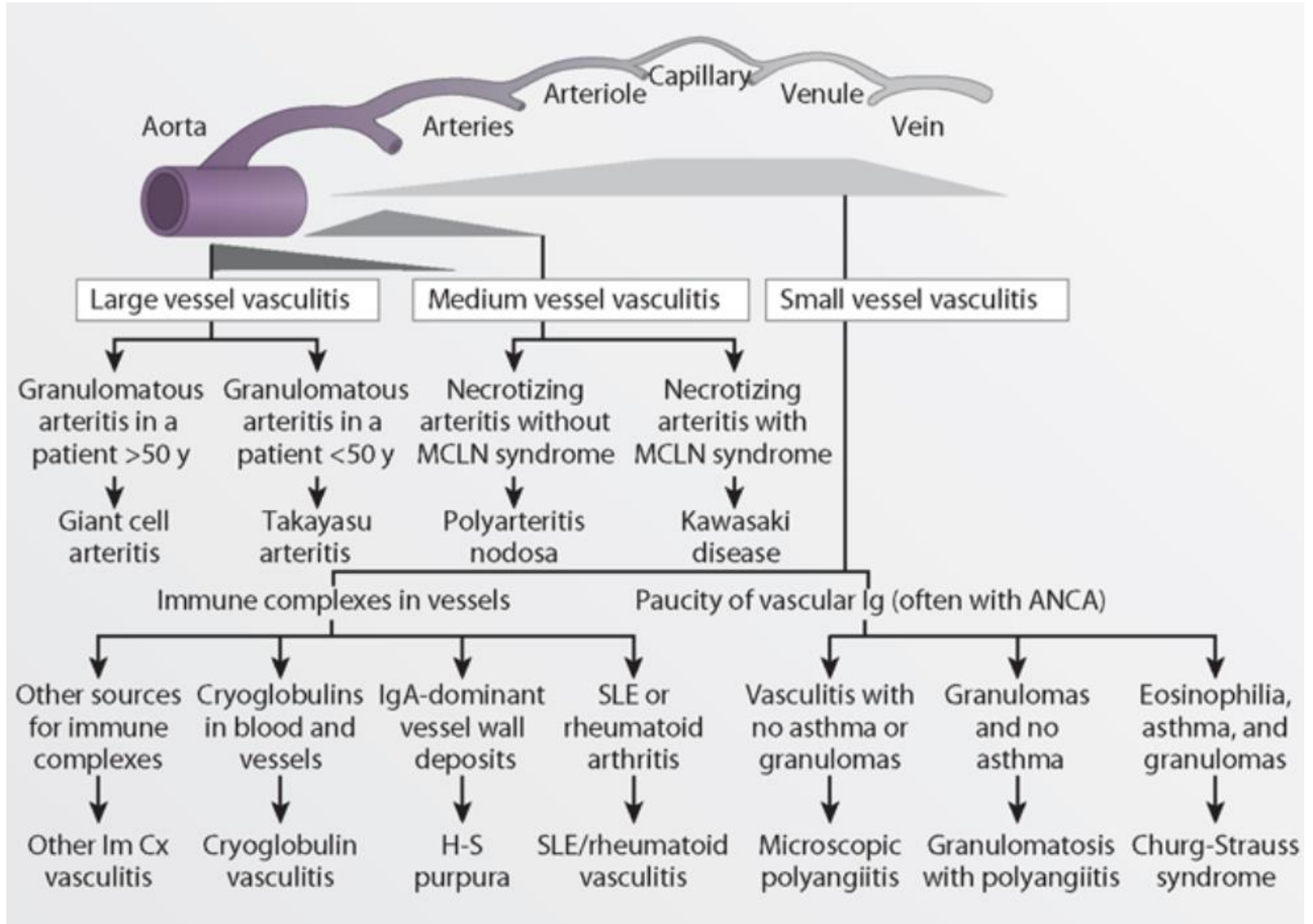
This change reflects a plan to gradually shift from honorific eponyms to a disease-descriptive or etiology-based nomenclature

1931 r. - Heinz Klinger, medical student (Periarteritis Nodosa)

1950 r. - Friedrich Wegener, german pathologist



# Vasculitis -classification



# ANCA positive vasculitis

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## Similarities:

- Pathogenesis connected with ANCA antibodies appearance
- Common pathomorphologic pattern of kidney injury (pauci-immune, necrotizing glomerulonephritis with crescent formation)

## Differences:

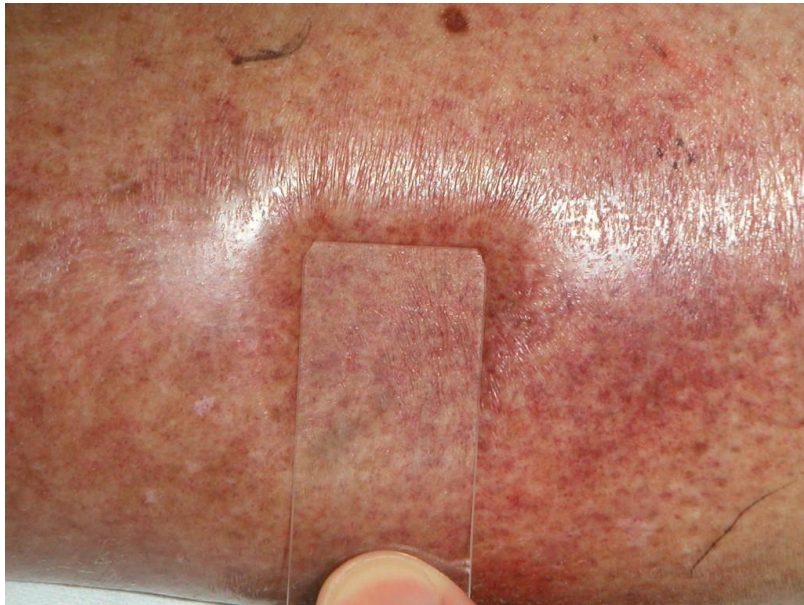
- Clinical picture
- Granulomas and their cells' composition

MPA - without granulomas

GPA - granulomas consist of different cells (macrophages, neutrophils, lymphocytes)

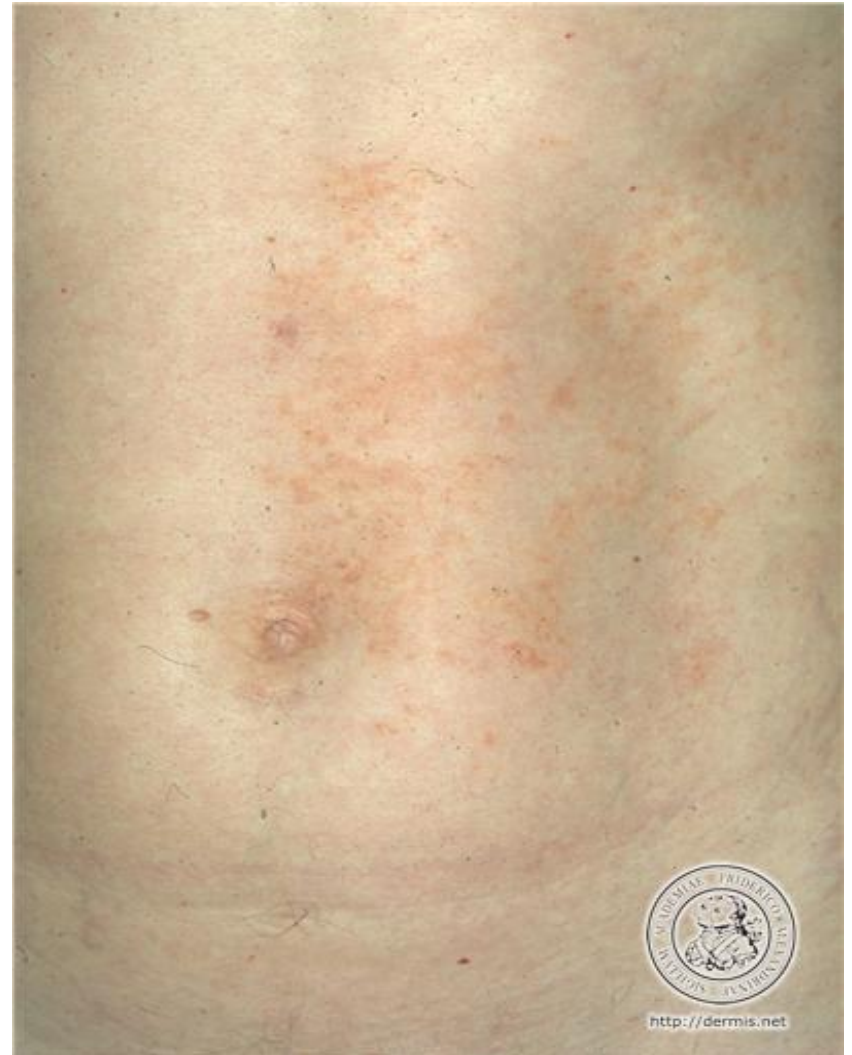
EGPA -granulomas with dominance of eosinophilic leucocytes





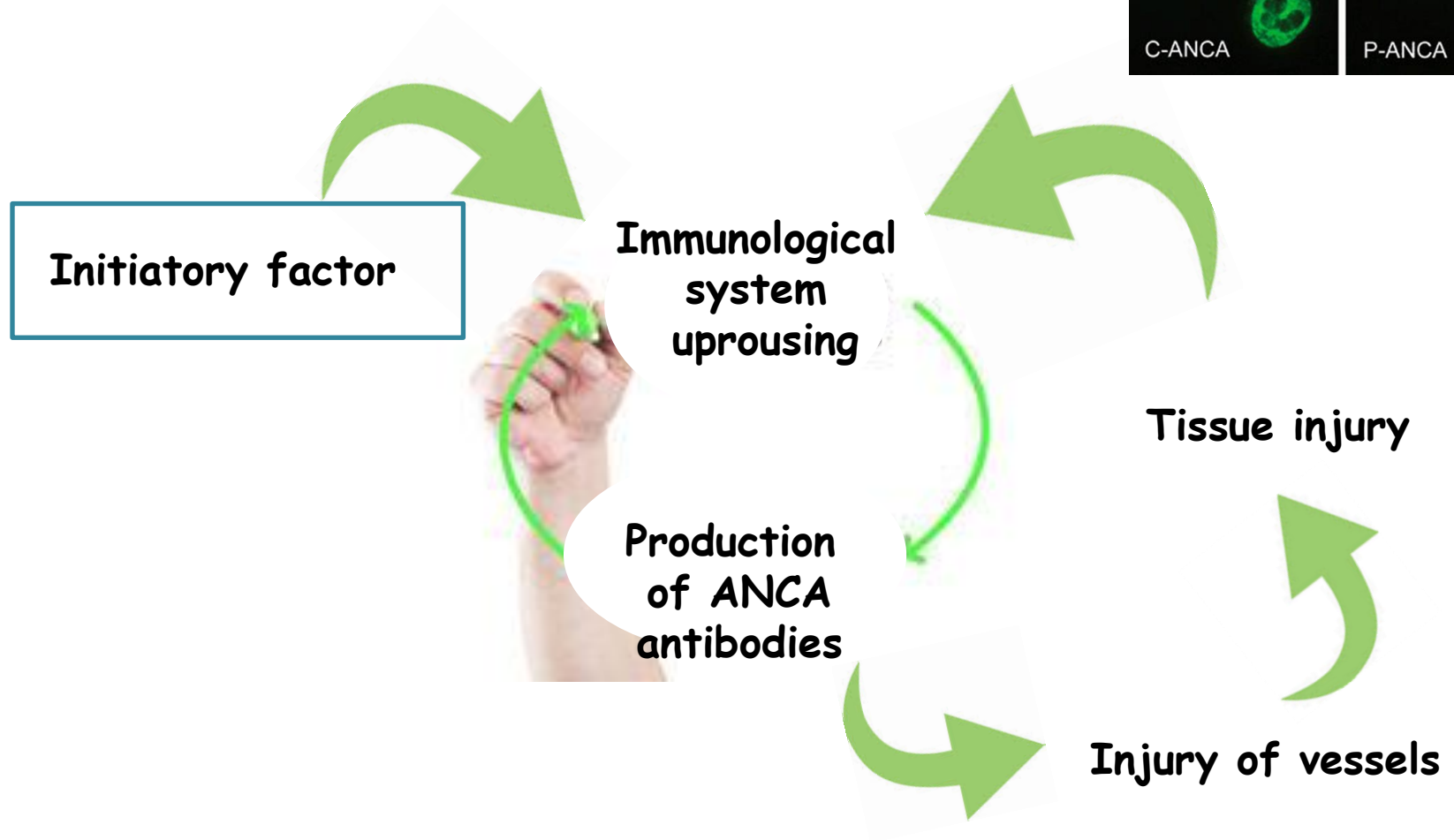
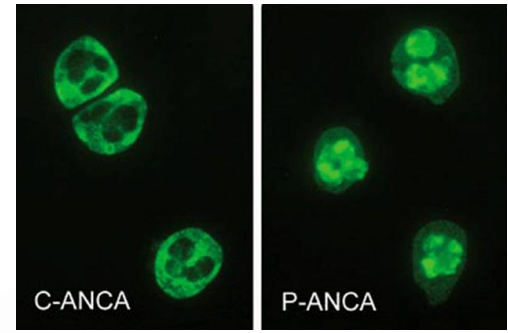
# Palpable purpura

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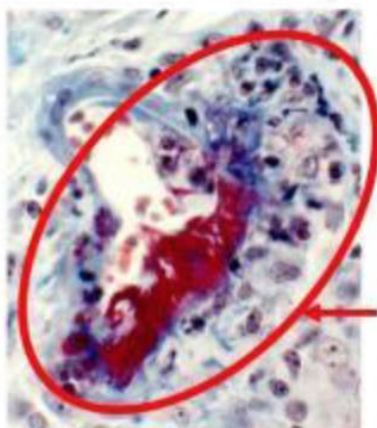
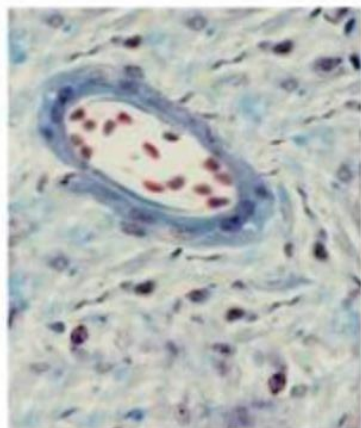
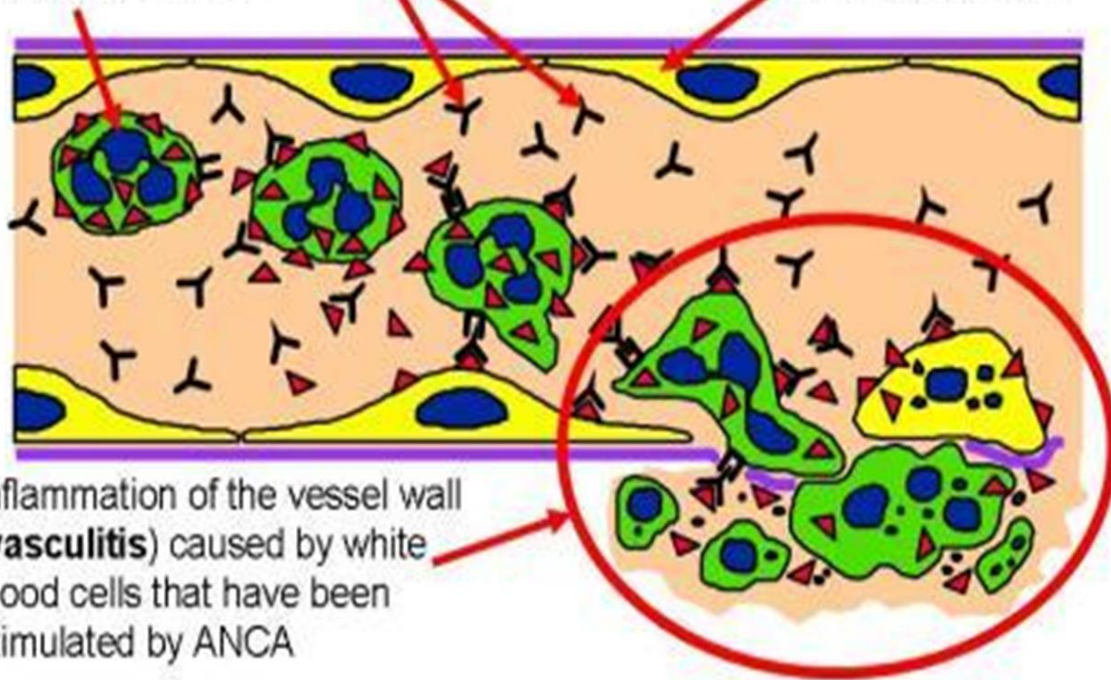
# Pathogenesis of ANCA-associated vasculitis



**Neutrophil type**  
of white blood cell

**ANCA (Anti-Neutrophil Cytoplasmic Autoantibody)**

Blood vessel wall



Inflammation of the vessel wall  
(**vasculitis**) caused by white  
blood cells that have been  
stimulated by ANCA

# Initiatory factors of GPA

## **Infections**

- Staphylococcus aureus carrier-states (nose)
- E. coli infection (strain producing FimH adhesin, 100% homology with LAMP-2 epitope, antibodies cross-reaction)

## **Genetic factors**

- MHC class II - allele HLA-DRB1-15
- gen PTPN22 - polymorphism of one nucleotide
- alpha-1-antitrypsin deficiency

## **Environmental factors**

- drugs - rifampicin, allopurinol, hydralazine, propylthiouracil
- exposition - noninfectious inhaled toxins (silica dust, mercury, lead)

# Immunological features of **ANCA-associated vasculitis**

GPA 80% ANCA positive

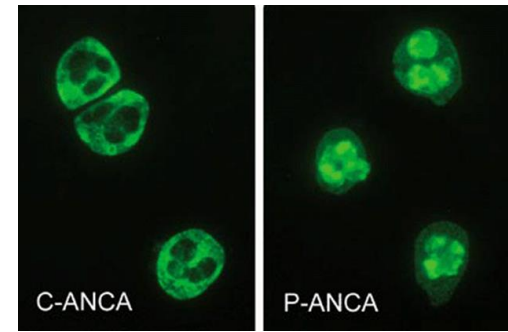
MPA/EGPA 50-70% ANCA positive

## GPA:

- PR3 (cANCA) 70-80% of cases
- MPO (pANCA) 10% of cases

anty LAMP-2 antibodies (*lysosome-associated membrane protein-2*)

*molecular mimicry, connection with infection 90% pts with RPGN*



↓  
**PR3**  
proteinaza 3

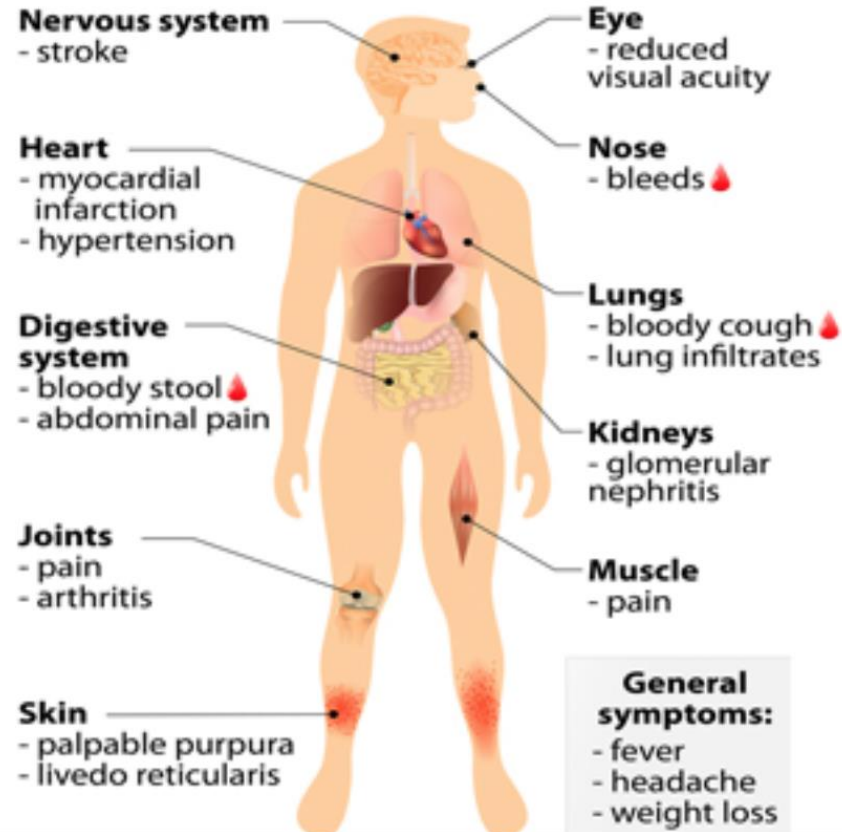
↓  
**MPO**  
mieloperoksydaza

## New Diagnosis and Classification Criteria in Vasculitis Study:

- PR3-ANCA (cANCA) vasculitis
- MPO-ANCA (pANCA) vasculitis
- ANCA negative vasculitis

# Symptoms

## VASCULITIS





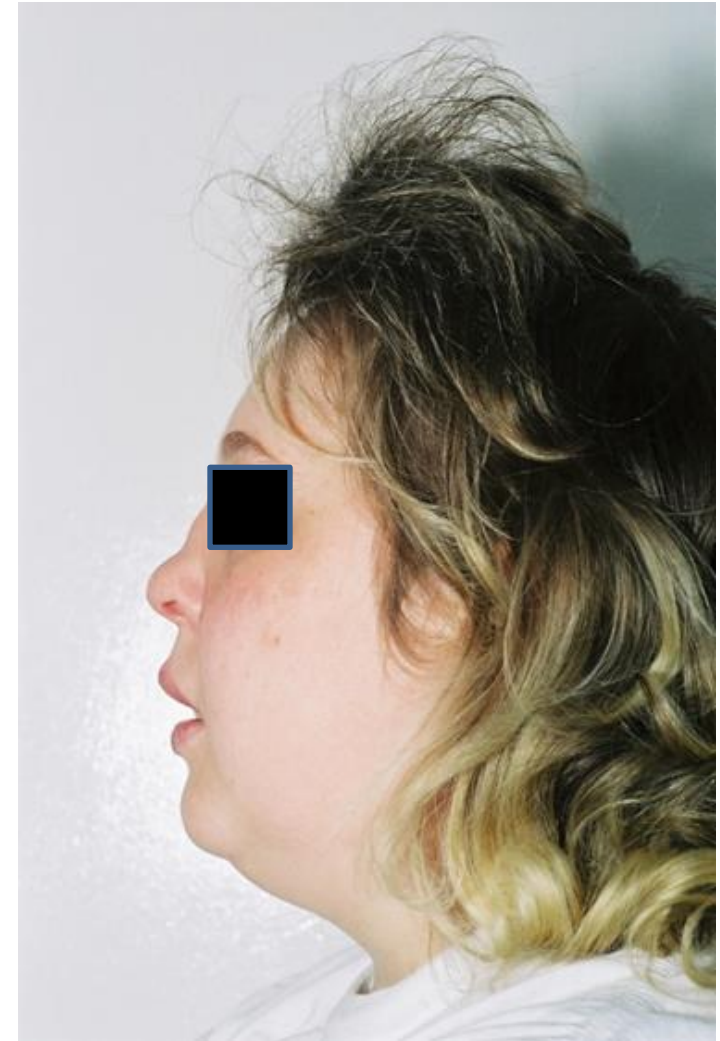
## Distinguishing Characteristics of Vasculitis Subtypes

	Large vessel		Medium vessel	Small vessel	
	TAK	GCA	PAN	ANCA-assoc.	IC
<b>Epidem</b>	Young, ♀ > ♂	Elderly, ♀ > ♂	Middle-aged to older	Variable	Variable
<b>Renal</b>	Arteries	None	Microaneurysms	GN	GN
<b>Pulm</b>	Rare	None	Rare	Frequent	Cryo > HSP
<b>Periph Neurop</b>	No		Yes	Yes	Yes
<b>GI</b>	Uncommon		Yes	Yes	HSP > Cryo
<b>Skin</b>	Rare	None	Common	Common	Common
<b>Granul.</b>	Yes		No	Yes, except MPA	No
<b>Other</b>			Mesenteric aneurysms, testicular involv.	GPA: upper airway EGPA: asthma	HSP: IgA-dep Cryo: HCV

TAK, Takayasu's arteritis; GCA, giant cell arteritis; PAN, polyarteritis nodosa; ANCA-assoc. is GPA, EGPA, & MPA; IC, immune complex small vessel vasculitis (eg, HSP, cryoglobulinemia); GN, glomerulonephritis.

# Upper respiratory truck

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# **Lower respiratory truck**



# Renal Manifestation of AAV (ANCA-associated vasculitis)

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National Institutes of Health (NIH)

18% pts with GPA/MPA at presentation have GN

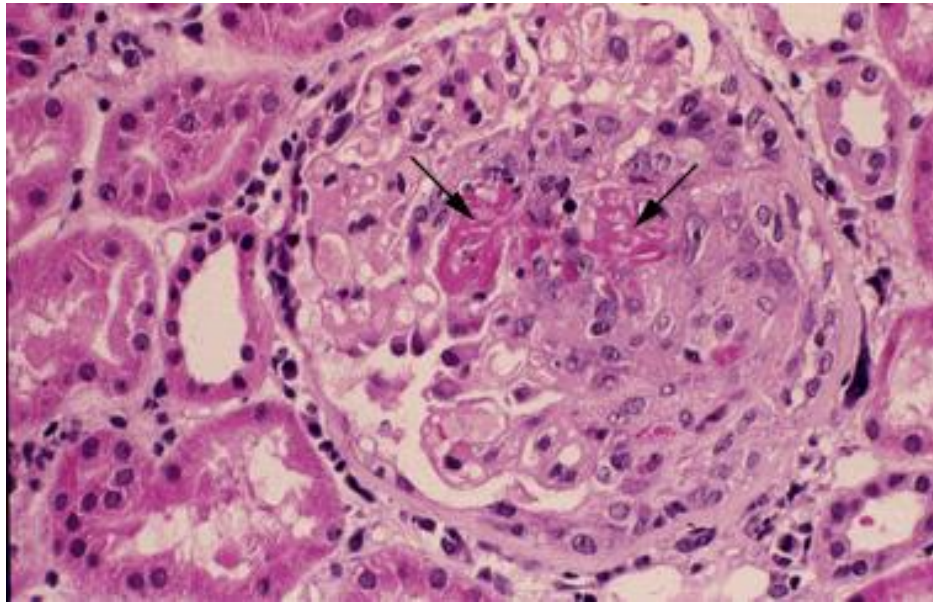
77 to 85% pts subsequently developed GN (usually within the first 2 yrs of disease onset)

- **Erythrocyturia** (remittent)
- **RPGN pauci-immune crescentic glomerulonephritis (ANCA +)**
  - renal-limited vasculitis (RLV) ANCA positive
  - **ANCA-negative pauci-immune crescentic glomerulonephritis**
- **Proteinuria** (subnephrotic)



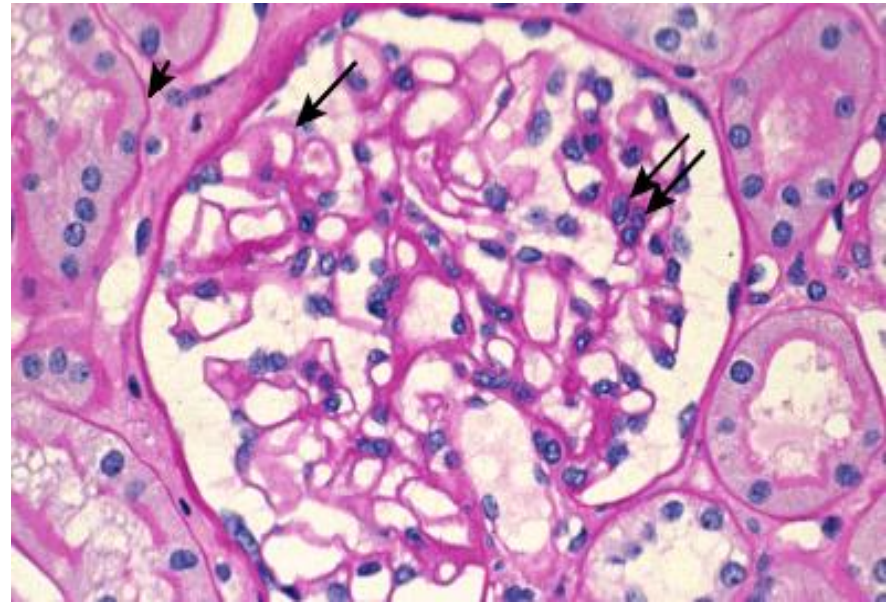


## Necrotizing glomerulonephritis



Light micrograph showing fresh segmental necrotizing lesions with bright red fibrin deposition (arrows). A necrotizing glomerulonephritis can be seen in a variety of inflammatory disorders including vasculitis and lupus nephritis. The latter has prominent immune complex deposition which is generally absent in vasculitis.

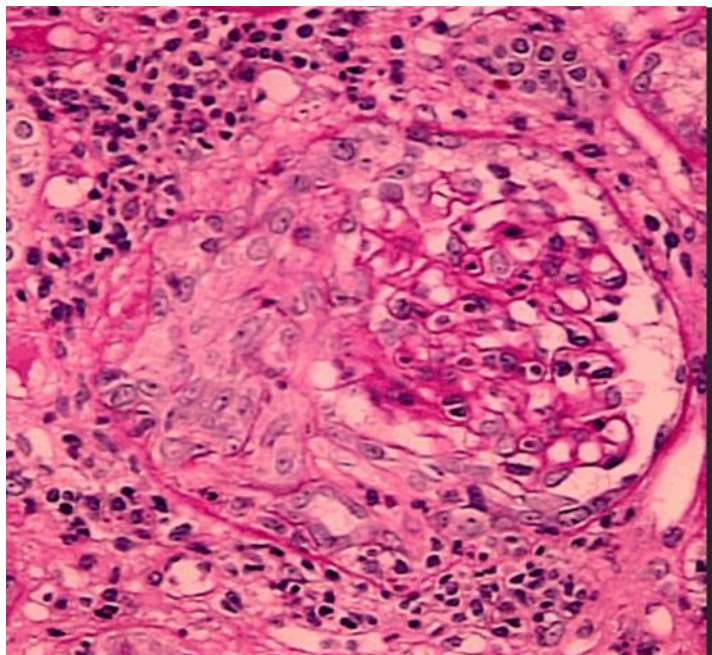
## Normal glomerulus



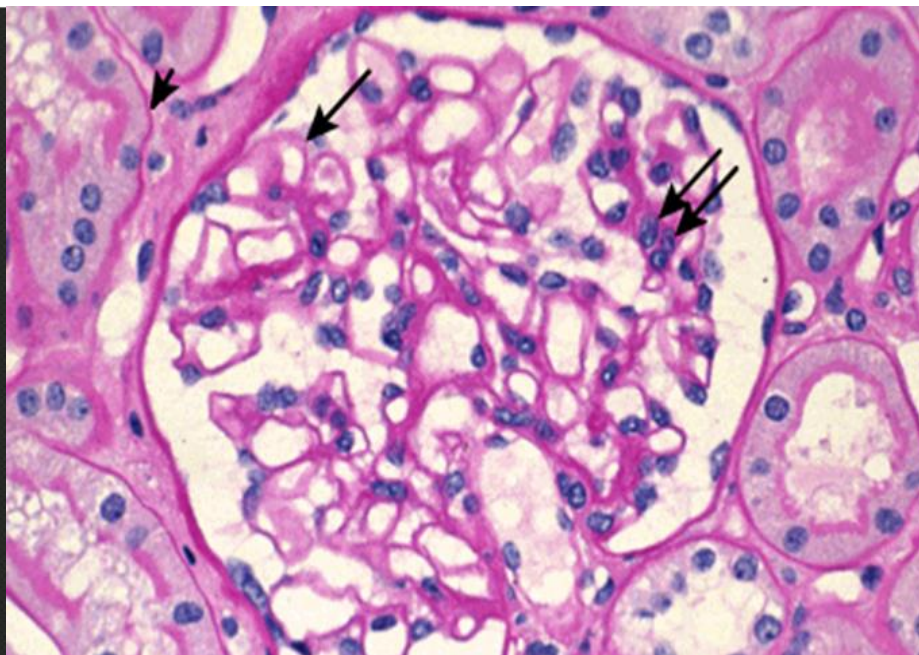
Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).



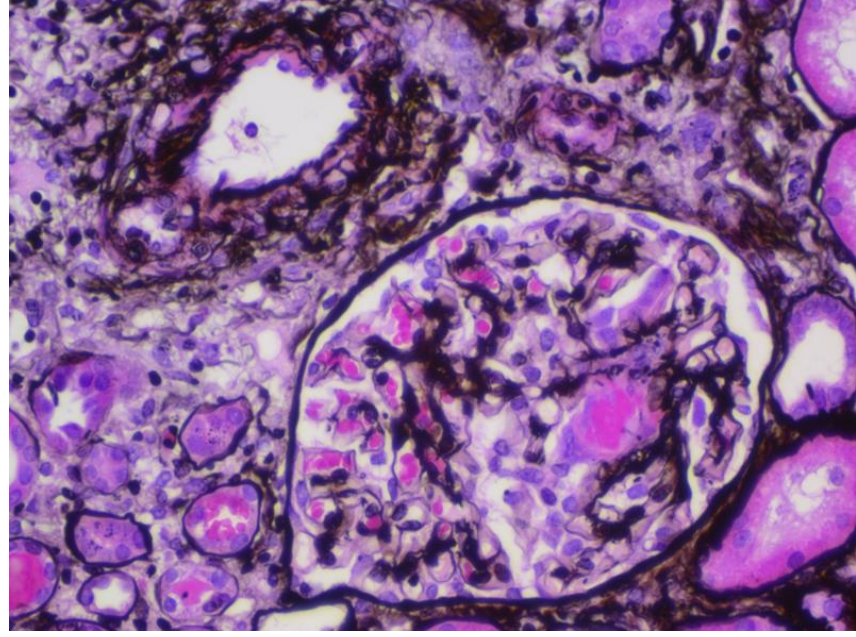
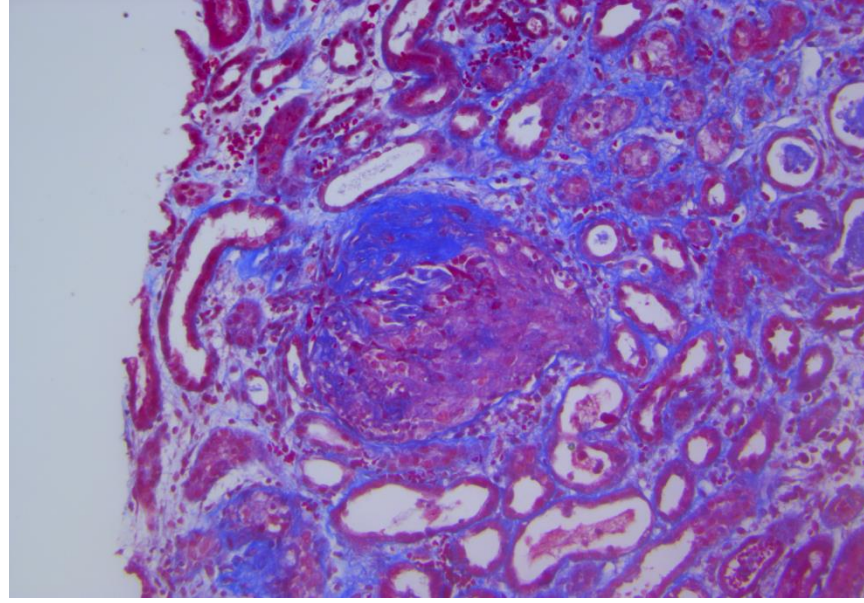
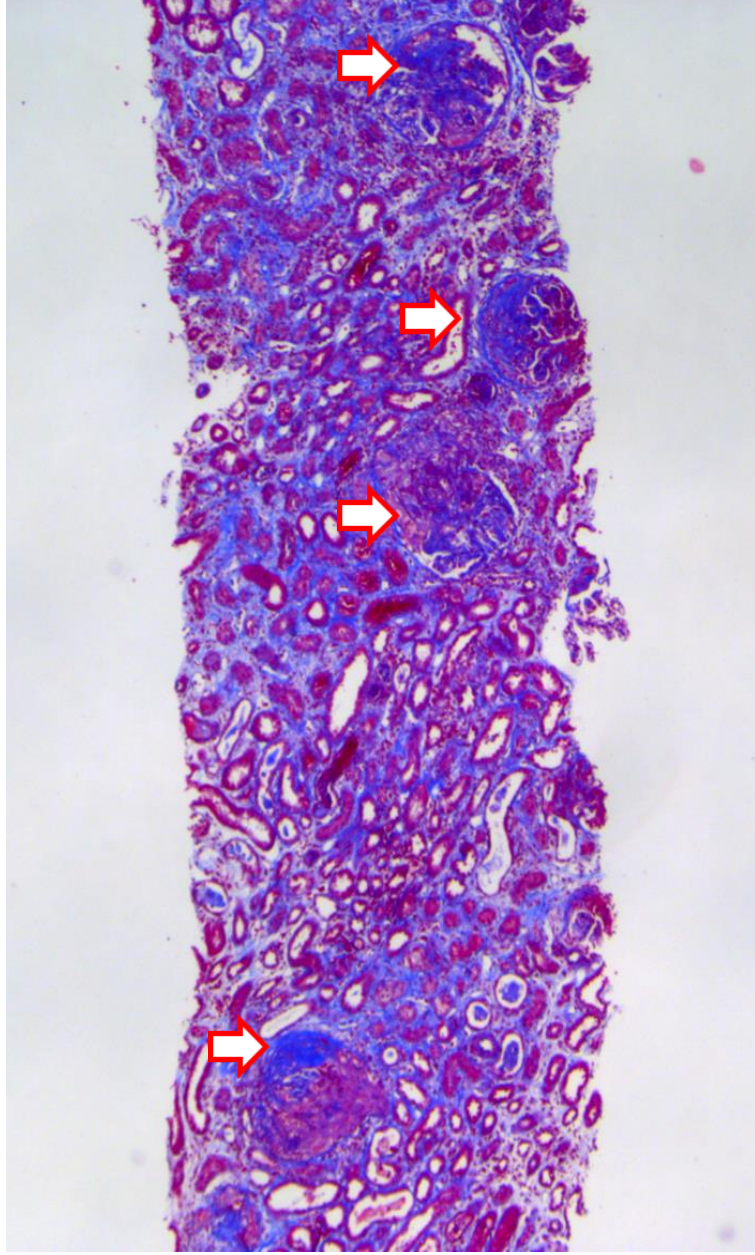
**Crescentic glomerulonephritis**



**Normal glomerulus**

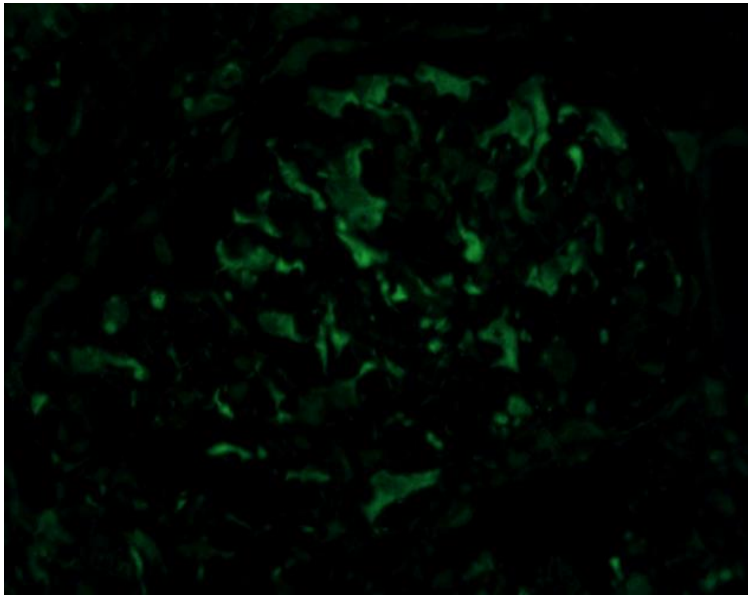




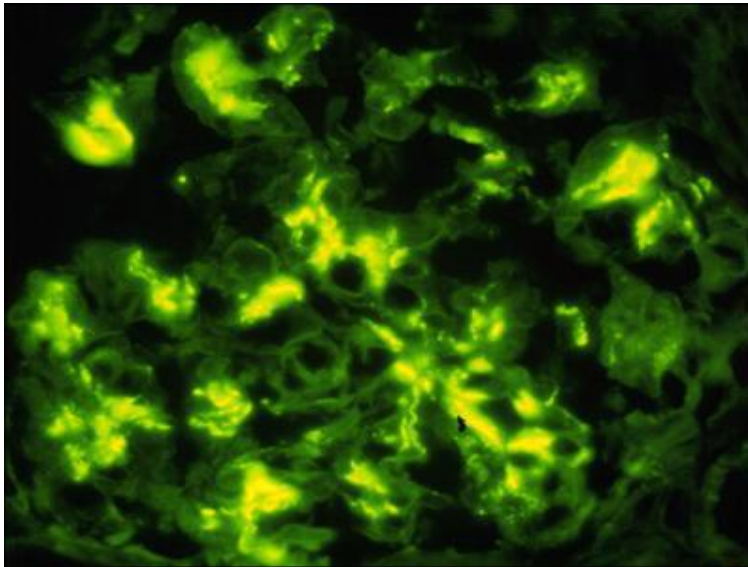
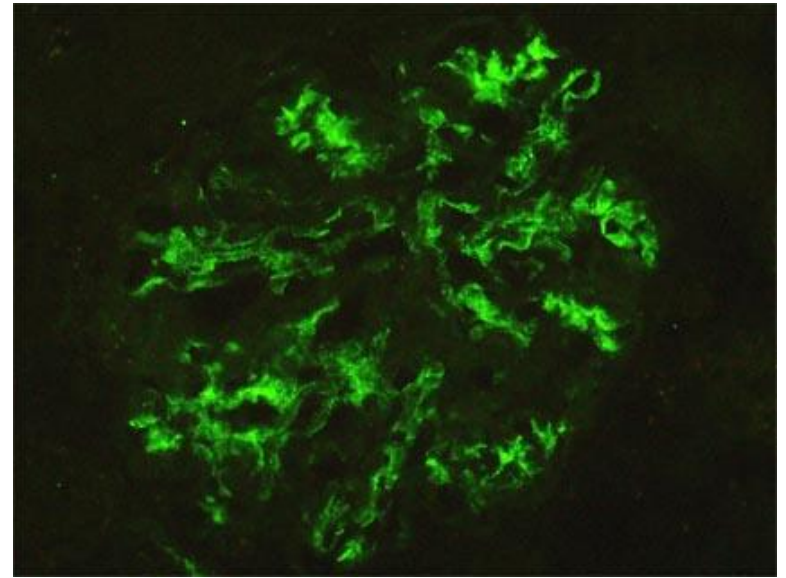




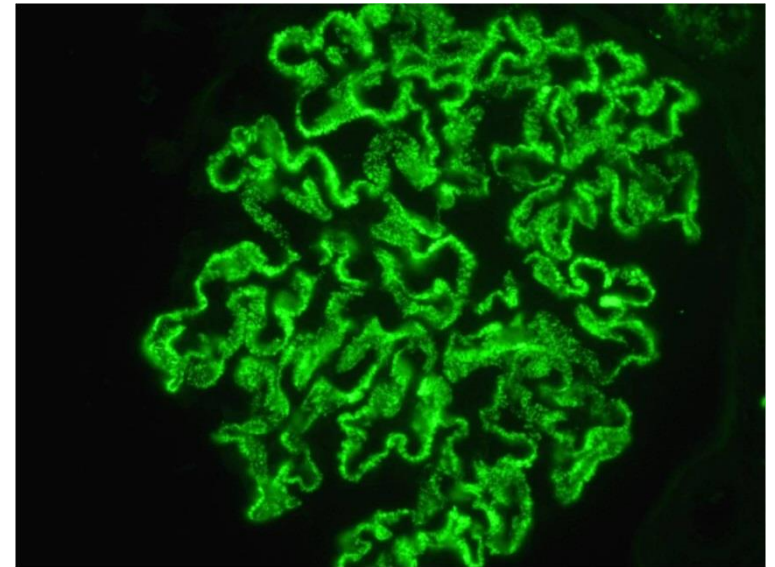
Pauci-immune GN



Lupus Nephritis III/IV



IgA Nephropathy



Goodpasture's Syndrome

# Clinical findings

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- Age - doesn't meter
- Sex - doesn't meter
- Race - white
- The most frequent cause of worry:

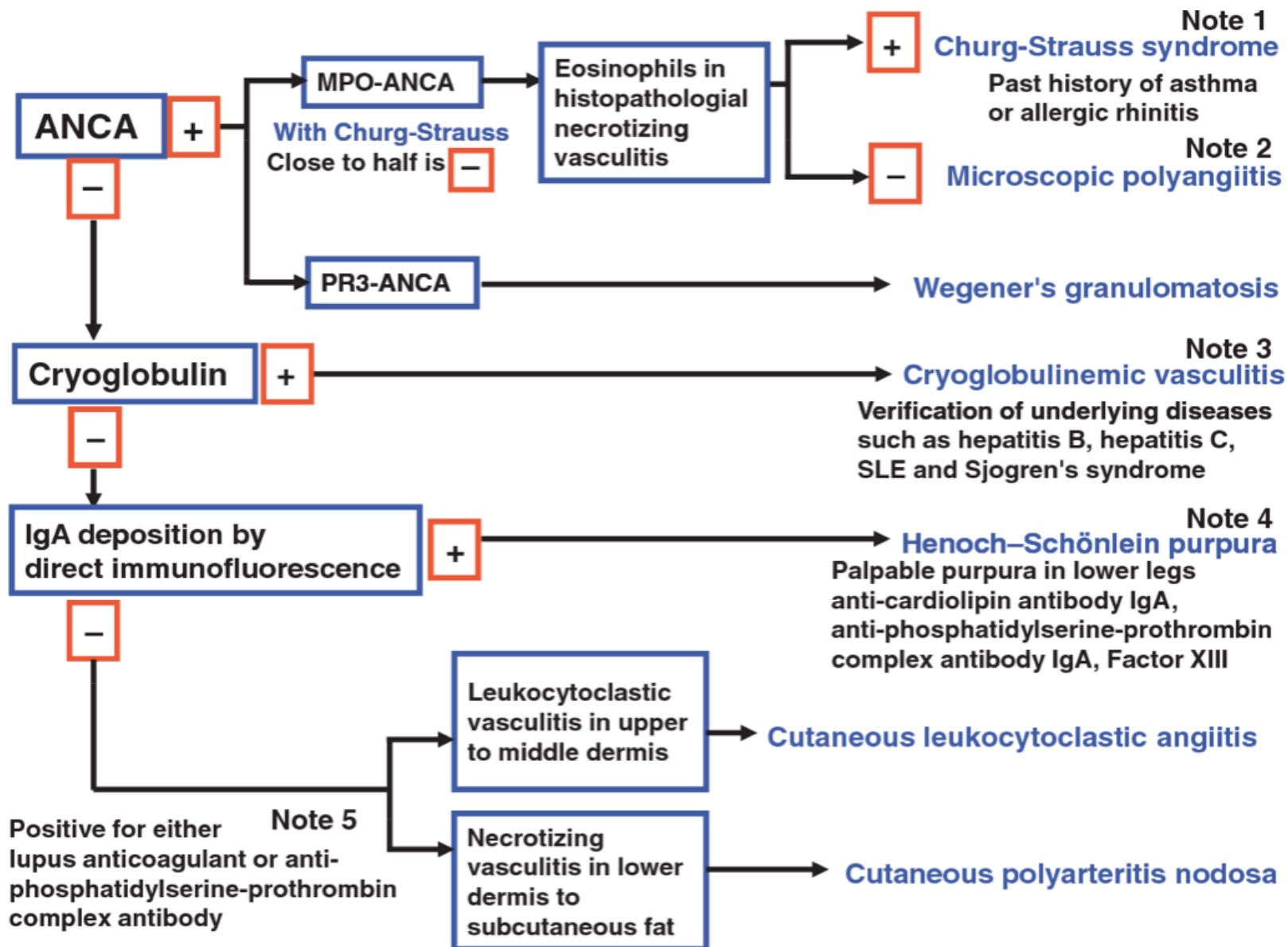
fatigue/bad filling  
sub febrile state/fever  
body weight loss  
arthritis

nasal obstruction/sinusitis  
hoarseness, stridor, snore  
cough, dyspnoea, hemoptysis  
skin lesion (purpura)

irregularity in urine sediment  
neurologic problems



# Algorithm of diagnosis





**Who to heal?**



**Everybody with active disease**

**Aim: to achieve full remission**

# Disease's Activity assessment

## **The Birmingham Vasculitis Activity Score (BVAS) GPA/MPA**

1. General symptoms - arthritis, fever, body weight loss, etc.
2. Main systems involvement

BVAS/GPA score 0-68 points

3 points:

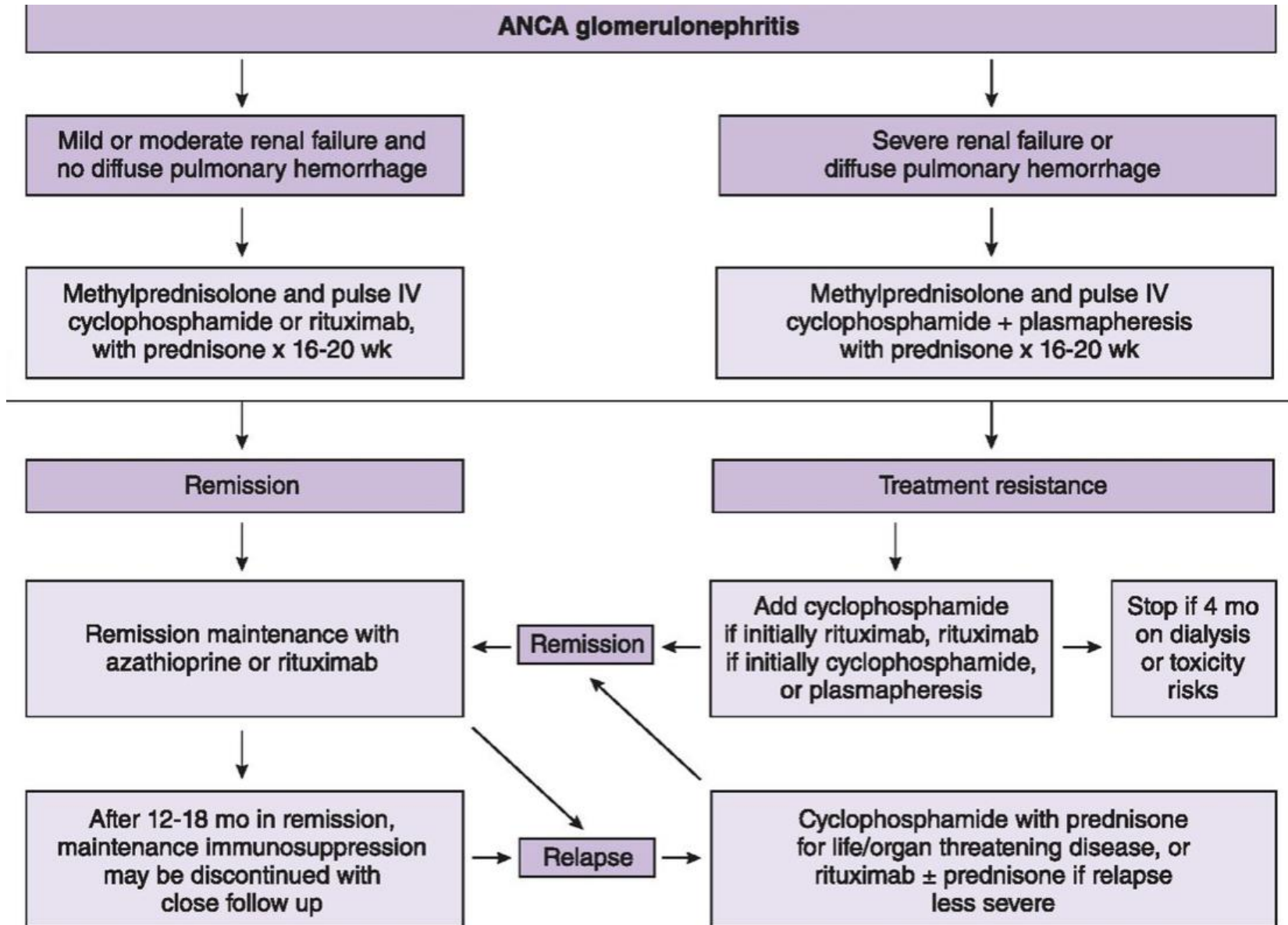
- gangrene
- alveolar bleeding
- respiratory insufficiency
- receiving hearing loss
- scleritis
- exudation/retinal bleeding
- abdominal angina (mesentery ischemia)
- erythrocytes casts
- eGFR decrease/ Crea increase
- neurologic symptoms

# BVAS score

**Table 3. Birmingham Vasculitis Activity Score**

Feature	None	Active disease	Feature	None	Active disease
<b>General</b>	<input type="checkbox"/>		<b>Cardiovascular</b>	<input type="checkbox"/>	
Arthralgia or arthritis		<input type="checkbox"/>	Cardiomyopathy		<input type="checkbox"/>
Fever $\geq 100^{\circ}\text{F}$ ( $38^{\circ}\text{C}$ )		<input type="checkbox"/>	Congestive cardiac failure		<input type="checkbox"/>
Myalgia		<input type="checkbox"/>	Ischemic cardiac pain		<input type="checkbox"/>
Weight loss $\geq 4$ lb (2 kg)		<input type="checkbox"/>	Loss of pulses		<input type="checkbox"/>
<b>Cutaneous</b>	<input type="checkbox"/>		Pericarditis		<input type="checkbox"/>
Gangrene		<input type="checkbox"/>	Valvular heart disease		<input type="checkbox"/>
Infarct		<input type="checkbox"/>	<b>Abdominal</b>	<input type="checkbox"/>	
Other skin vasculitis		<input type="checkbox"/>	Bloody diarrhea		<input type="checkbox"/>
Purpura		<input type="checkbox"/>	Ischemic abdominal pain		<input type="checkbox"/>
Ulcer		<input type="checkbox"/>	Peritonitis		<input type="checkbox"/>
<b>Mucous membranes/eyes</b>	<input type="checkbox"/>		<b>Renal</b>	<input type="checkbox"/>	
Adnexal inflammation		<input type="checkbox"/>	Creatinine 1.41 to 2.82 mg per dL (125 to 249 $\mu\text{mol}$ per L)		<input type="checkbox"/>
Blepharitis/keratitis		<input type="checkbox"/>	Creatinine 2.83 to 5.64 mg per dL (250 to 499 $\mu\text{mol}$ per L)		<input type="checkbox"/>
Blurred vision		<input type="checkbox"/>	Creatinine $\geq 5.65$ mg per dL (500 $\mu\text{mol}$ per L)		<input type="checkbox"/>
Genital ulcers		<input type="checkbox"/>	Creatinine clearance decrease of $> 25$ percent		<input type="checkbox"/>
Mouth ulcers/granulomata		<input type="checkbox"/>	Hematuria ( $\geq 10$ red blood cells per high-power field)		<input type="checkbox"/>
Red eye conjunctivitis/retinal hemorrhages		<input type="checkbox"/>	Hypertension		<input type="checkbox"/>
Red eye (epi)scleritis		<input type="checkbox"/>	Proteinuria $> 1+$		<input type="checkbox"/>
Retinal vasculitis		<input type="checkbox"/>	<b>Nervous system</b>	<input type="checkbox"/>	
Significant proptosis		<input type="checkbox"/>	Cord lesion		<input type="checkbox"/>
Sudden vision loss		<input type="checkbox"/>	Cranial nerve palsy		<input type="checkbox"/>
Thrombosis/retinal exudates		<input type="checkbox"/>	Headache		<input type="checkbox"/>
Uveitis		<input type="checkbox"/>	Meningitis		<input type="checkbox"/>
<b>Ears, nose, throat</b>	<input type="checkbox"/>		Motor mononeuritis multiplex		<input type="checkbox"/>
Bloody nasal discharge/nasal crusts/conductive hearing loss		<input type="checkbox"/>	Seizures (not hypertensive)		<input type="checkbox"/>
Paranasal sinus involvement		<input type="checkbox"/>	Sensory peripheral neuropathy		<input type="checkbox"/>
Sensorineural hearing loss		<input type="checkbox"/>	Stroke		<input type="checkbox"/>
Subglottic stenosis		<input type="checkbox"/>	<b>Other</b>	<input type="checkbox"/>	
Ulcers or granulomata		<input type="checkbox"/>			<input type="checkbox"/>
<b>Chest</b>	<input type="checkbox"/>				<input type="checkbox"/>
Endobronchial involvement		<input type="checkbox"/>			<input type="checkbox"/>
Hemorrhage		<input type="checkbox"/>			<input type="checkbox"/>
Infiltrate		<input type="checkbox"/>			<input type="checkbox"/>
Massive hemoptysis/alveolar nodules or cavities		<input type="checkbox"/>			<input type="checkbox"/>
Pleural effusion/pleurisy		<input type="checkbox"/>	<b>Persistent disease only</b>		<input type="checkbox"/>
Respiratory failure		<input type="checkbox"/>	All the above abnormalities are caused by low-grade disease and not new or worse disease		
Wheeze		<input type="checkbox"/>			

# Therapy





***Dziękuję za uwagę***