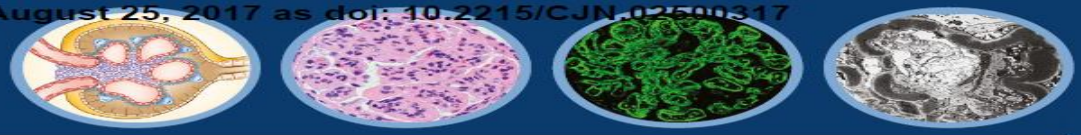
VASCULITIS

Ιωάννης Γ. Γριβέας,MD,PhD

athens-NEPHROLOGY

CJASN ePress. Published on August 25, 2017 as doi: 10.2215/CJN.02500317



ANCA Glomerulonephritis and Vasculitis

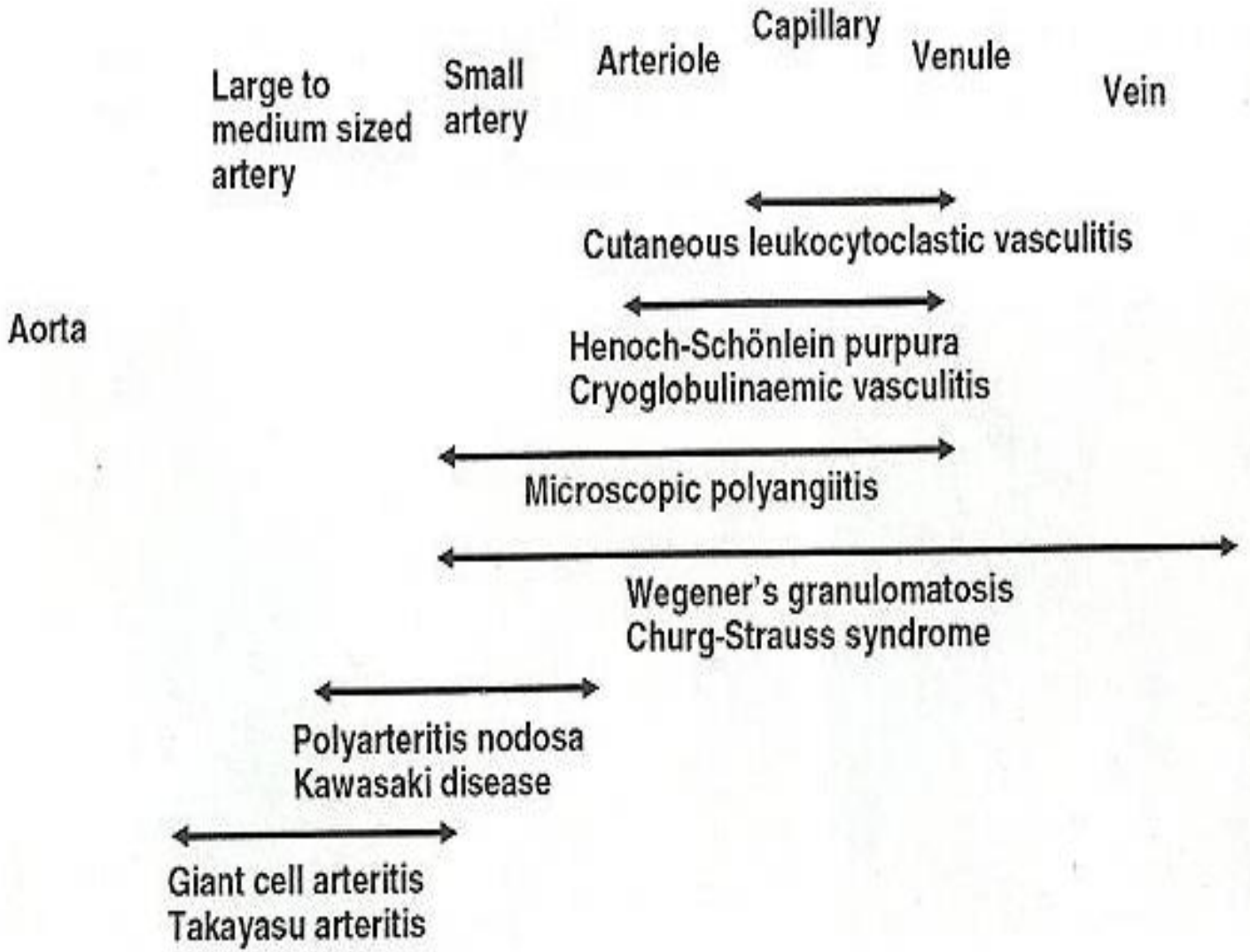
J. Charles Jennette and Patrick H. Nachman

Table 1. CHCC 2012 categories of ANCA-associated vasculitis (modified from reference (1))

CHCC 2012 Name	CHCC 2012 Definition
ANCA-associated vasculitis	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (*i.e.*, capillaries, venules, arterioles, and small arteries), associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity, *e.g.*, MPO-ANCA, PR3-ANCA, ANCA-negative.
Microscopic polyangiitis	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (*i.e.*, capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing GN is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.
Granulomatosis with polyangiitis (Wegener)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small-to-medium vessels (*e.g.*, capillaries, venules, arterioles, arteries, and veins). Necrotizing GN is common.
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small-to-medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when GN is present.

CHCC 2012, 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides.

Chapel Hill Consensus Nomenclature of Vasculitis



CP1071102-3

Chapel Hill Consensus Nomenclature of Vasculitis

Capillary

Large to medium sized artery | Small artery | Arteriole | Venule | Vein

Cutaneous leukocytoclastic vasculitis

Aorta

Henoch-Schönlein purpura
Cryoglobulinaemic vasculitis

Microscopic polyangiitis

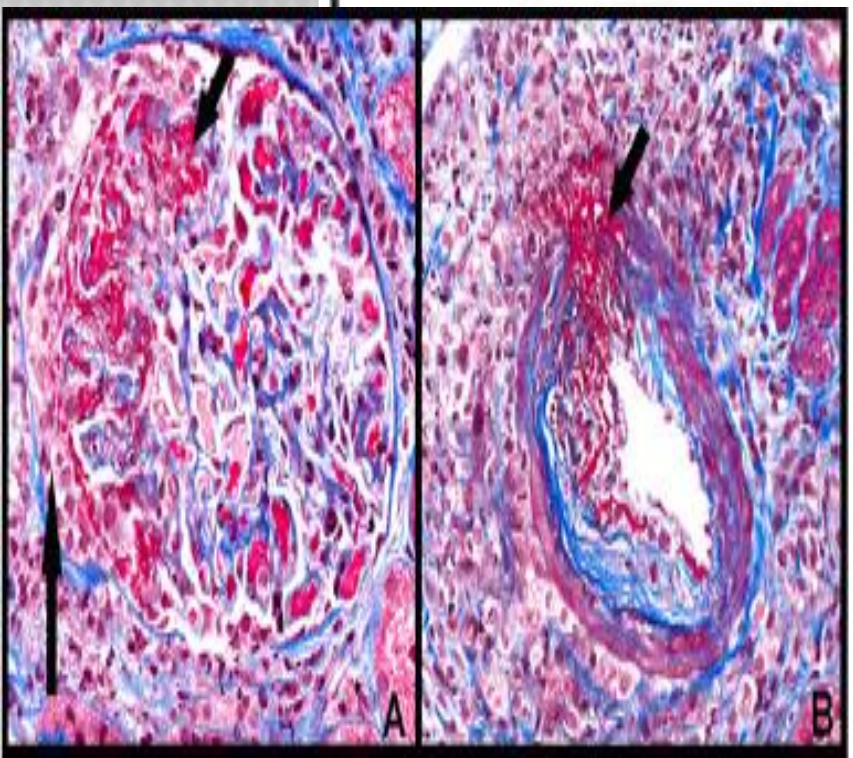
Wegener's granulomatosis
Churg-Strauss syndrome

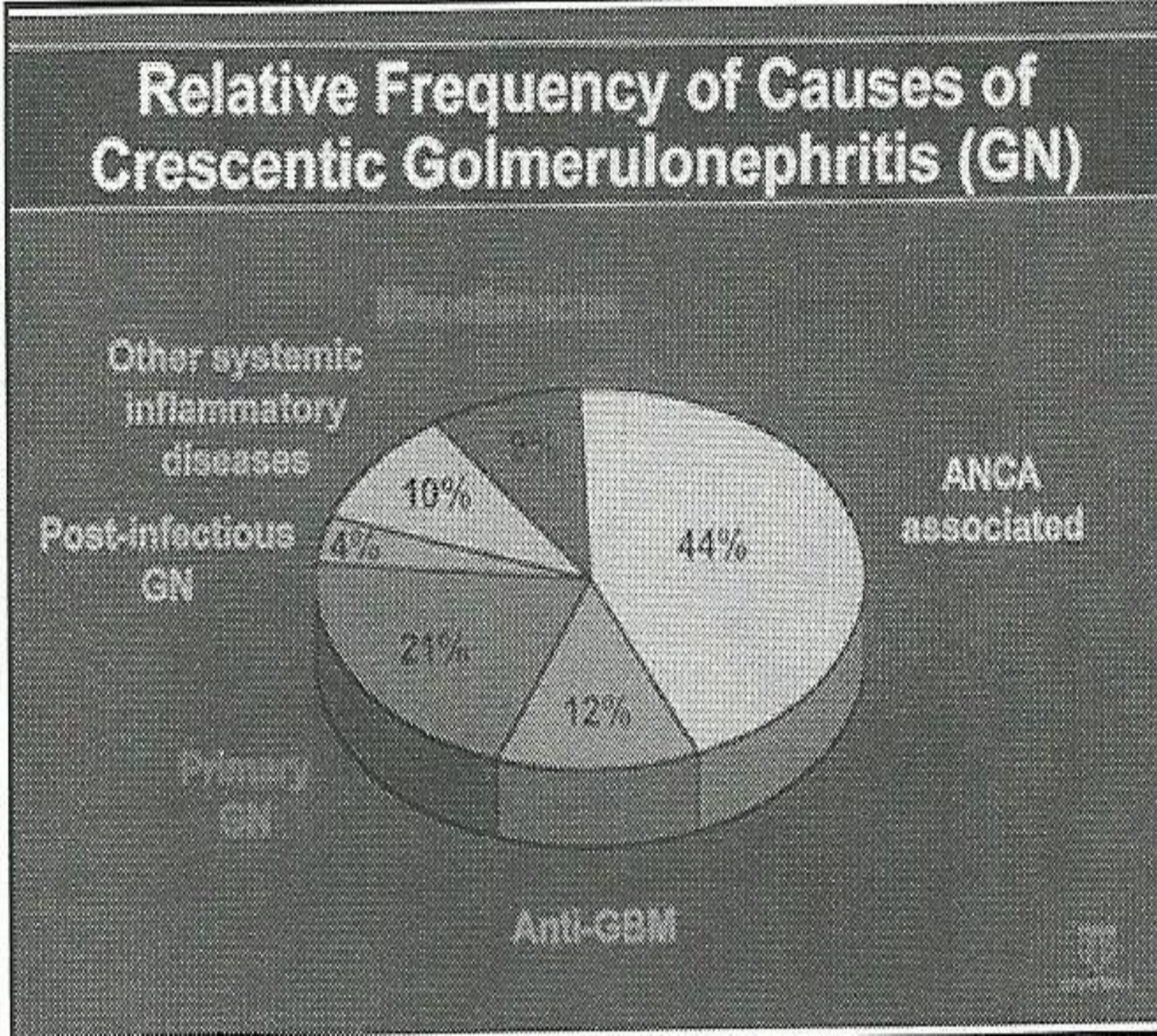
teritis nodosa
aki disease

ANCA-associated

ritis
ritis

Arthritis Rheum 1994; 37:187-192




Relative Frequency of Causes of Crescentic Golmerulonephritis (GN)
Other systemic inflammatory diseases
10%
Post-infectious GN
4%
21%
44%
ANCA associated
12%
Anti-GBM

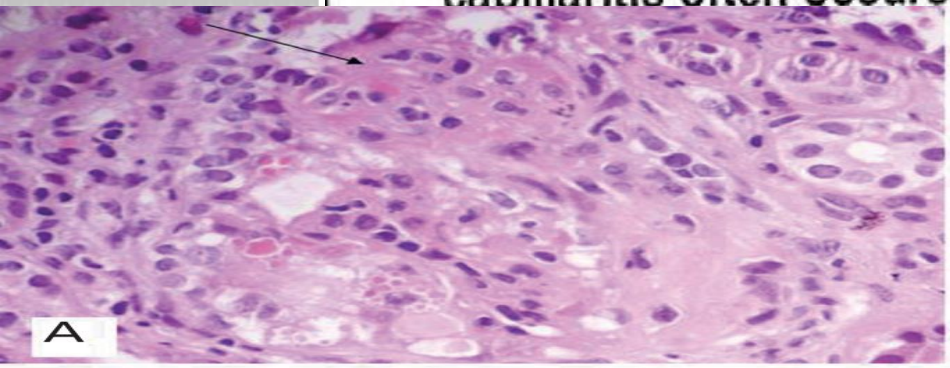
Frequency of Different Types of Crescentic GN in Consecutive Native Renal Biopsies at the UNC

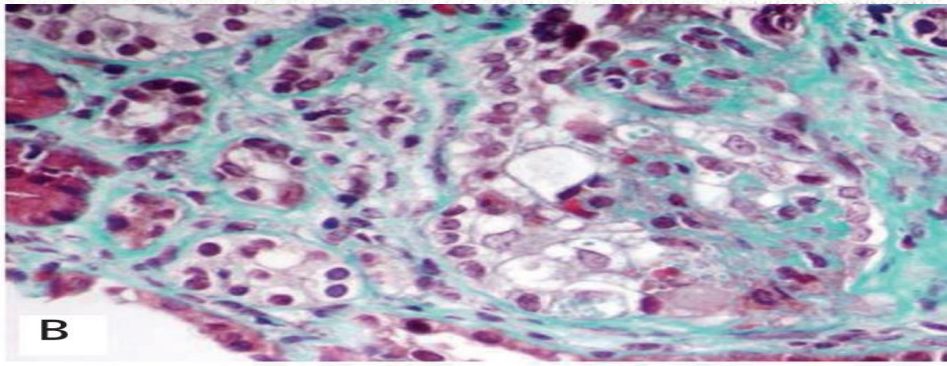
	Pauci-immune		Immune-complex		Anti-GBM		Others	
	%	No.	%	No.	%	No.	%	No.
All (n=632)	60	377/632	24	154/632	15	92/632	1	9/632
Age 1-20 yr (n=73)	42	31/73	45	33/73	12	9/73	0	0
Age 21-60 yr (n=303)	48	145/303	35	106/303	15	44/303	3	8/303
Age 61-100 yr (n=256)	79	201/256	6	15/256	15	39/256	0	1/256

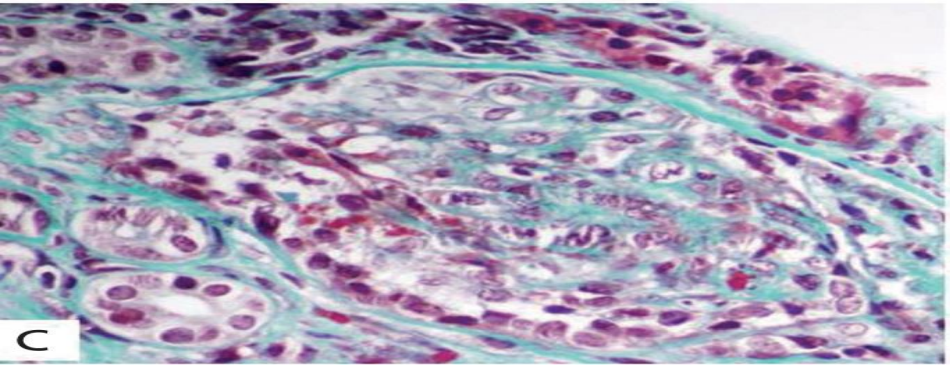
Jennette JC: Kidney Int 63:1166, 2003

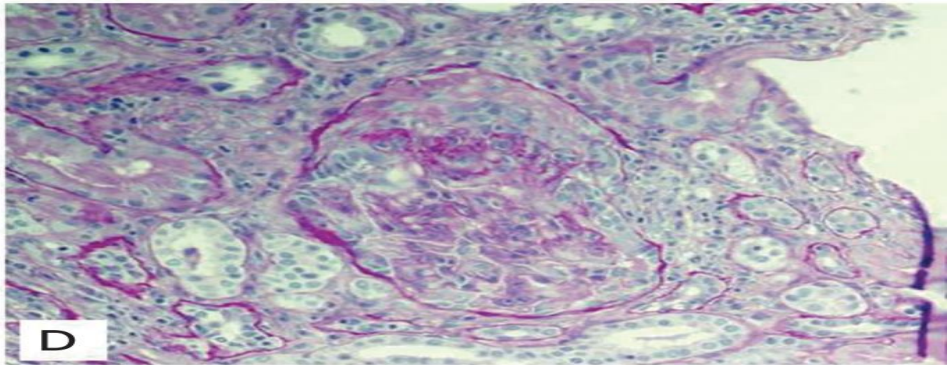
Microscopic Polyangiitis

- Necrotizing vasculitis with few or no immune deposits affecting small vessels (ie, capillaries, venules, or arterioles)
- Necrotizing arteritis involving small- and medium-sized arteries can be present
- Necrotizing glomerulonephritis is very common, pulmonary capillaritis often occurs



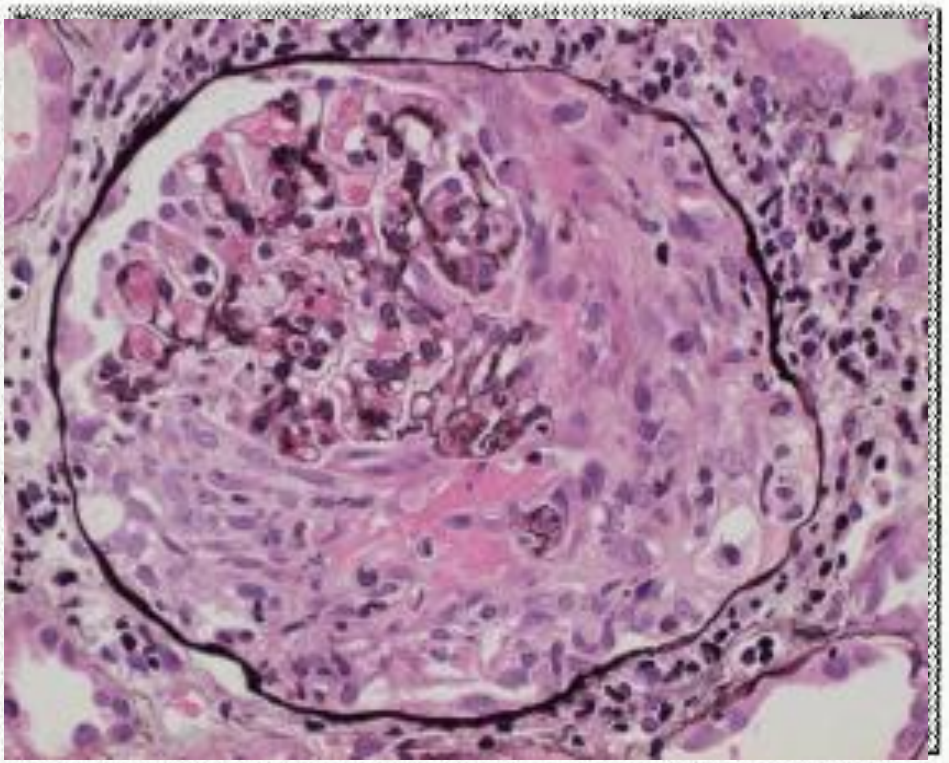






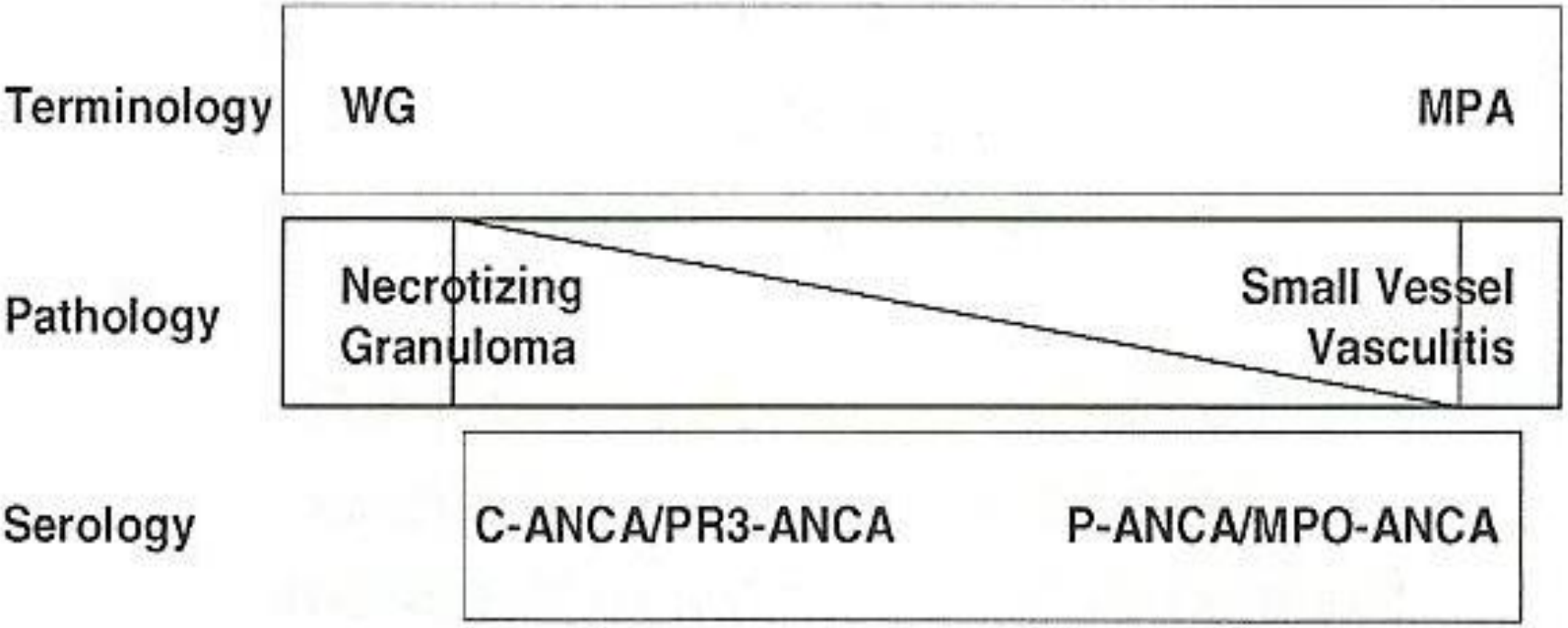
Wegener's Granulomaotsis

Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels (eg, capillaries, venules, arterioles, and arteries); necrotizing glomerulonephritis is common

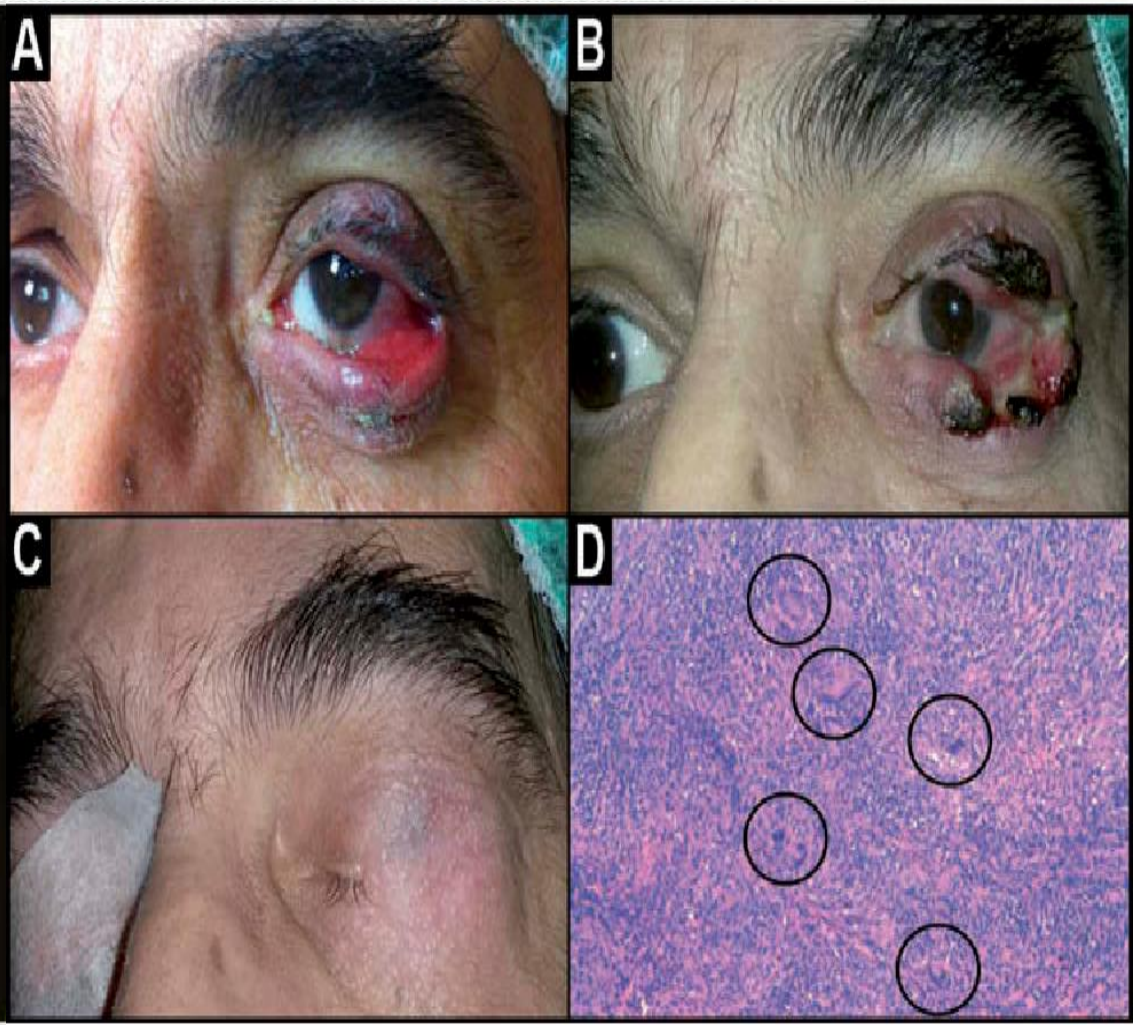


CP1042320-2

The Spectrum of WG-MPA

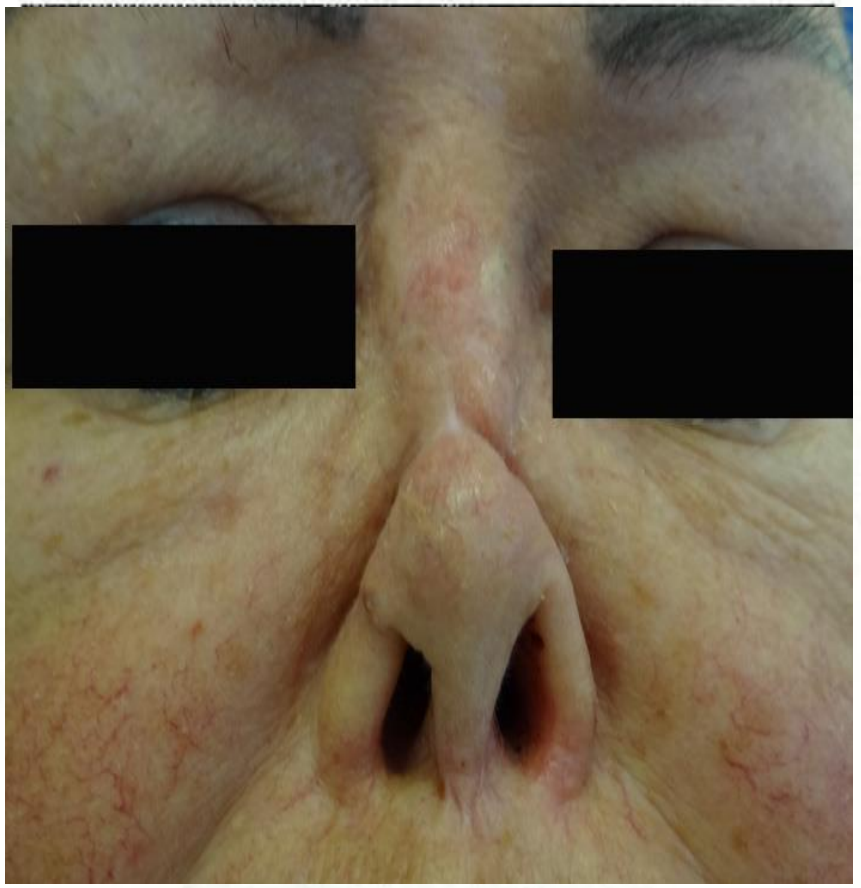


Ophthalmologic Manifestations of Wegener's Granulomatosis



ENT Manifestations of WG

- Diffuse ulceration
- Septal perforations now rarer
- Pansinusitis
- Face pain
- Large crusts pathognomic
- Hard palate intact

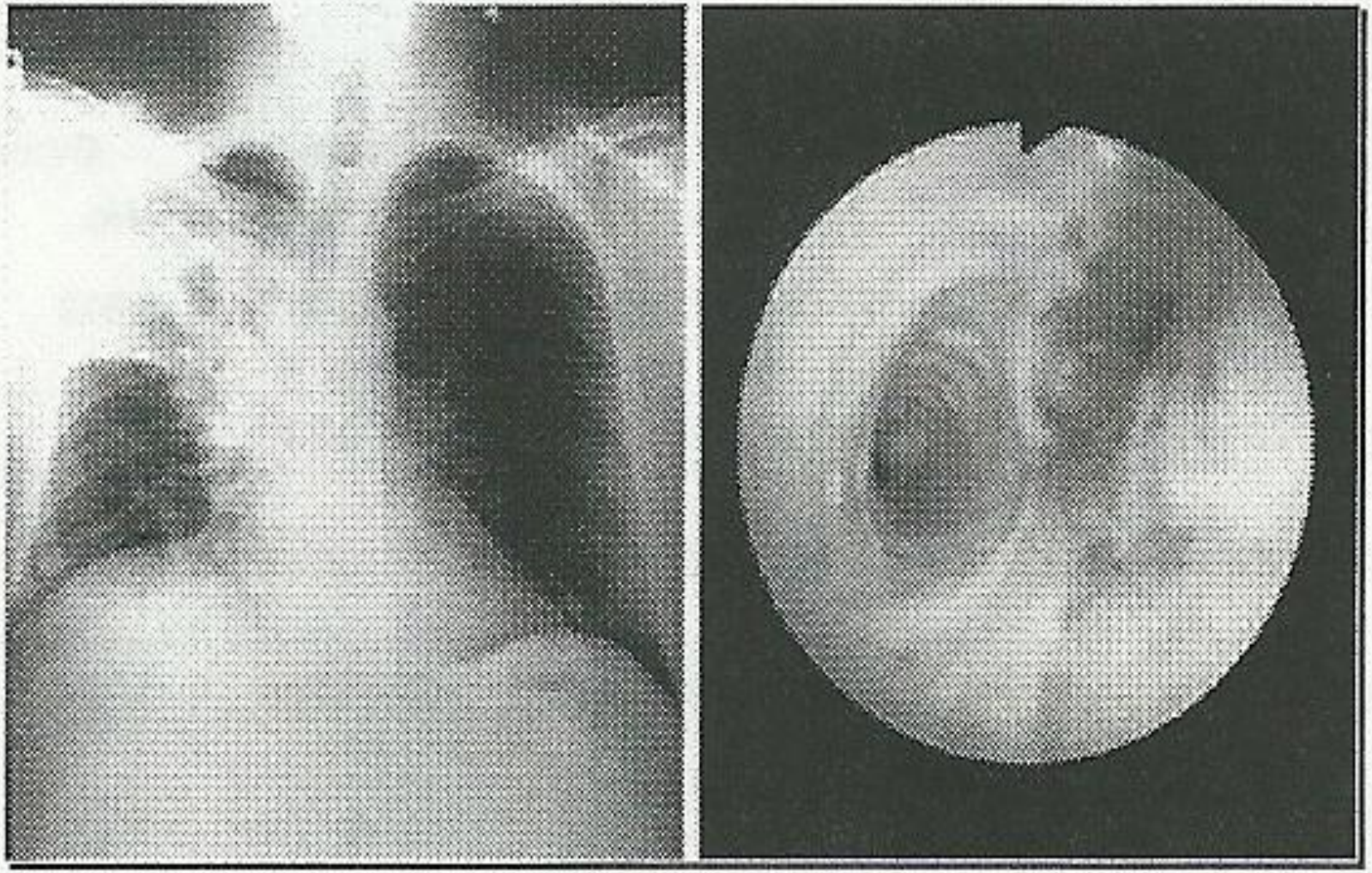


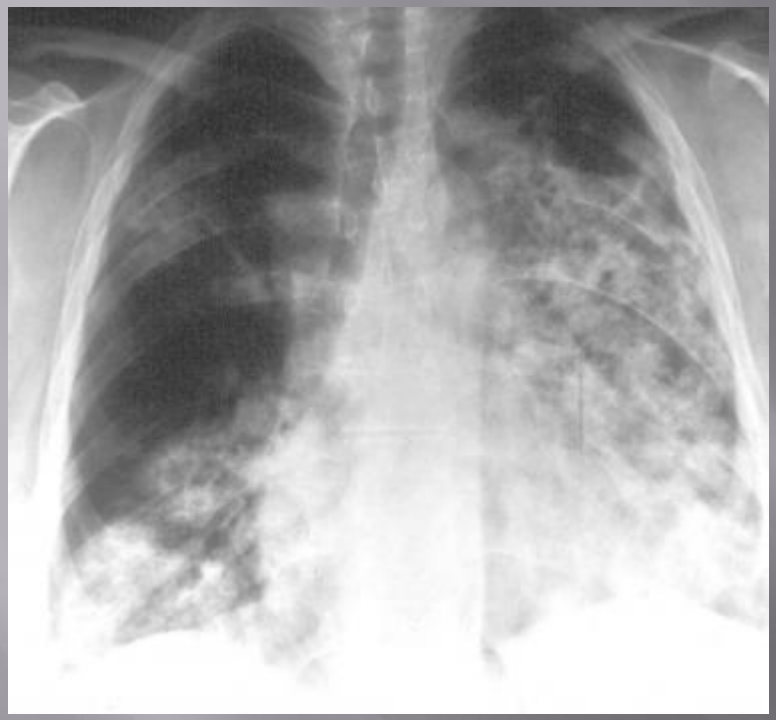
Subglottic Stenosis in WG

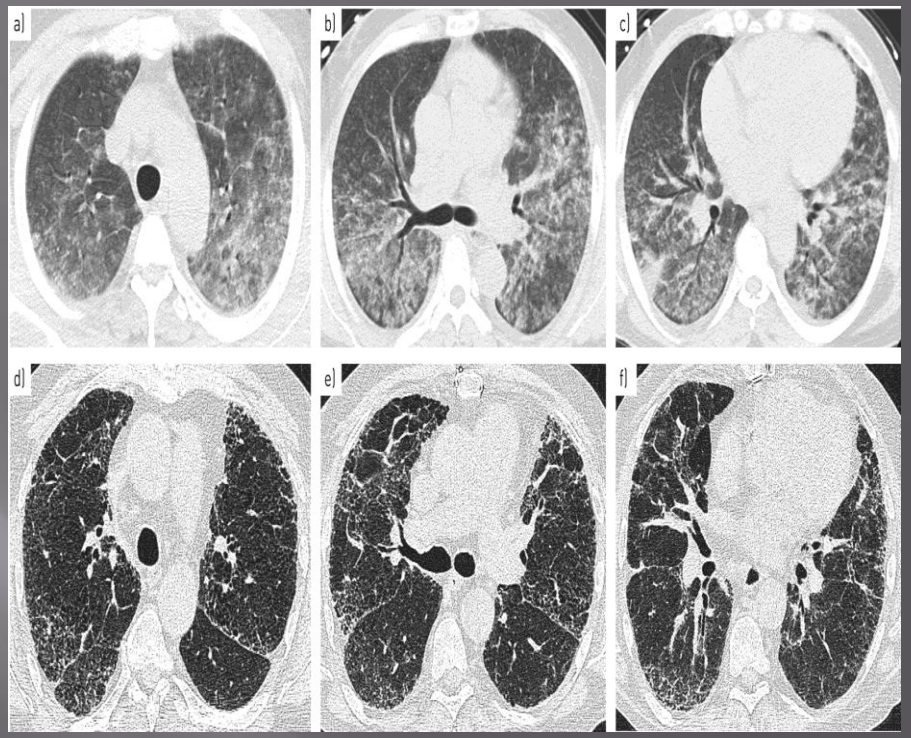
- Occurs in about 25% of WG patients.
- Frequently occurs in the absence of other disease activity or during therapy.
- Tracheostomy necessary in 56%.
- Treatment with dilatation and injection of long-acting corticosteroid or mitomycin C.

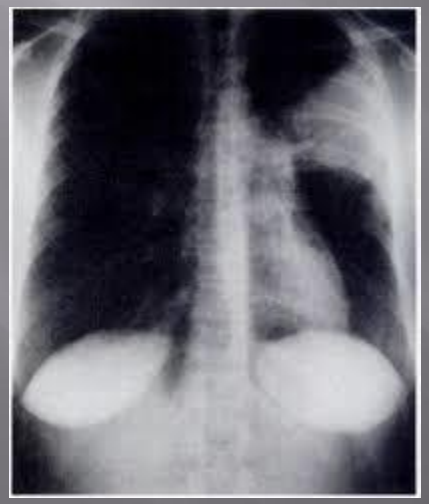
Langford. Arthritis Rheum. 1996; 39:1754-1760

Endobronchial Involvement of WG



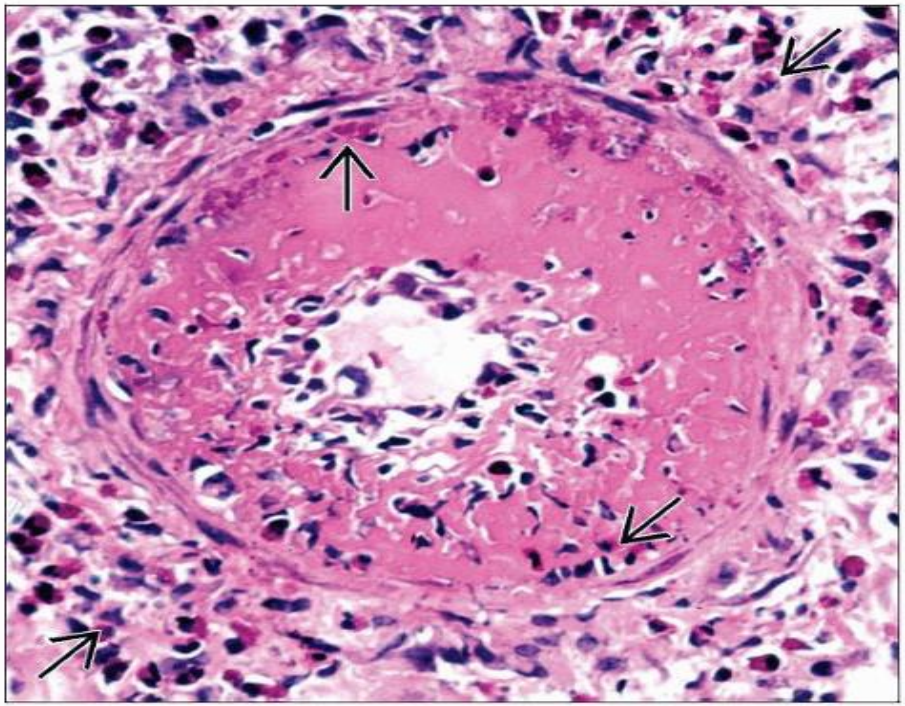


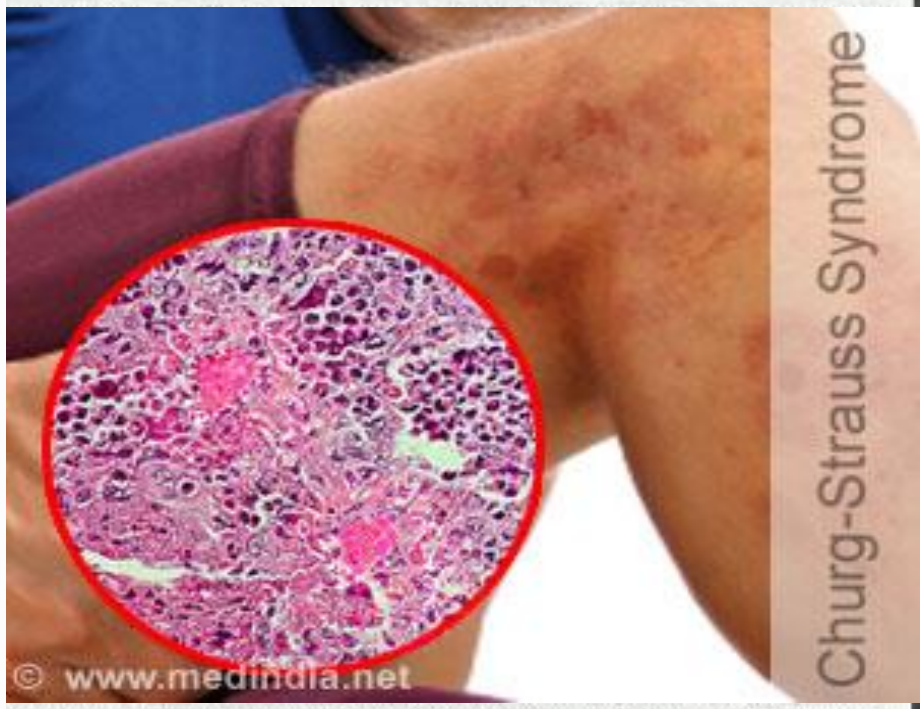

a)
b)
c)
d)
e)
f)



Churg-Strauss Syndrome

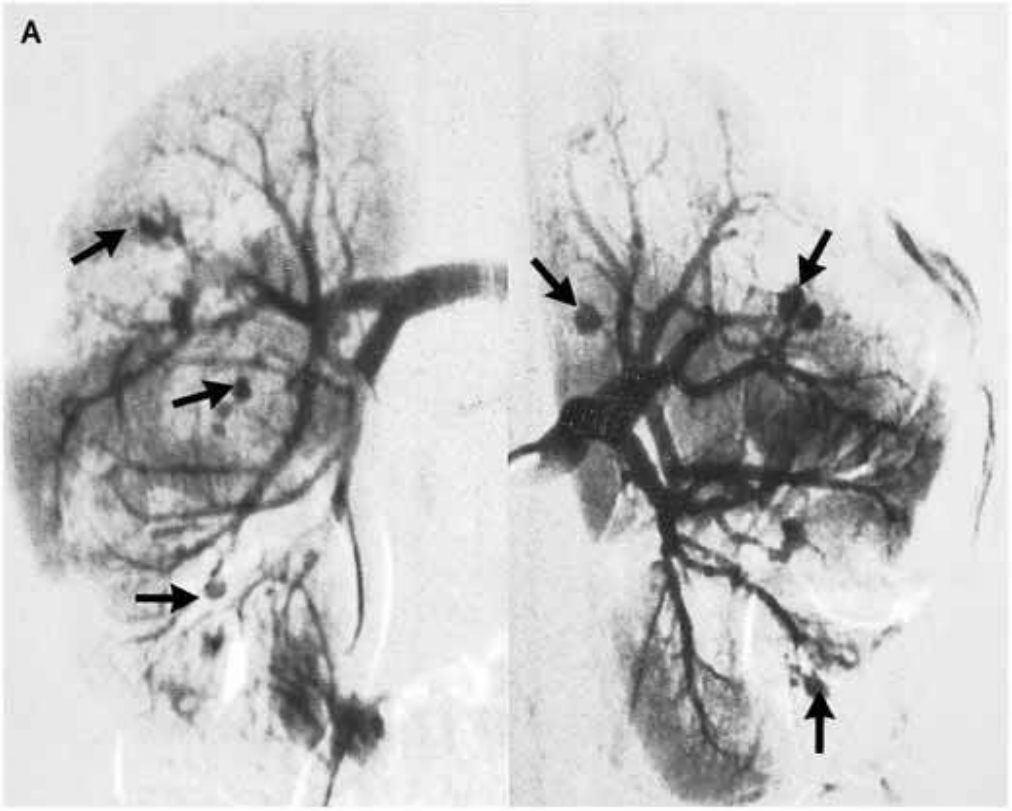
Eosinophil rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels; associated with blood eosinophilia and usually asthma or other form of atopy

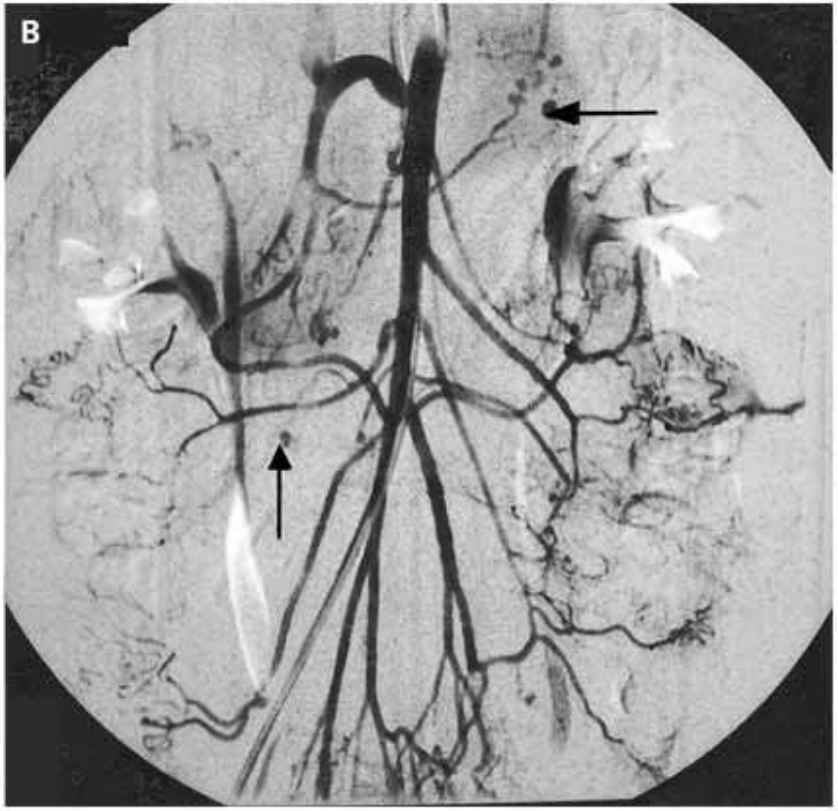




Polyarteritis Nodosa

Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules





Signs and Symptoms of Necrotizing Small Vessel Vasculitis

- Cutaneous purpura, nodules and ulcerations
- Peripheral neuropathy (mononeuritis multiplex)
- Abdominal pain and blood in stools
- Hematuria, proteinuria and renal failure
- Hemoptysis and pulmonary infiltrates or nodules
- Necrotizing (hemorrhagic) sinusitis
- Myalgias and arthralgias
- Muscle and pancreatic enzymes in blood

Approximate Frequency of ANCA with Specificity for Proteinase 3 (PR3-ANCA) or Myeloperoxidase (MPO-ANCA) in Patients with Active Untreated Microscopic Polyangiitis, Wegener's Granulomatosis, and Churg-Strauss Syndrome

	Microscopic polyangiitis	Wegener's granulomatosis	Churg-Strauss syndrome
PR3-ANCA (%)	40	75	10
MPO-ANCA (%)	50	20	60
Negative (%)	10	5	30

Jennette and Falk: Sem Diag Path, 2001

Cutaneous Manifestations of Vasculitis

- Purpura
- Petechiae
- Ecchymoses
- Erythematous macules
- Papules
- Nodules
- Urticaria
- Livedo reticularis

Necrosis

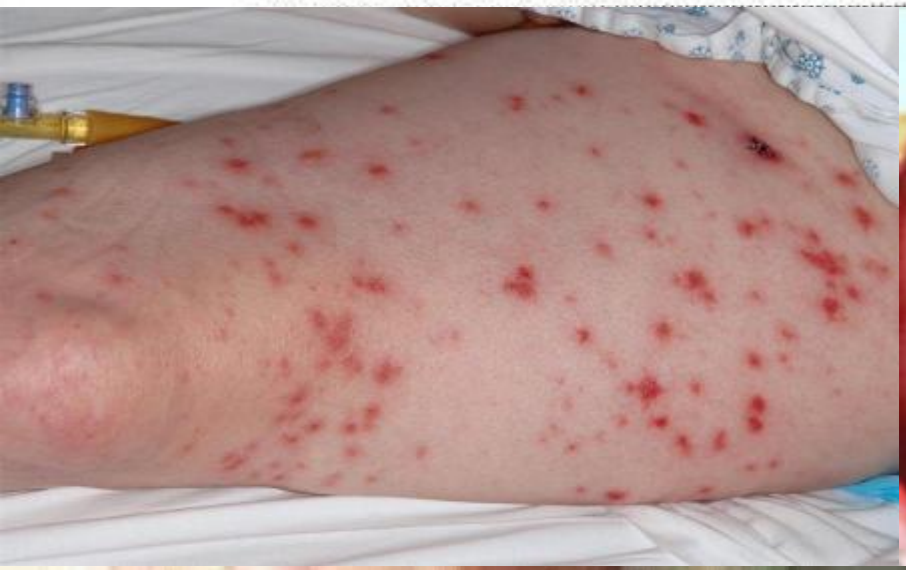
Ulcerations

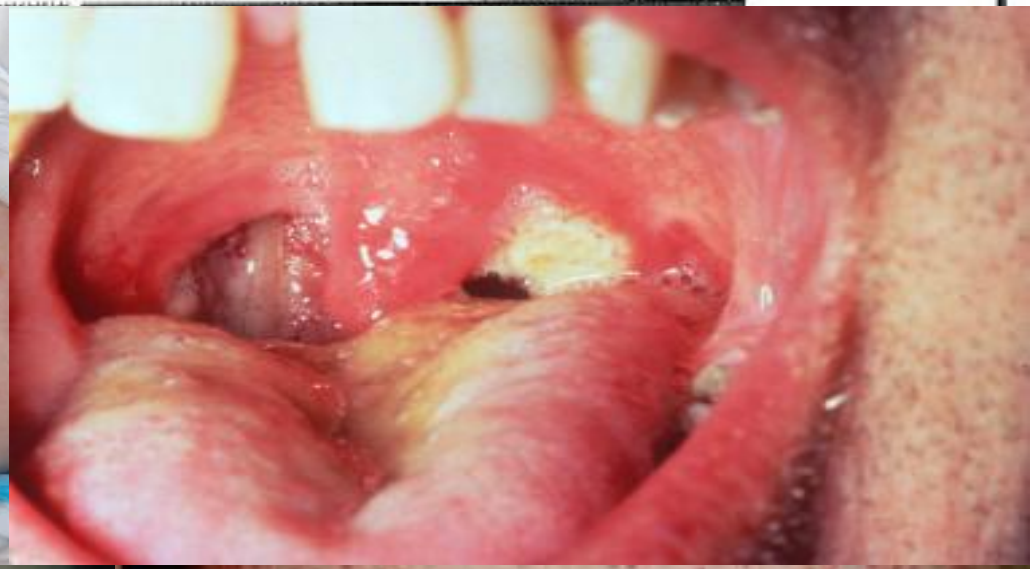
Vesicles

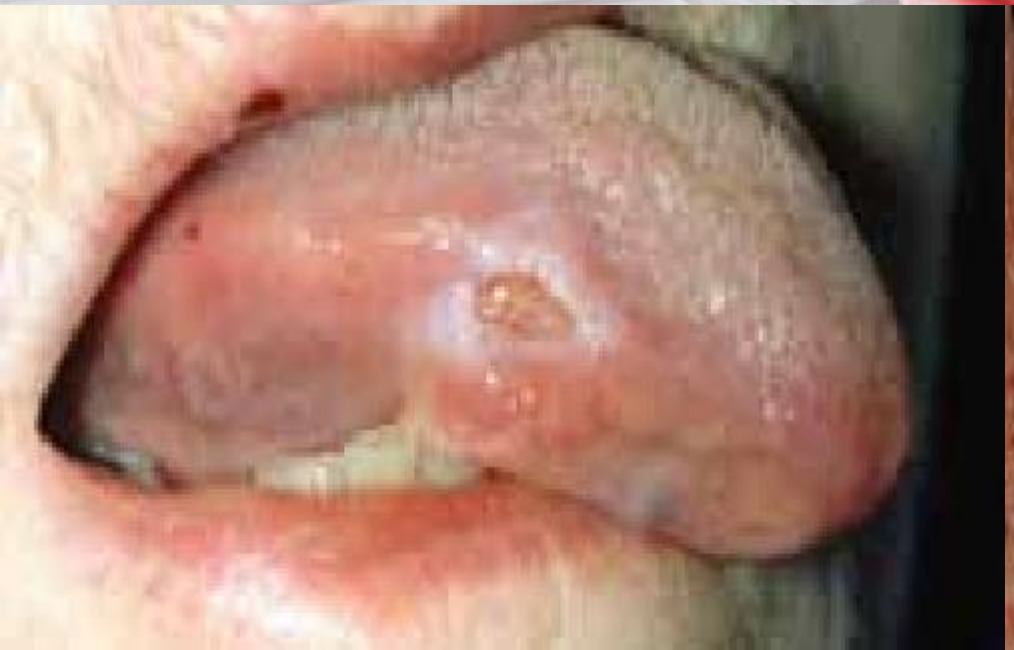
Bullae

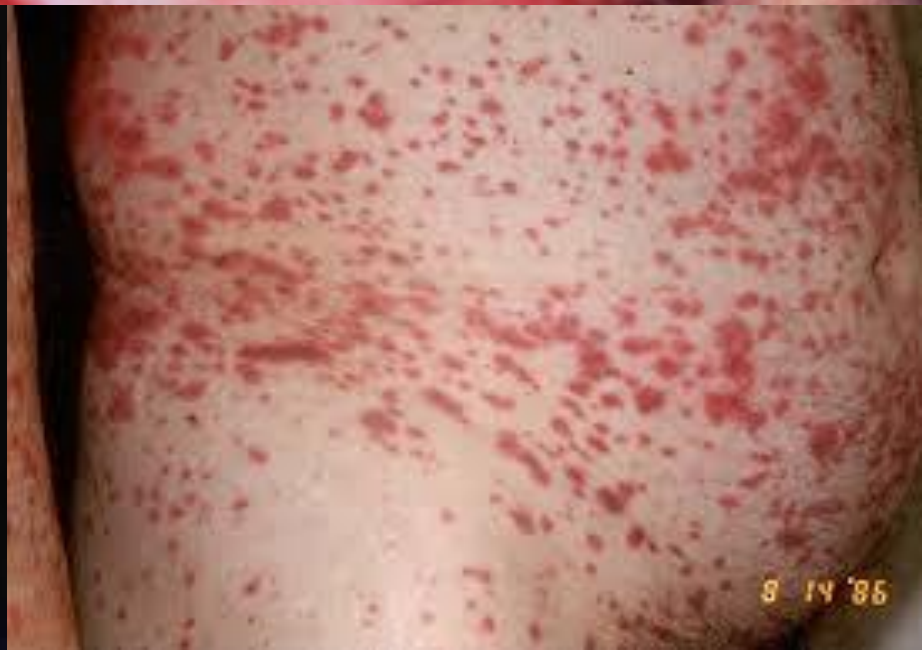
- Pyoderma gangrenosum - like lesions
- Sweet's like lesion

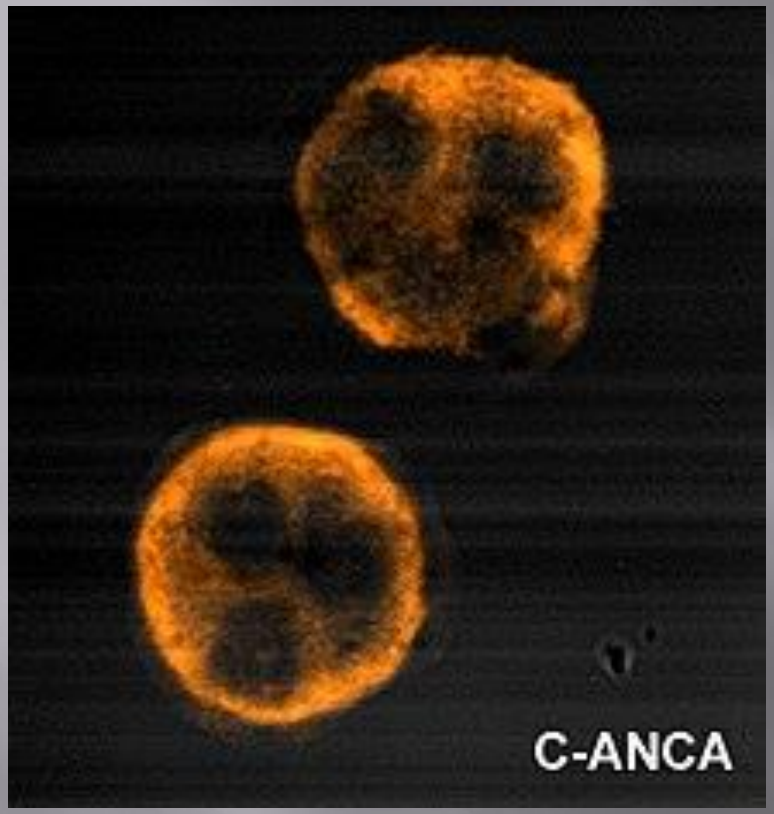
Skin Manifestations of WG

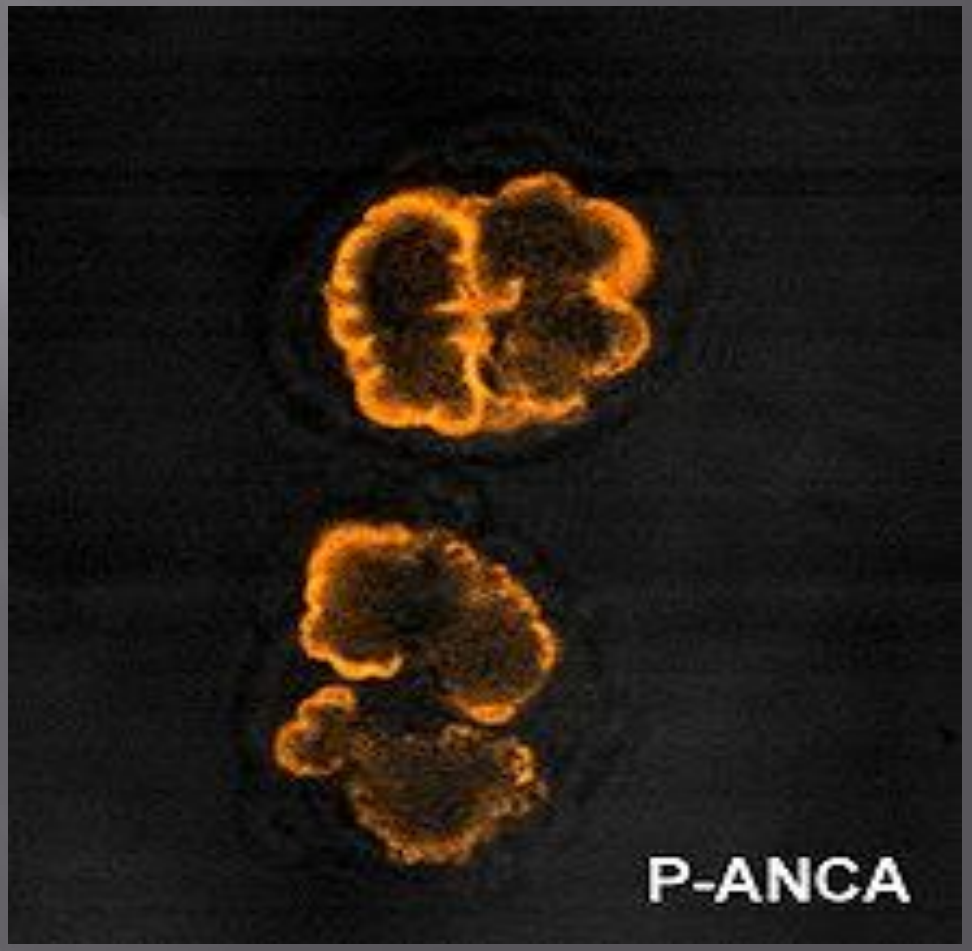


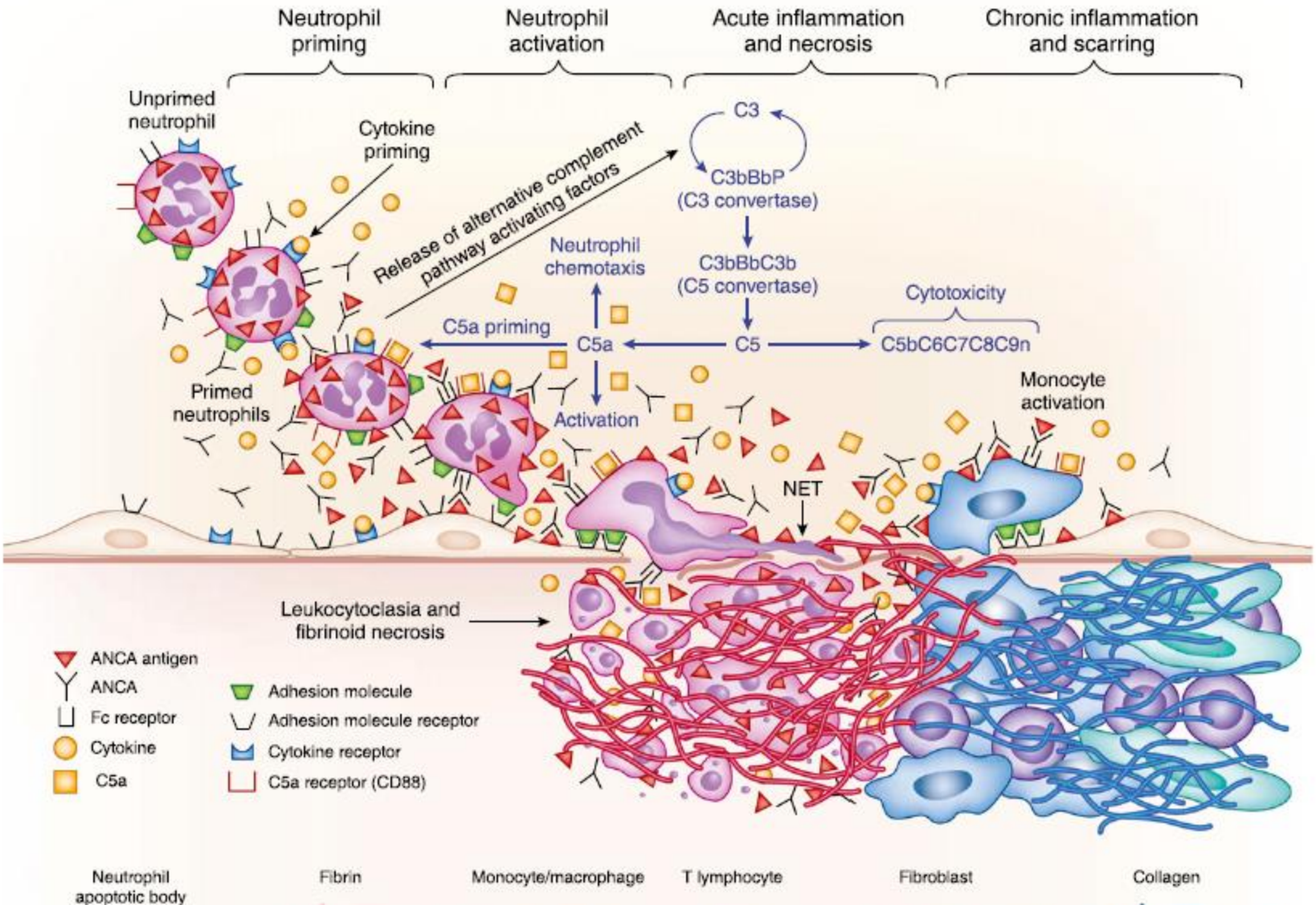







C-ANCA


P-ANCA


Neutrophil priming
Neutrophil activation
Acute inflammation and necrosis
Chronic inflammation and scarring
Unprimed neutrophil
Cytokine priming
Release of alternative complement pathway activating factors
C3
C3bBbP (C3 convertase)
C3bBbC3b (C5 convertase)
Neutrophil chemotaxis
Cytotoxicity
C5a priming
C5a
C5
C5bC6C7C8C9n
Primed neutrophils
Activation
Monocyte activation
NET
Leukocytoclasia and fibrinoid necrosis
ANCA antigen
ANCA
Fc receptor
Cytokine
C5a
Adhesion molecule
Adhesion molecule receptor
Cytokine receptor
C5a receptor (CD88)
Neutrophil apoptotic body
Fibrin
Monocyte/macrophage
T lymphocyte
Fibroblast
Collagen

How should we treat patients with ANCA Vasculitis?

Treatment Induction: Corticosteroids Alone Do Not Work

- Remission Rate
  - Cyclophosphamide 85%
  - Corticosteroids 56% ($p = 0.003$)
- Risk of relapse increased 3-fold in corticosteroids alone group
  - (RP = 3.2, 95% CI = 1.2, 8.3*)
  - *controlling for age, serum creatinine, duration of treatment, and presence of arteriosclerosis on biopsy

Induction of Remission

- High-dose corticosteroids and cyclophosphamide

  Combined therapy will induce remission in > 80% of cases
- Dose, route, and duration of therapy vary
- Prednisone at 1 mg/kg/day (maximum of 80mg) reducing to 10mg/day by 3 months
- Cyclophosphamide at 2 mg/kg/day, adjusted for age and renal function, for 3 months, provided the white blood cell count remains above $4 \times 10^9/l$

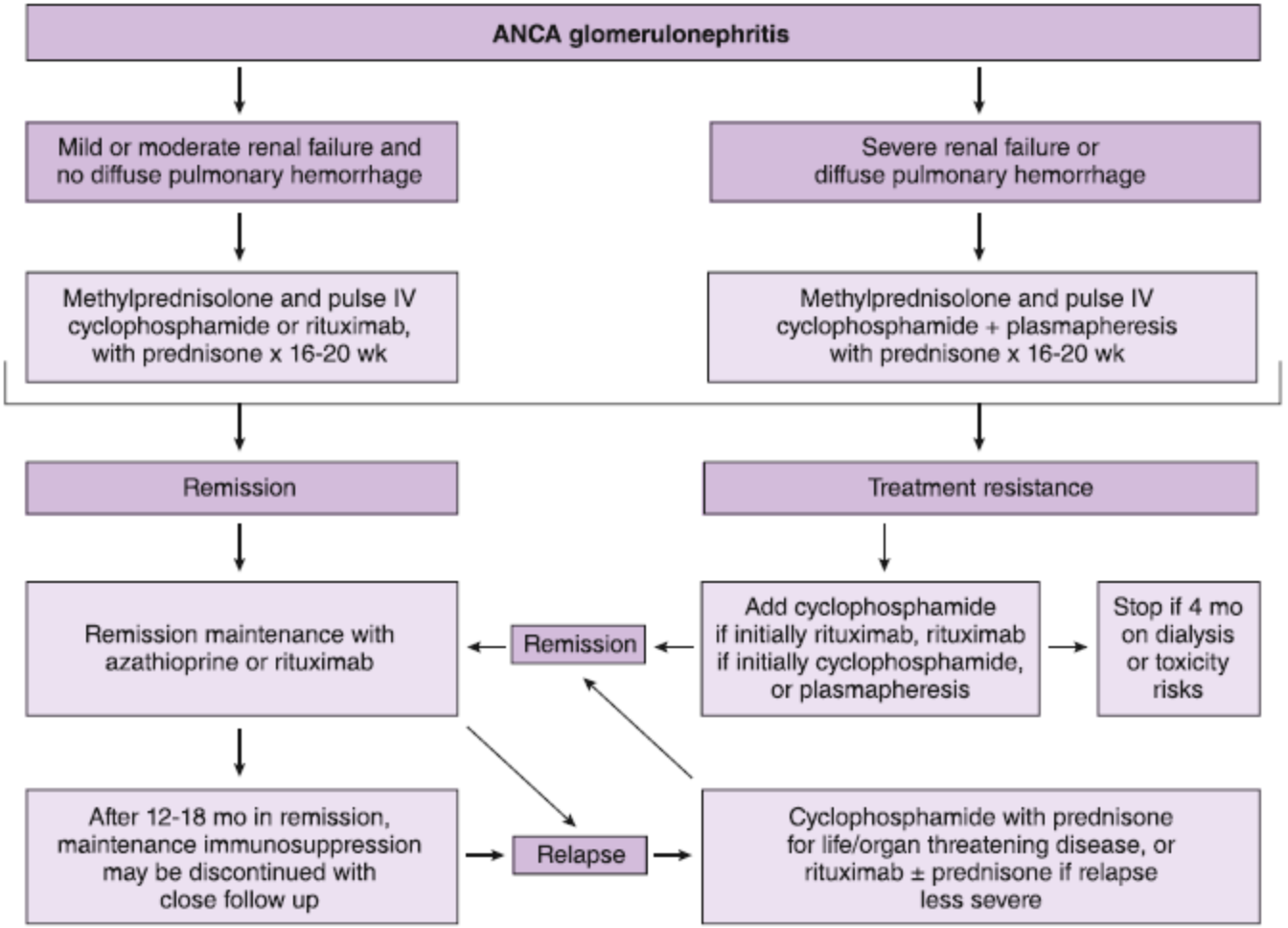
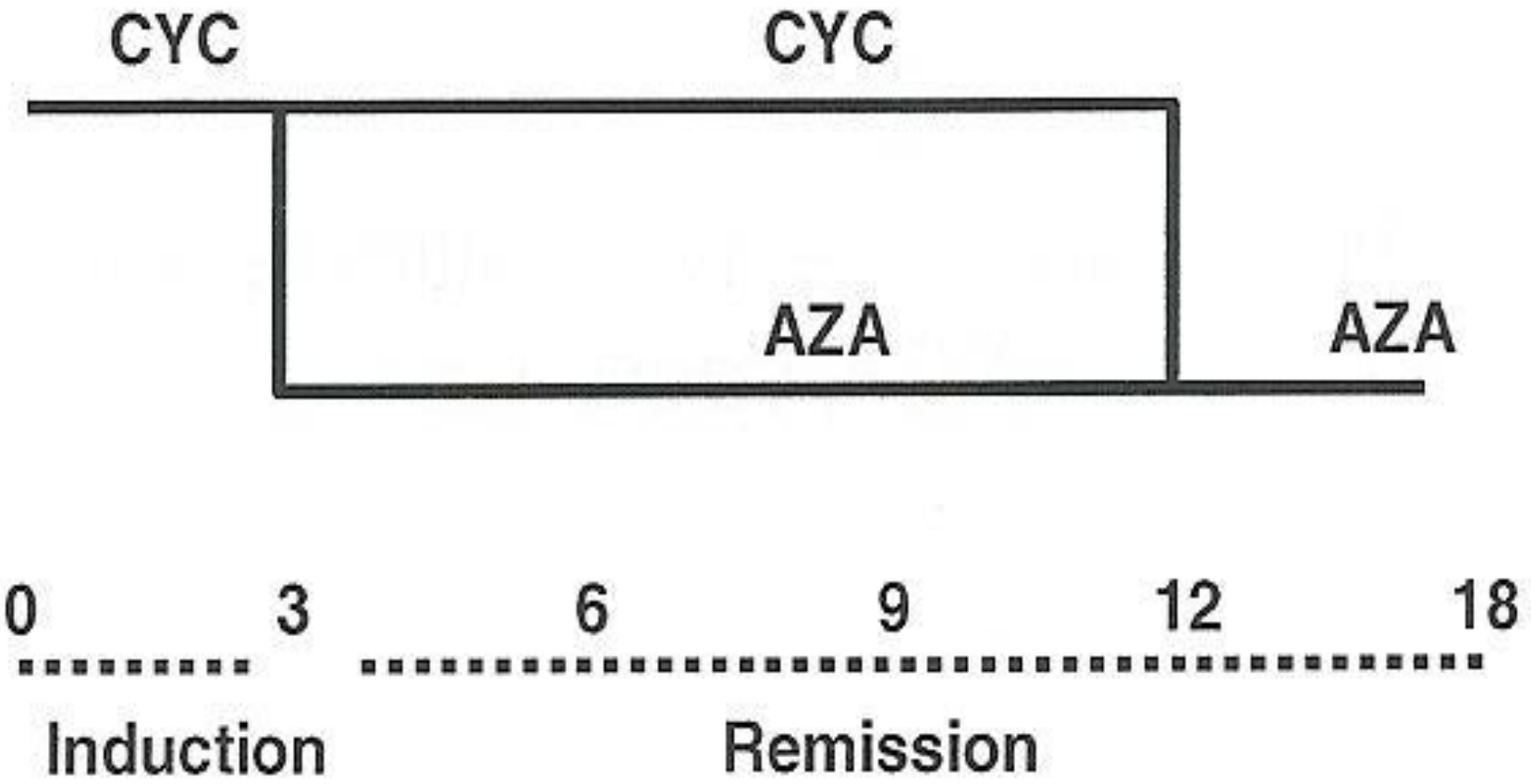


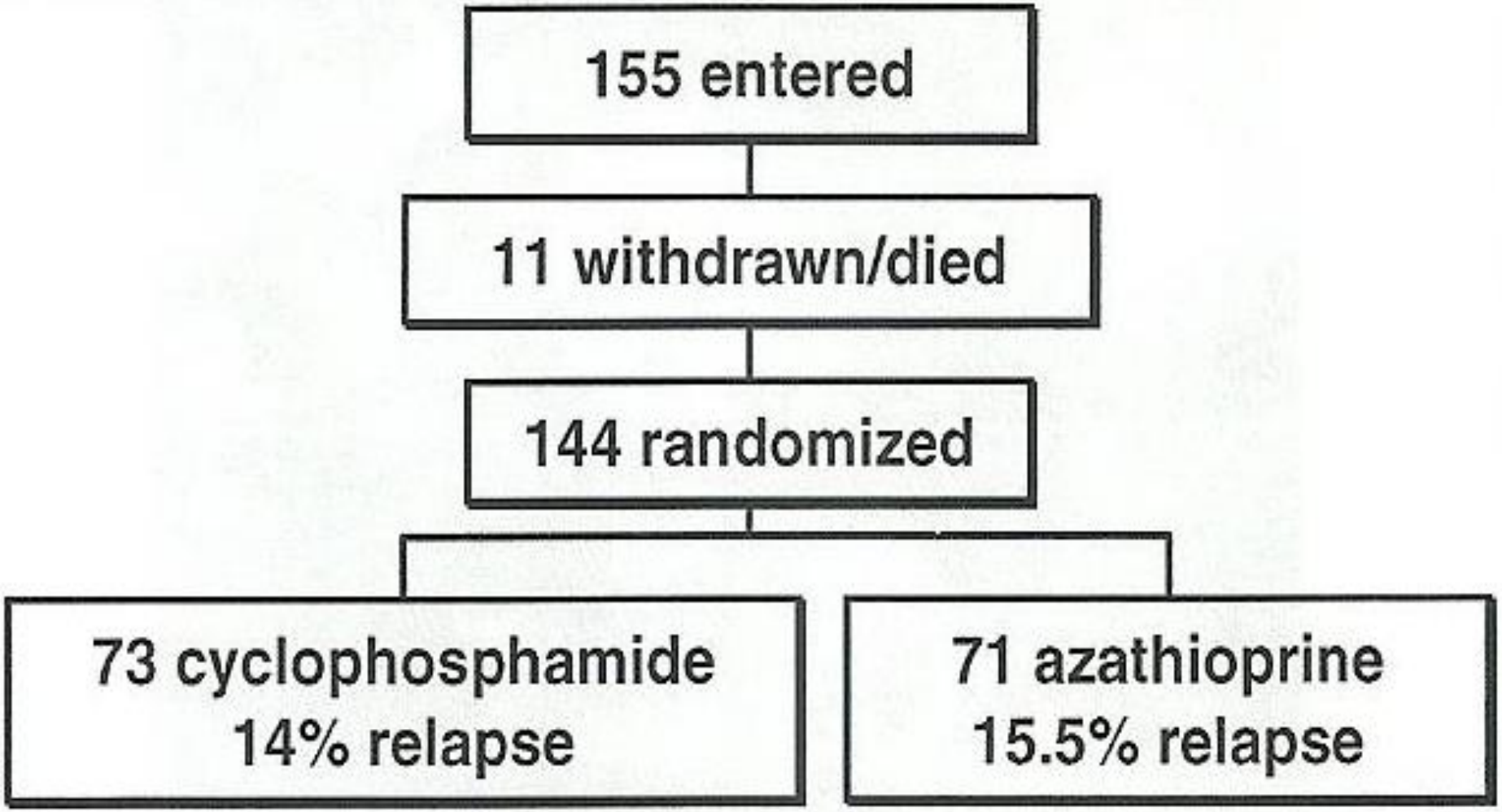
Figure 5. | ANCA vasculitis treatments algorithm in accord with current practice at the University of North Carolina Kidney Center. IV, intravenous.

CYCAZAREM: Design



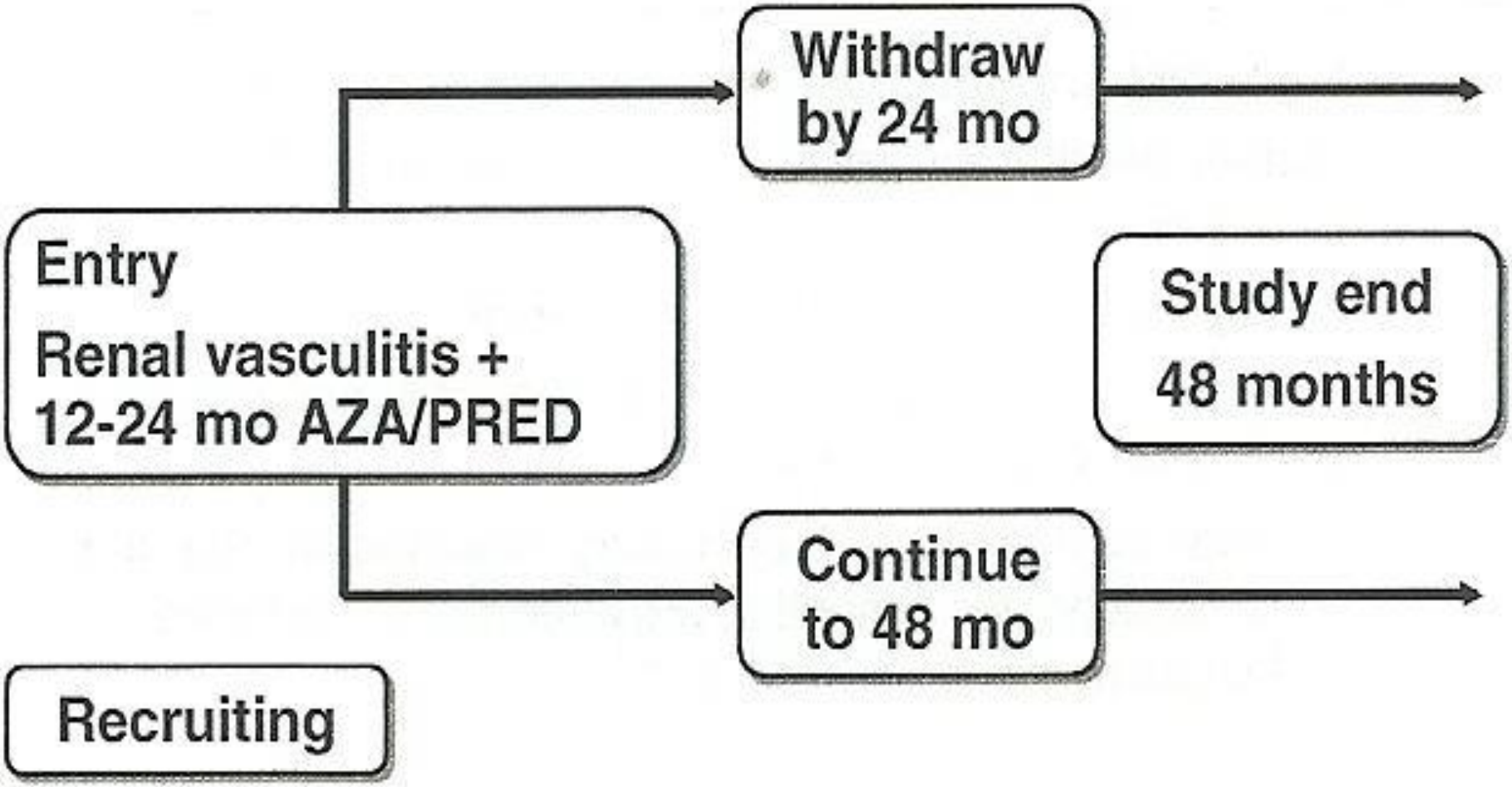
EUVAS

CYCAZAREM: Results



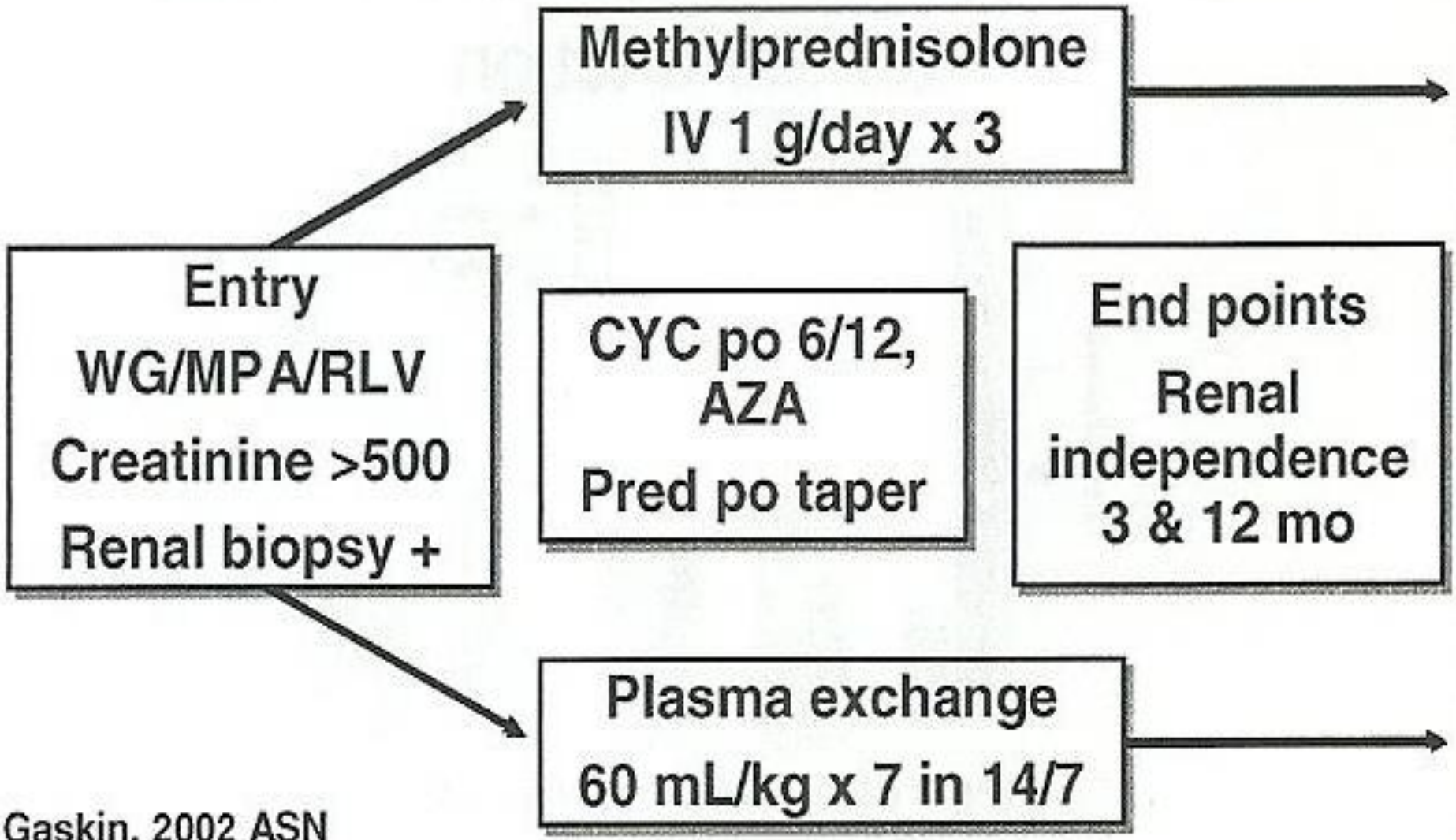
EUVAS

Prolonged Remission
REMAIN



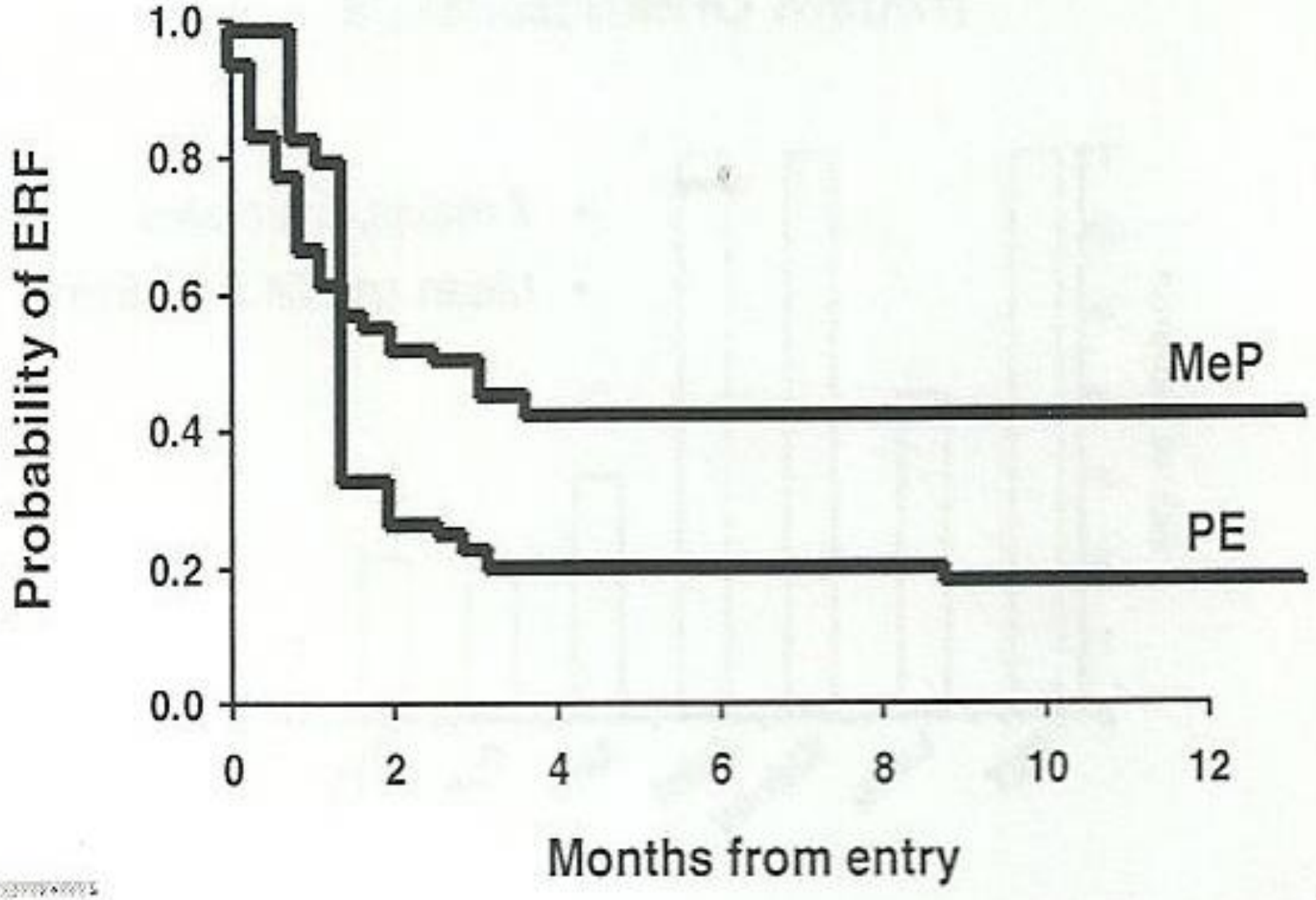
Does plasma exchange have a role in the treatment of ANCA vasculitis?

MEPEX



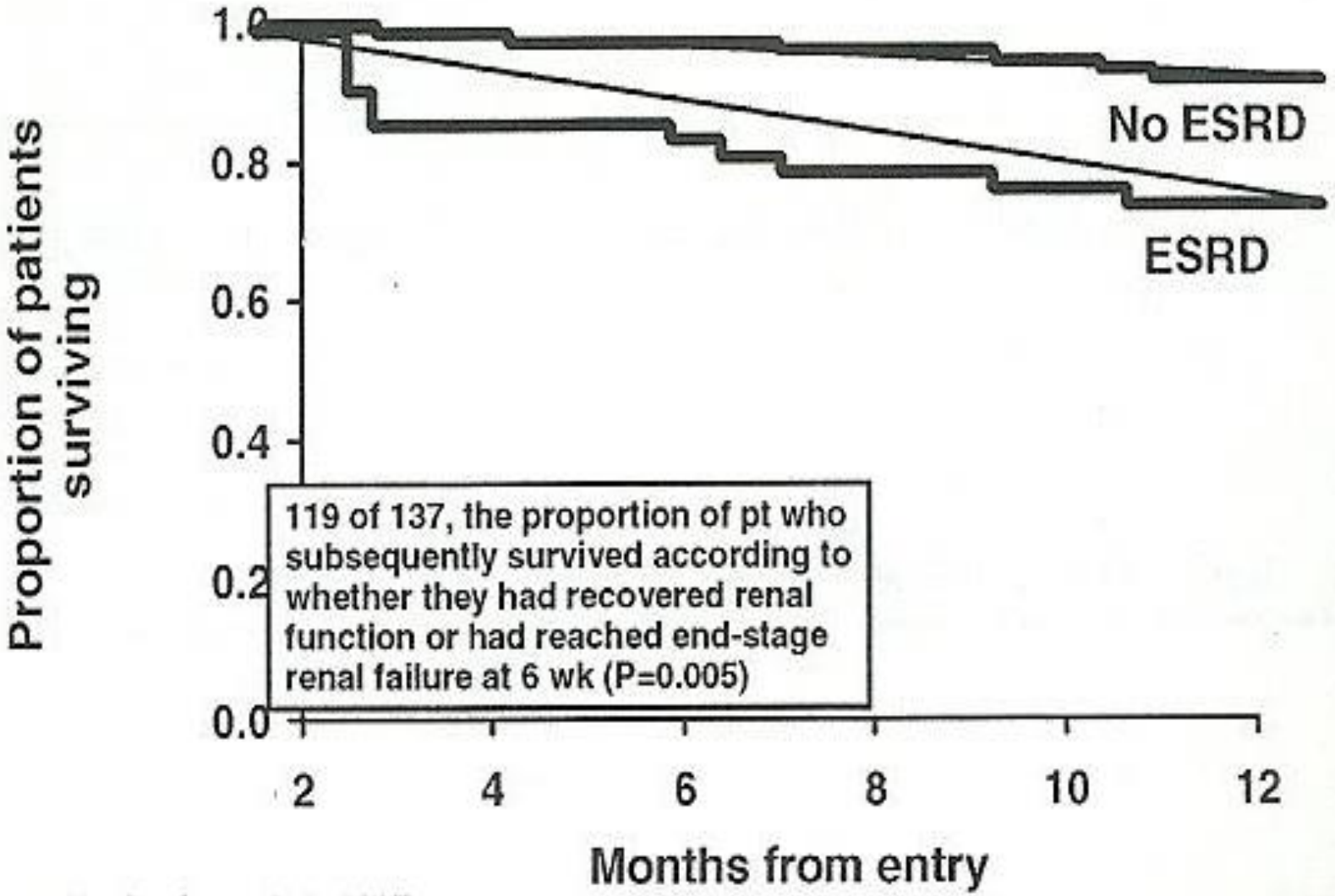
Gaskin, 2002 ASN

MEPEX – Renal Recovery



CP1171651-7

Patients Alive at 6 Weeks



J Am Soc Nephrol 18:2180, 2007

PE in AASV
Conclusion

- The MEPEX trial confirms that PE improves recovery of renal function in patients with severe renal failure or who are dialysis-dependent.
- The hazard ratio for ESRD over 12 mo for PLEX versus MTP was 0.47 (P=0.03)
- The risk reduction for ESRD at 3 and 12 mo was 22% and 24% favoring PLEX

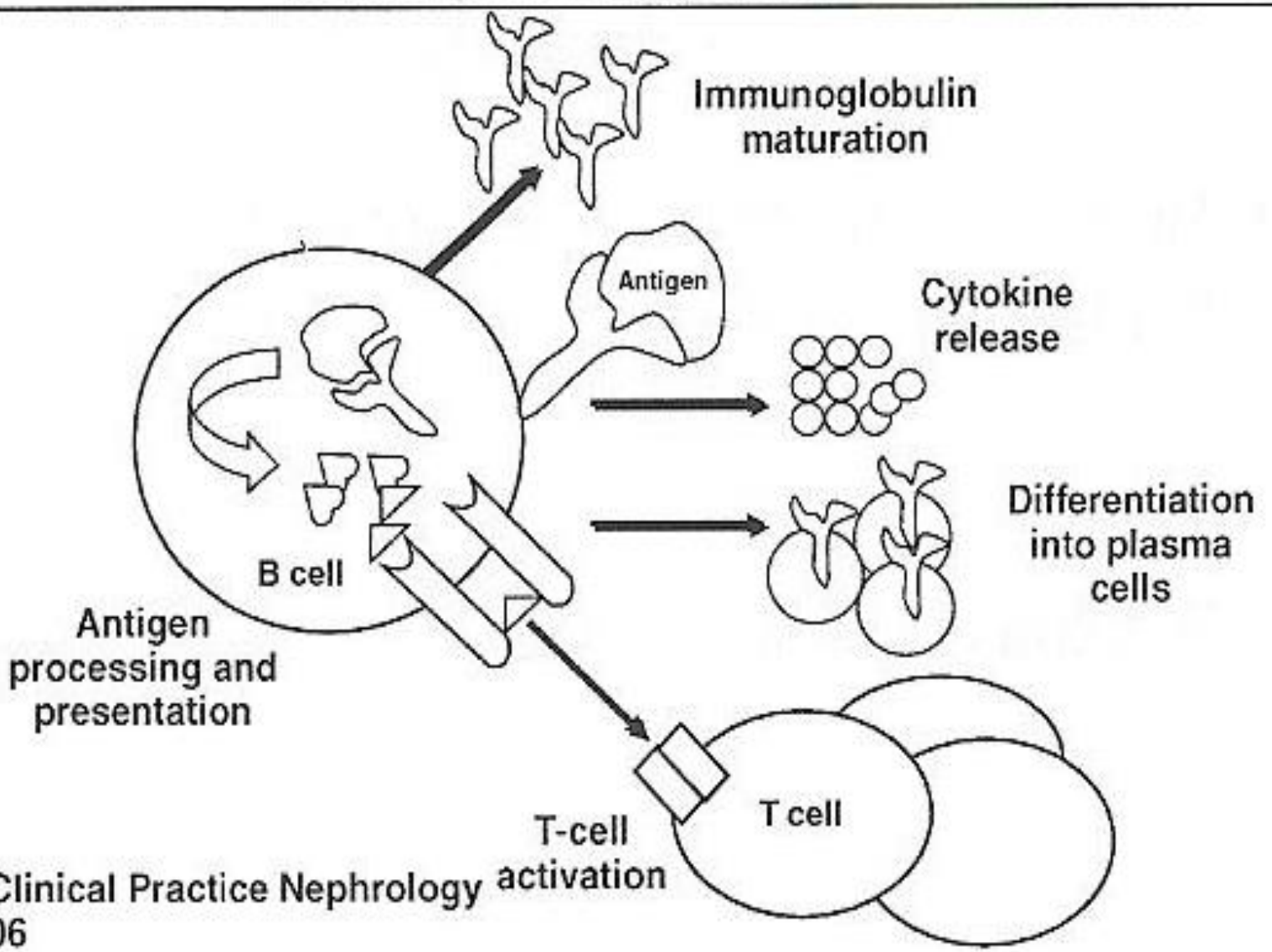
Preliminary Results with B Cell Depletion in AAV

Remission Induction in Refractory Disease

- N = 11 Keogh et al. *Arthritis Rheum 2005; 52:262-8*
- N = 9 Erikkson. *J Intern Med 2005; 257:540-8*
- N = 3 Omdal et al. *Scand J Rheumatol 2005; 34:229-32*
- N = 10 Keogh et al. *Am J Respir Crit Care Med 2006; 173:180-7*
- N = 5 Other single case reports
- N = 11 Smith et al. *Arthritis Rheum 2006; 54:2970-82*
- N = 10 Stasi et al. *Rheumatology 2006; 45:1432-6*
- N = 8 Aries et al. *Ann Rheum Dis. 2006; 65:853-858* (only 3/8 resp)
- N = 8 Brihaye et al. *Clin Exp Rheumatol. 2007; 25 (suppl 44) S-23* (only 6/8)

91.6 % Success Rate

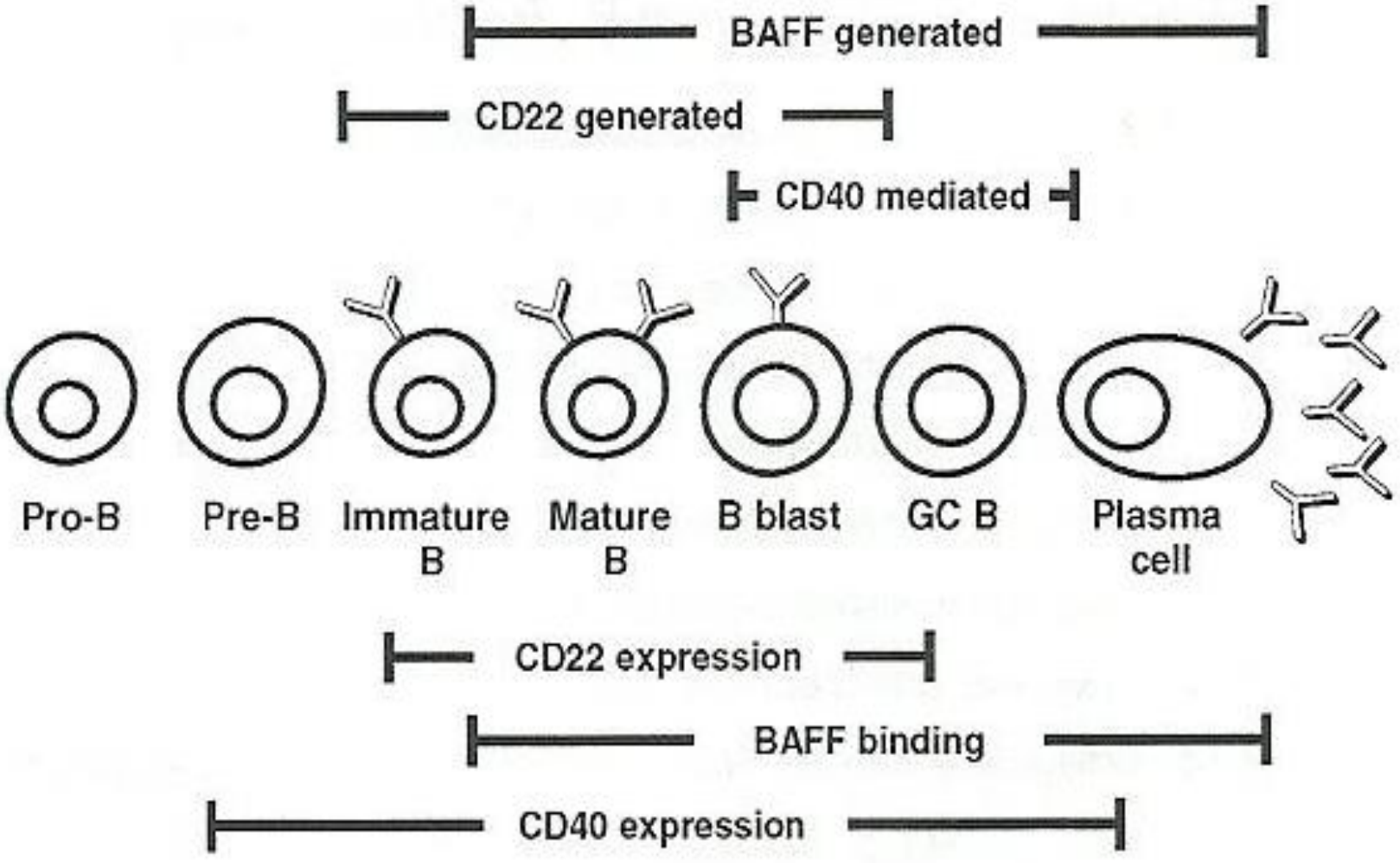
B-Cell Functions are Inhibited Following Cell Depletion by Rituximab



Nature Clinical Practice Nephrology 2(4), 2006

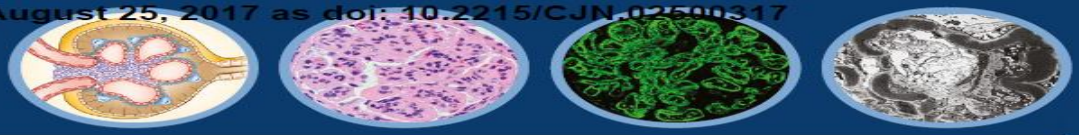
CP1242313-1

Essential B Lymphocyte Receptor-Mediated Survival Signals



CP1239119-2

CJASN ePress. Published on August 25, 2017 as doi: 10.2215/CJN.02500317



ANCA Glomerulonephritis and Vasculitis

J. Charles Jennette and Patrick H. Nachman

Prompt diagnosis and rapid initiation of effective treatment are the most important factors for optimum outcome in patients with ANCA disease. Prompt diagnosis requires an appropriate index of suspicion, familiarity with the broad range of presenting symptoms and signs, and the knowledge required to accurately distinguish ANCA vasculitis and GN from other forms of small vessel vasculitis and GN with similar presentations. Optimum treatment requires an understanding of the implications on treatment regimens of different serotypes, different clinicopathologic phenotypes, and different degrees of activity, chronicity, and severity. Current management strategies are superior to those in earlier decades because of more effective and more targeted drugs, and treatment regimens that are more personalized to the nature of the disease in individual patients. Ongoing advances in understanding ANCA disease mechanisms, and development of more effective, less toxic, and more targeted therapies, undoubtedly will lead to even better outcomes in the future.