
بسم الله الرحمن الرحيم

ANCA-associated Vasculitis

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No conflict of interest to declare.

AGENDA

- Classification
- Pathophysiology
- Clinical presentation
- Investigations
- Treatment

2022

SPRINGER NATURE
Reference

FRANCESCO EMMA
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Pediatric Nephrology

Eighth Edition

OFFICIALLY ENDORSED BY IPNA

Springer

OXFORD TEXTBOOKS IN RHEUMATOLOGY

2014

INCLUDES ACCESS TO OXFORD MEDICINE ONLINE

Oxford Textbook of

Vasculitis

THIRD EDITION

Edited by
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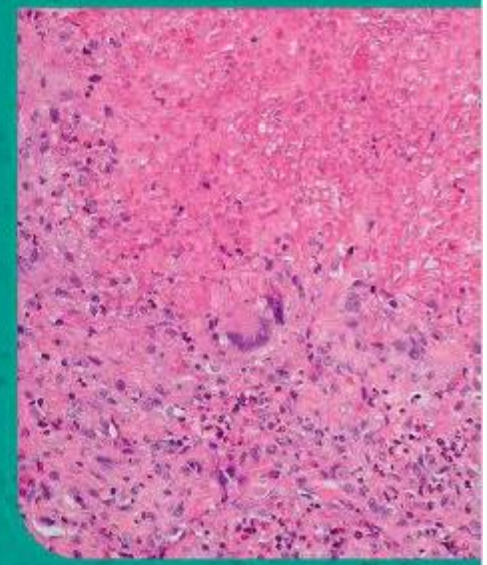

OXFORD

AGENDA

- **Classification**
- Pathophysiology
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Large-vessel vasculitis
Takayasu arteritis (TAK)
Giant cell arteritis (GCA)
Medium-vessel vasculitis
Polyarteritis nodosa (PAN)
Kawasaki disease (KD)
Small-vessel vasculitis
Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV): Microscopic polyangiitis (MPA); granulomatosis with polyangiitis (Wegener, GPA); Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome, EGPA)
Immune complex vasculitis: Anti-glomerular basement membrane (anti-GBM) disease; cryoglobulinemic vasculitis; IgA vasculitis (Henoch-Schönlein); hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
Variable vessel vasculitis
Behçet disease
Cogan syndrome
Single-organ vasculitis
Cutaneous leukocytoclastic angiitis
Cutaneous arteritis
Primary central nervous system vasculitis
Isolated aortitis
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Vasculitis with probable etiology
Hepatitis C associated cryoglobulinemic vasculitis
Hepatitis B associated vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis
Drug-associated ANCA-associated vasculitis
Cancer-associated vasculitis
Others

Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum. 2013;65(1):1–11.

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV) are a group of disorders that can cause a rapidly progressive glomerulonephritis with chronic, often relapsing disease, which can be organ or life threatening with high morbidity and mortality despite immunosuppression.

There are three main conditions characterized by necrotizing inflammation of small to medium vessels in association with autoantibodies against the cytoplasmic region of the neutrophil (ANCA), including:

- Granulomatosis with polyangiitis (GPA; formerly Wegener granulomatosis) is the commonest condition
- Microscopic polyangiitis (MPA)
- Eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg-Strauss syndrome).

Children with all three conditions present with rapidly progressive glomerulonephritis associated with necrotizing glomerulonephritis (capillaritis) and is characteristically pauci-immune (i.e. immunoglobulin and complement do not seem to play a prominent role in their pathogenesis as they are not usually found in histopathology).

Renal limited vasculitis is a term used for renal histopathology in the absence of vasculitis in other organs.

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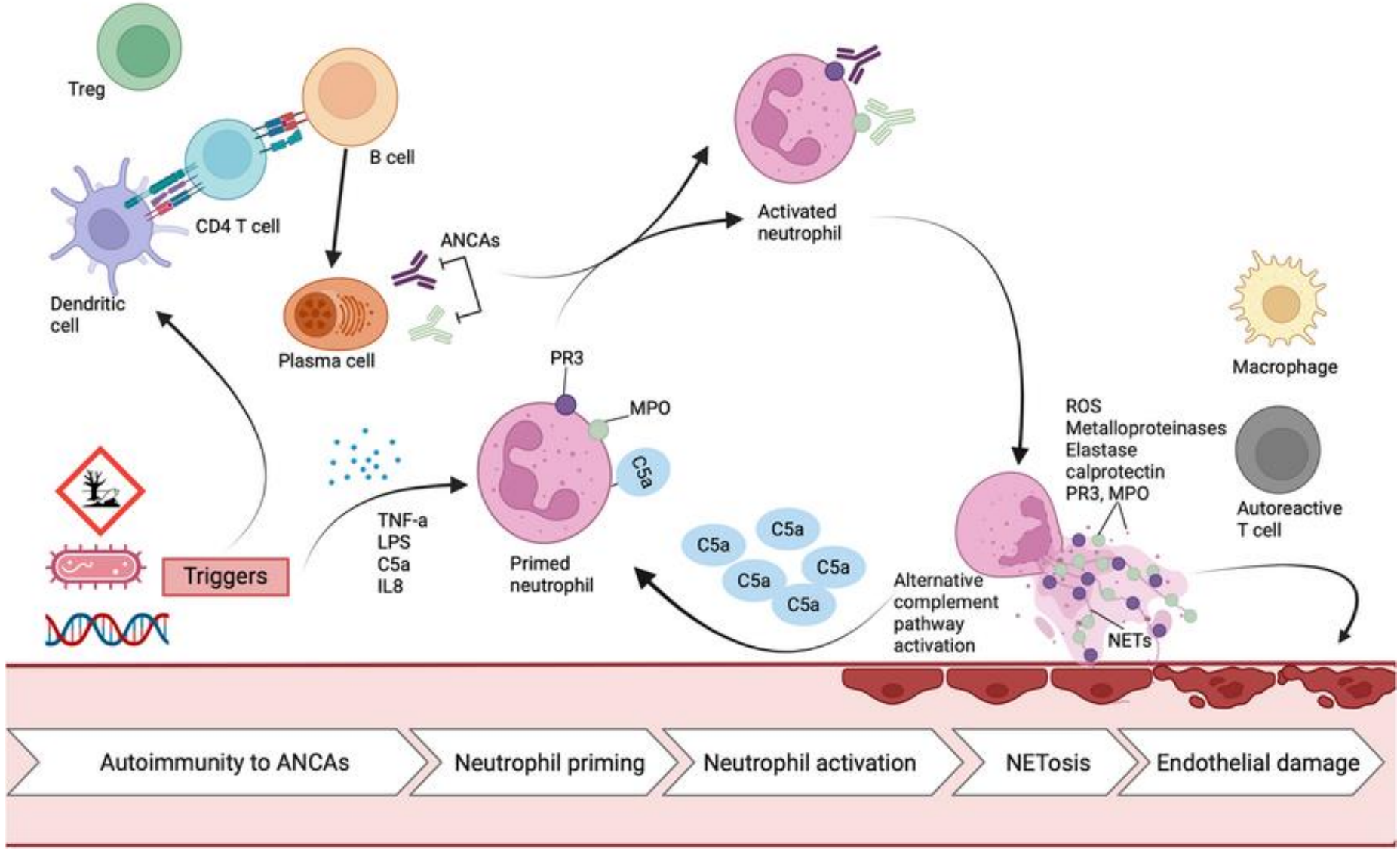
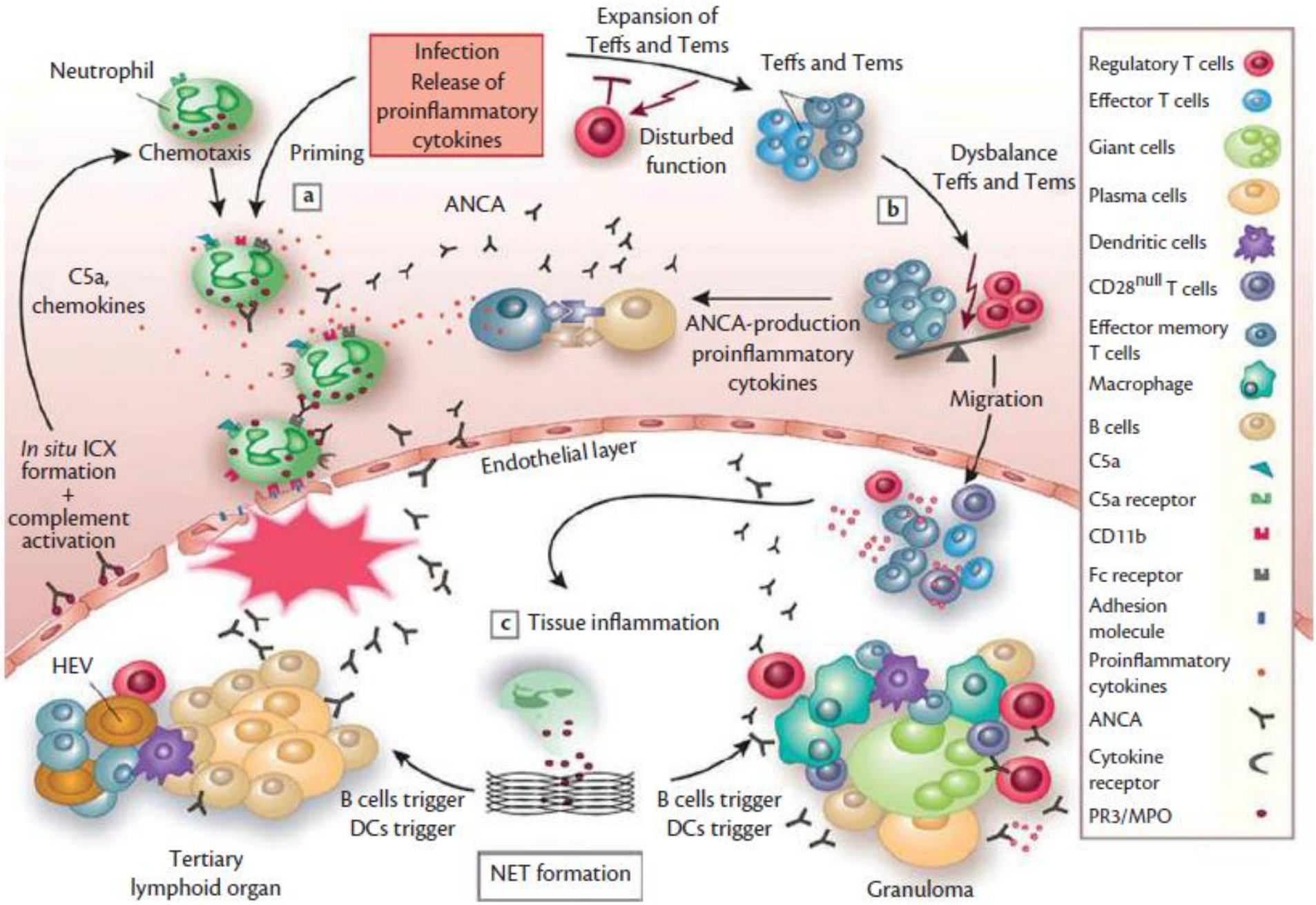
The pathogenesis of AAV




Neutrophil
Chemotaxis
Priming
Infection
Release of proinflammatory cytokines
Expansion of Teffs and Tems
Teffs and Tems
Disturbed function
Dysbalance Teffs and Tems
a
b
ANCA
C5a, chemokines
ANCA-production proinflammatory cytokines
Migration
In situ ICX formation + complement activation
Endothelial layer
c Tissue inflammation
HEV
Tertiary lymphoid organ
B cells trigger DCs trigger
NET formation
B cells trigger DCs trigger
Granuloma
Regulatory T cells
Effector T cells
Giant cells
Plasma cells
Dendritic cells
CD28null T cells
Effector memory T cells
Macrophage
B cells
C5a
C5a receptor
CD11b
Fc receptor
Adhesion molecule
Proinflammatory cytokines
ANCA
Cytokine receptor
PR3/MPO

The complement system in antineutrophil cytoplasmic antibody-associated vasculitis: pathogenic player and therapeutic target

Curr Opin Rheumatol 2023, 35:31–36

Martina Mazzariol[a,b], *Lucio Manenti*[c] *and Augusto Vaglio*[b,d]

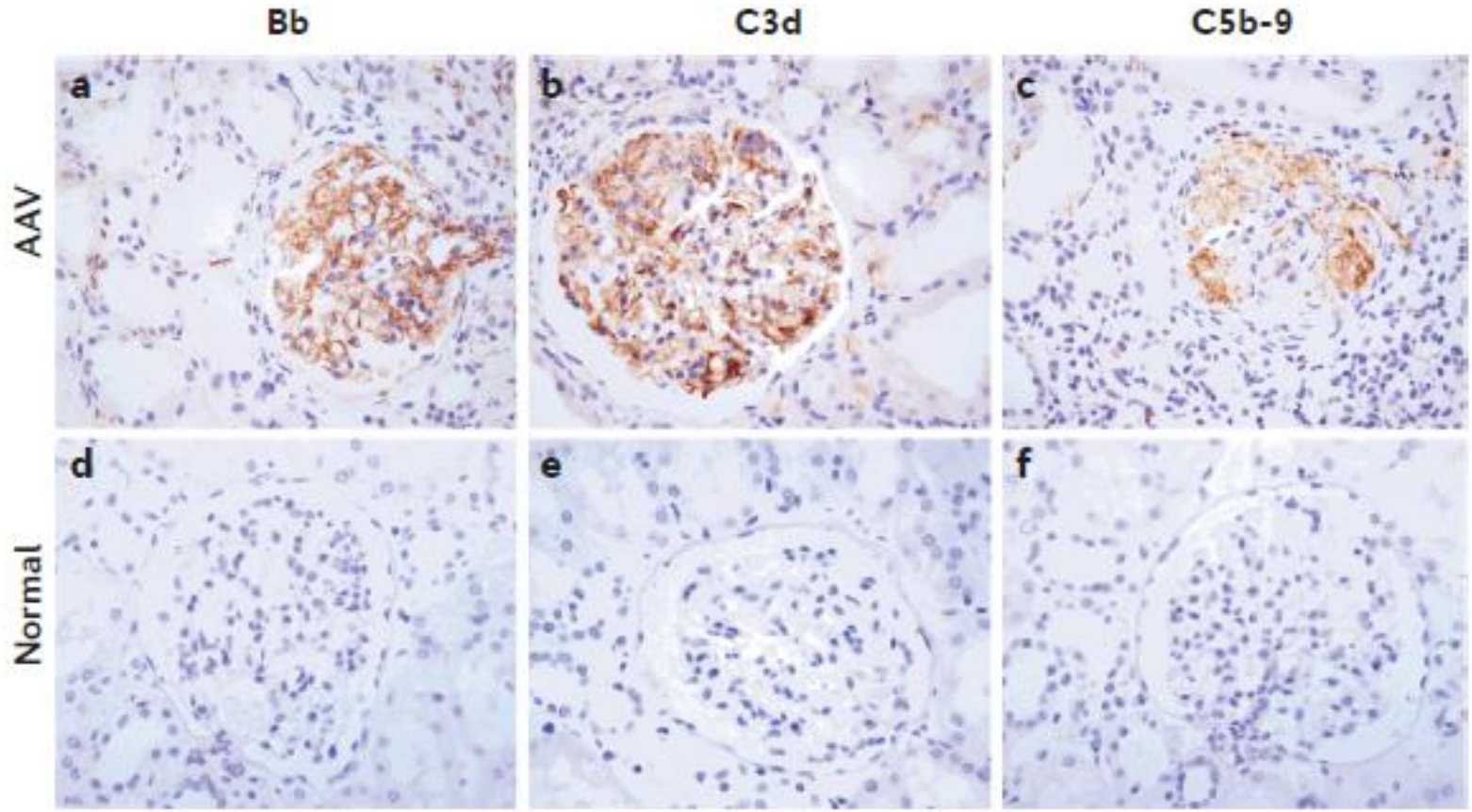
Table 1. Evidence supporting the role of the complement system in AAV

Serum complement components in AAV	ANCA-associated NCGN	C5aR inhibitor (avacopan) trials in AAV
Neutrophils stimulated with cytokines or coagulation-derived factors released properdin, which can trigger the alternative complement pathway [16] Circulating levels of C3a, C5a, C4d, soluble C5b-9, fragment Bb were higher in patients with active AAV compared with controls [13▪▪,14] Plasma fragment Bb concentration correlated with plasma levels of C3a, C5a, and C5b-9 and with markers of systemic and renal disease activity (e.g. erythrocyte sedimentation rate, BVAS, crescents proportion in renal biopsies) [14]	C3d, C4d, C5b-9, and properdin deposition were found in glomeruli and small renal vessels in active AAV [20] C3d and properdin glomerular deposits were associated with crescents and proteinuria [20] Low-serum C3 levels were associated with worse renal prognosis and reduced long-term survival [24–27] Plasma concentrations and glomerular deposits of fragment Bb correlated with renal involvement [13▪▪,14,29]	Phase II trial (CLEAR): patients treated with avacopan (with or without steroids) showed at least 50% reduction in BVAS score at 12 weeks and a decrease in the urinary albumin/urinary creatinine ratio [37] Phase II trial (CLASSIC): no significant differences were found in adverse events in patients treated with different avacopan doses (10 or 30 mg twice daily) + steroids compared with standard-of-care [38] Phase III trial (ADVOCATE): Remission at week 26: avacopan was noninferior but not superior to steroid therapy Remission at week 52: avacopan achieved both noninferiority and superiority compared to placebo [39▪▪]

Complement in ANCA-associated vasculitis: mechanisms and implications for management

Min Chen[1], David R. W. Jayne[2] and Ming-Hui Zhao[1]

Nature Reviews Nephrology – Online 20 Mar 2017



Complement System Inhibitors in Nephrology: An Update—Narrative Review

Int. J. Mol. Sci. **2025**, *26*, 5902

Mugurel Apetrii [1,2], Alexandru Dan Costache [1,3,*], Irina Iuliana Costache Enache [1,4], Luminita Voroneanu [1,2], Andreea Simona Covic [1,2], Mehmet Kanbay [5] and Adrian Covic [1,2]

Table 2. The degree of involvement of the complement system in renal diseases.

High Complement Involvement	Intermediate Complement Involvement	Low Complement Involvement
Atypical hemolytic uremic syndrome C3-glomerulopathy Primary immune complex MPGN	ANCA-associated vasculitis IgA nephropathy Systemic lupus erythematosus Antiphospholipid antibody syndrome Membranous nephropathy Secondary TMA Secondary MPGN	Diabetic nephropathy Focal–segmental glomerulosclerosis

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Metric	Estimate (Pediatric)	Reference
Overall prevalence	**~3.41–4.28 per million**	***Int. J. Mol. Sci. 2024, 25(24), 13704***
Annual incidence	**~0.4–6.39 per million/year**	***Rheum Dis Clin North Am. 2021 Aug 27;47(4):781–796.***
Subtype frequency	**GPA (generally), followed by MPA then EGPA**	***Int. J. Mol. Sci. 2024, 25(24), 13704***

Microscopic Polyangiitis(MPA)

Necrotizing glomerulonephritis and arteritis involving small and medium-sized arteries and pulmonary capillaritis.

Clinical features:

The presence of histopathologically proven necrotizing glomerulonephritis along with a positive ANCA (often MPO-ANCA) titer in the absence of granulomatous lesions and upper respiratory tract involvement leads to a diagnosis of MPA. Childhood cases have been reported as small series.

Laboratory investigations:

An immunofluorescence testing for ANCA often reveals a p-ANCA pattern and a high titer of MPO-ANCA. Urinalysis shows proteinuria, hematuria, and an active urine sediment with casts. Renal function tests are impaired in 30–60% of patients reported in a pediatric series.

A chest x-ray is required in all patients and in patients with abnormalities chest CT defines the extent of lung involvement.

Pathology:

Renal biopsy is indicated in children with renal involvement. MPA is characterized by necrotizing vasculitis with few or no immune deposits. Kidneys show necrotizing glomerulonephritis, which is focal and segmental to severe diffuse and crescentic. No immune deposits are detected on immunofluorescence or electron microscopy.

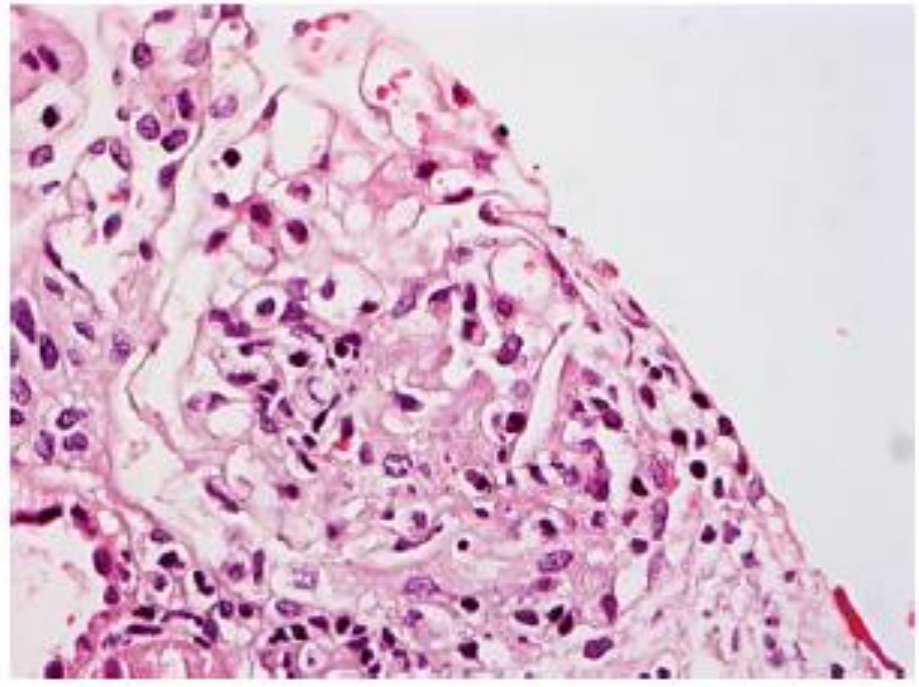

Fig. 1 Microscopic polyangiitis with segmental necrosis and proliferation of parietal cells of the Bowman's capsule in the periphery of the glomerulus

Granulomatous Polyangiitis (GPA) (Wegener Granulomatosis)

GPA is defined as a necrotizing granulomatous inflammation of the upper and lower respiratory tract, necrotizing vasculitis affecting small to medium-sized vessels and glomerulonephritis. GPA has major renal involvement like MPA. Children frequently have constitutional symptoms, such as fever, anorexia, and weight loss with multiorgan or generalized disease.

According to the Ankara 2008 criteria revised for childhood, three of the following six should be present to classify as GPA:

- Renal involvement
- Upper airway involvement with recurrent epistaxis or sinusitis
- Laryngo-tracheo-bronchial stenosis
- Pulmonary involvement (chest x-ray or CT showing diffuse pulmonary infiltrates, pulmonary nodules, cavitating lesions, and granulomata without cavitation)
- Histopathology (granulomatous inflammation)
- Positive ANCA

Clinical and laboratory features:

90% of children with GPA present with respiratory symptoms. Upper (sinusitis, epistaxis, and nasal inflammation), lower (cough, dyspnea and hemoptysis). Renal involvement occurs in 10 to 100% of affected children.

Clinical findings include blurred vision, eye pain, conjunctivitis, episcleritis, and otitis media. Neurological involvement presents as cranial nerve palsies, seizures, or neuropathies.

Skin lesions include palpable purpura, nodules, ulceration, and gangrene.

Cardiac affection is rare.

A cytoplasmic pattern on immunofluorescent staining of ANCA (c-ANCA) is present in 70–90% of patients with active GPA. ELISA tests detecting PR3-ANCA confirm this specificity. Investigations show elevated white blood count and acute phase reactants. Urinalysis shows hematuria, proteinuria, and casts when there is renal involvement. Chest x-ray and pulmonary function tests are indicated for assessment of lung disease. The chest x-ray may show nodular infiltrates and nodules that might require assessment with chest CT.

Pathology: Necrotizing vasculitis of small arteries and veins, usually with granuloma formation. Renal involvement is observed as necrotizing glomerulonephritis, often with necrosis, cellular crescents, and usually with glomerular thrombosis. Interstitial inflammation is common.

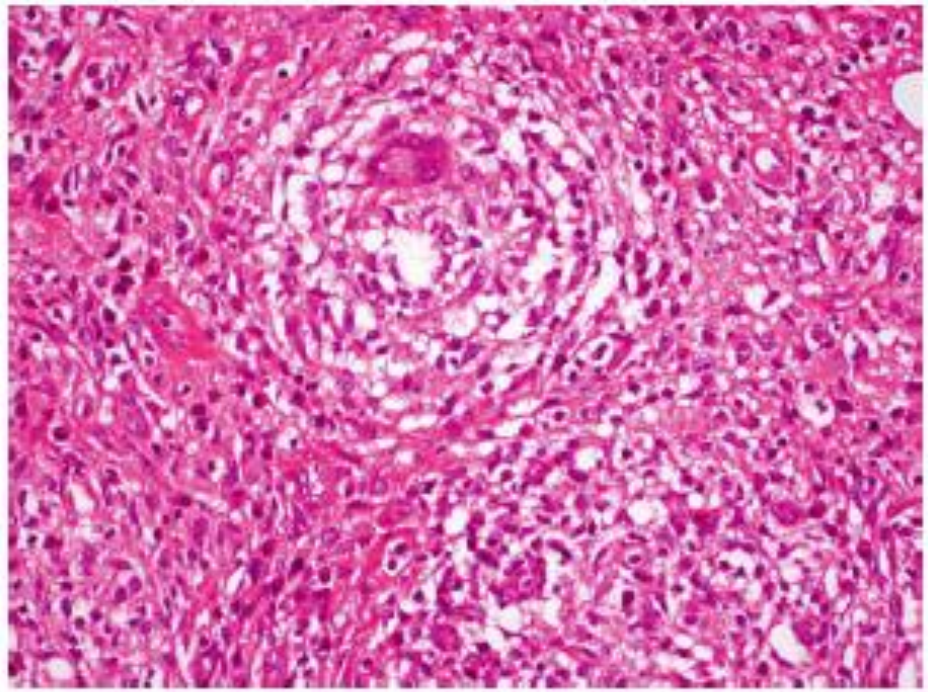

Fig. 2 GPA/WG. Necrotizing granulomatous inflammation of the vessel with multinucleate giant cells

Eosinophilic Granulomatosis with Polyangiitis (EGPA) (Churg- Strauss Syndrome)

EGPA is very rare in childhood and accounts for ~2% children with primary systemic vasculitis.

EGPA is a systemic necrotizing vasculitis with hypereosinophilia and extravascular granulomas along with asthma. Patients present with history of asthma and allergy, involvement of paranasal sinuses and peripheral nervous system, and eosinophilia.

Skin involvement and vasculitis is similar to PAN.

Among adult patients, ~20% show glomerulonephritis and renal dysfunction.

The laboratory work-up: the presence of ANCA is less common in children (0 to 25%). Typically, p-ANCA pattern is expected.
Pathology: eosinophil-rich, granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels. Renal manifestations include necrotizing and crescentic glomerulonephritis without immune complex deposition, fibrinoid necrosis of arteries, and interstitial nephritis with eosinophilia.

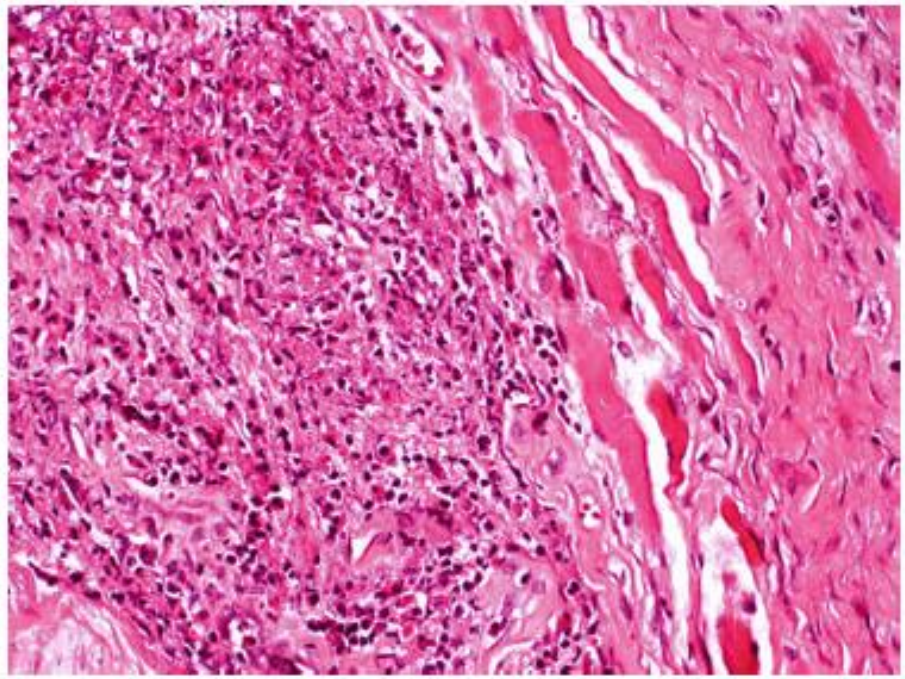

Fig. 3 EGA/CSS. Granulomatous vasculitis with multinucleate giant cell and eosinophils

Genetics of ANCA-associated vasculitis: role in pathogenesis, classification and management

Giorgio Trivioli[1,2], Ana Marquez[3], Davide Martorana[4,5], Michelangelo Tesi[2], Andreas Kronbichler[6,7], Paul A. Lyons[6,8] and Augusto Vaglio[1,2]

Table 1 | **Major features of the three AAV syndromes**

	GPA	MPA	EGPA
Definition	Necrotizing granulomatosis and necrotizing SVV	Necrotizing SVV, absence of granuloma	Asthma, eosinophilia, eosinophilic granulomatosis and SVV
Ear, nose and throat	Crusting rhinitis, saddle nose, subglottic stenosis	Serous rhinitis	Nasal polyposis, rhinitis
Lung	Nodules, DAH	DAH, ILD	Transient infiltrates
Heart	Rare	Rare	Endo-myocarditis, pericarditis
Kidney	CNGN, granulomatous TIN	CNGN (also RLV)	Segmental CNGN
Skin	Purpura, nodules	Purpura	Purpura, rash
PNS	20–30%	20–30%	70–80%
ANCA	PR3 > MPO	MPO > PR3	MPO (40%)

ANCA, anti-neutrophil cytoplasmic antibodies; CNGN, crescentic necrotizing glomerulonephritis; DAH, diffuse alveolar haemorrhage; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; ILD, interstitial lung disease; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PNS, peripheral nervous system; PR3, proteinase-3; RLV, renal-limited vasculitis; SVV, small-vessel vasculitis; TIN, tubulo-interstitial nephritis. > symbol denotes 'more commonly associated with disease subset than'.

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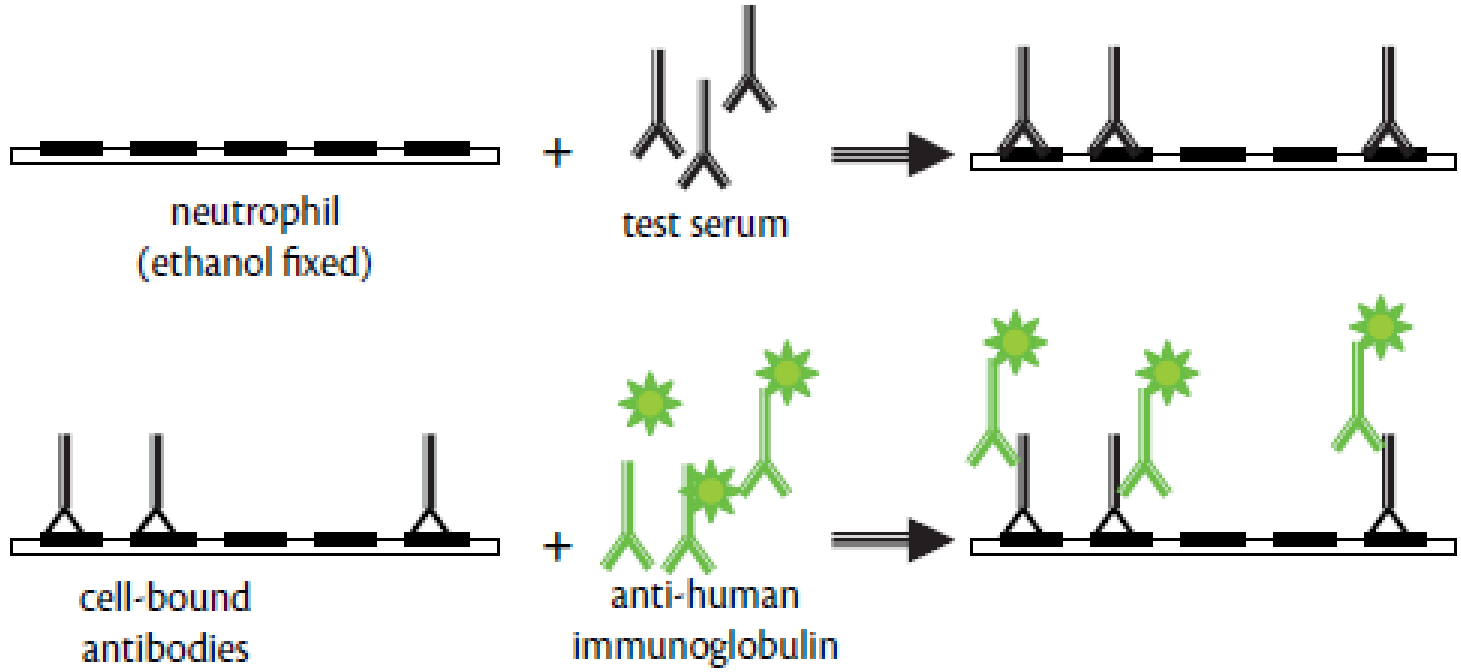
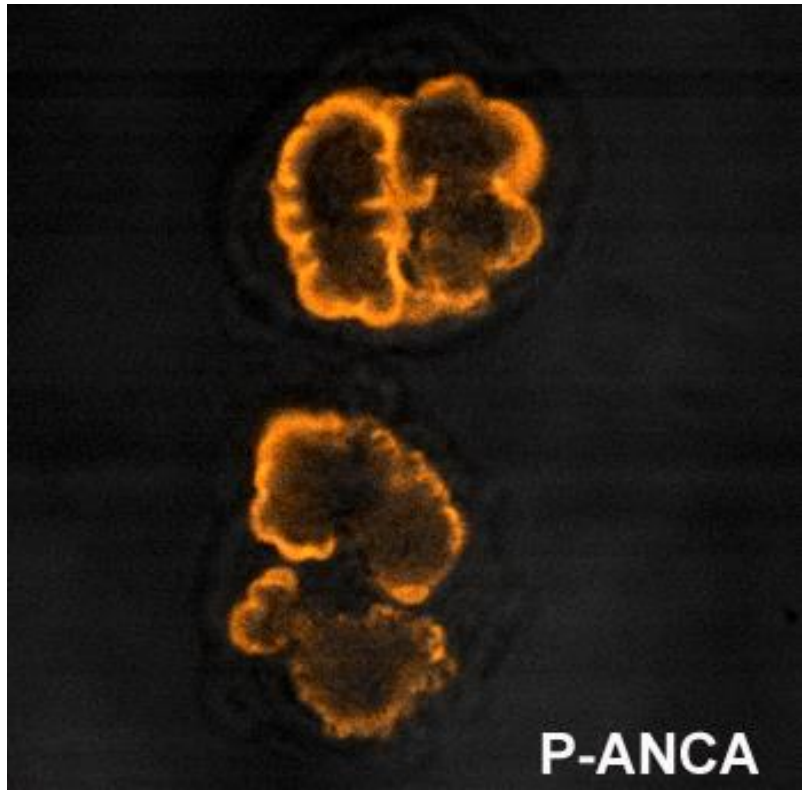
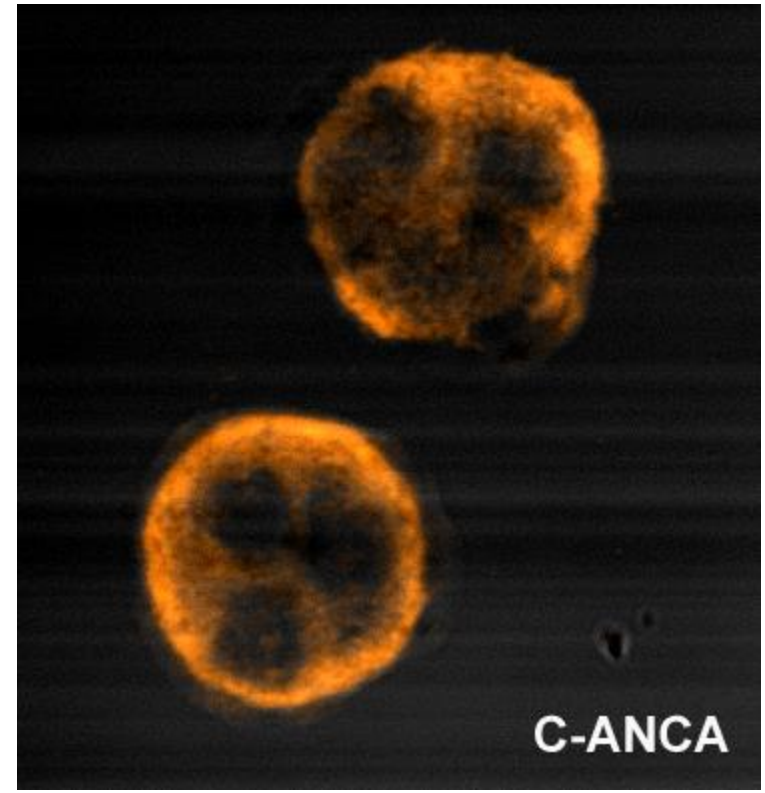

neutrophil
(ethanol fixed)
test serum
cell-bound
antibodies
anti-human
immunoglobulin

Antigen	Autoantibody	Disease
Proteinase 3 (PR3)	c-ANCA	GPA
Myeloperoxidase (MPO)	p-ANCA	MPA/EGPA





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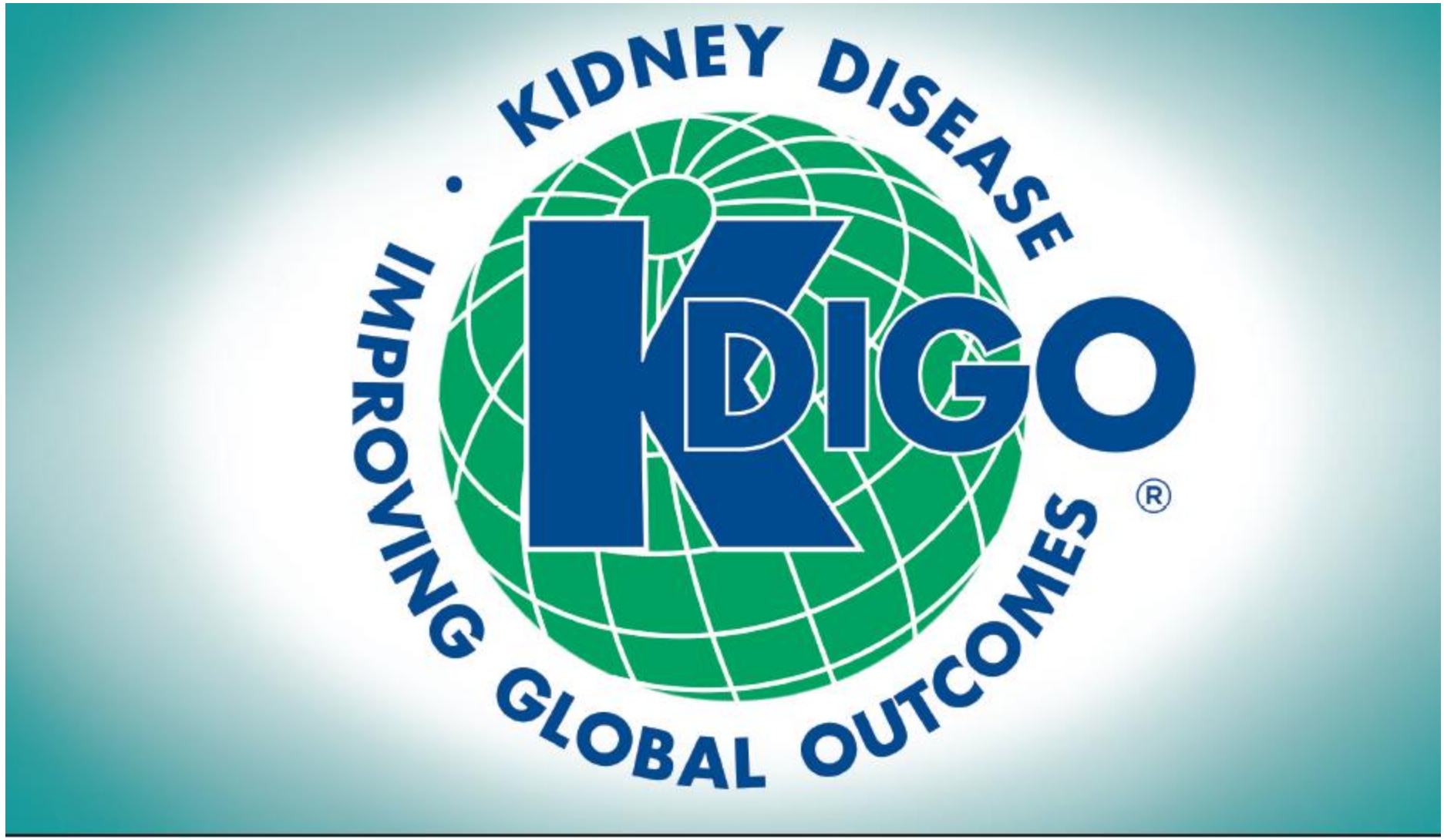
American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis Care & Research
Vol. 73, No. 8, August 2021, pp 1088–1105
DOI 10.1002/acr.24634

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis



KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases

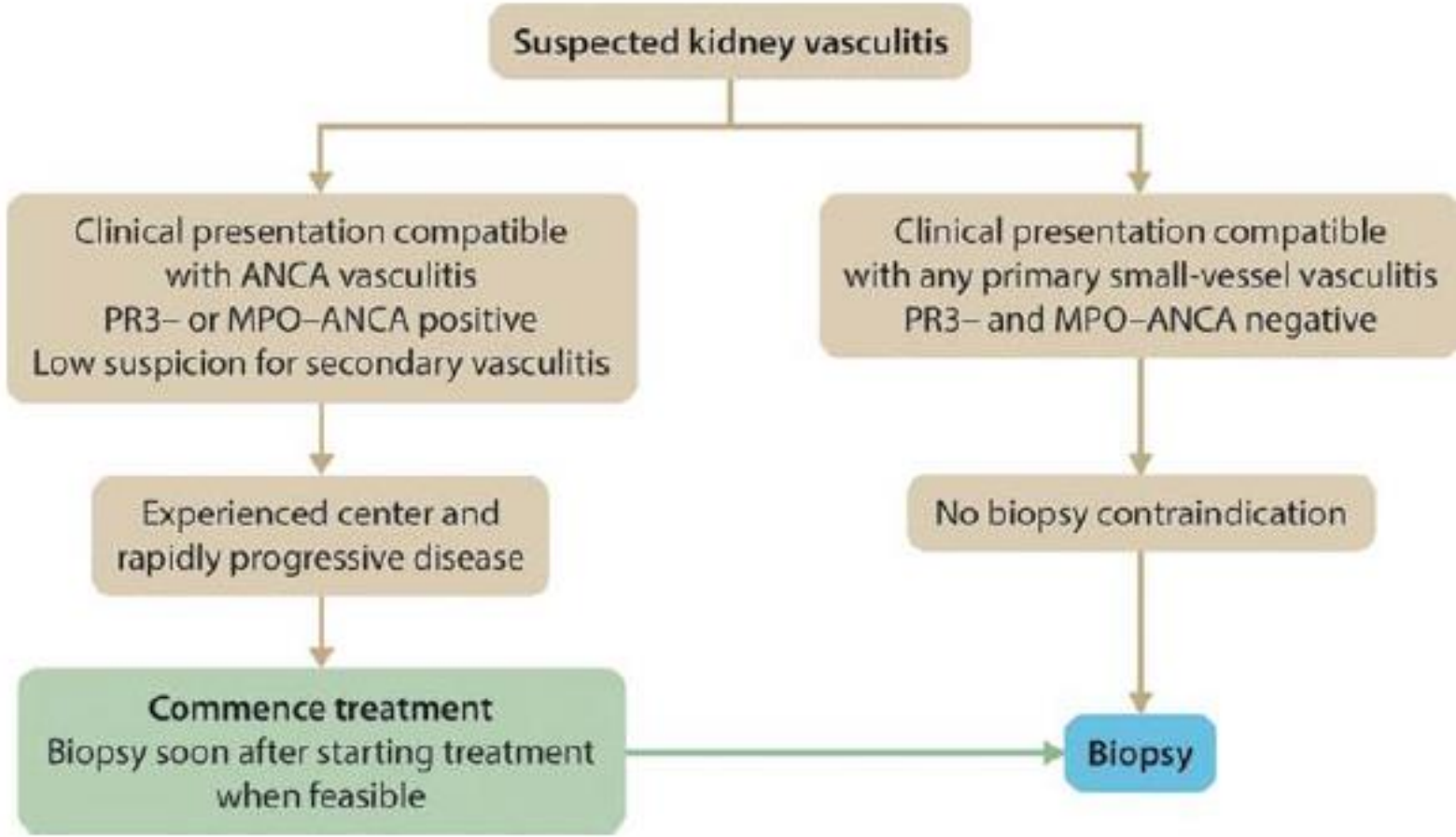
VOLUME 100 | ISSUE 4S | OCTOBER 2021

Chapter 9: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

9.1 Diagnosis

Practice Point 9.1.1: In the case of a clinical presentation compatible with small-vessel vasculitis in combination with positive myeloperoxidase (MPO)- or proteinase 3 (PR3)-ANCA serology, waiting for a kidney biopsy to be performed or reported should not delay starting immunosuppressive therapy, especially in patients who are rapidly deteriorating (Figure 71).

Practice Point 9.1.2: Patients with ANCA-associated vasculitis (AAV) should be treated at centers with experience in AAV management.



9.2.3 Relapses

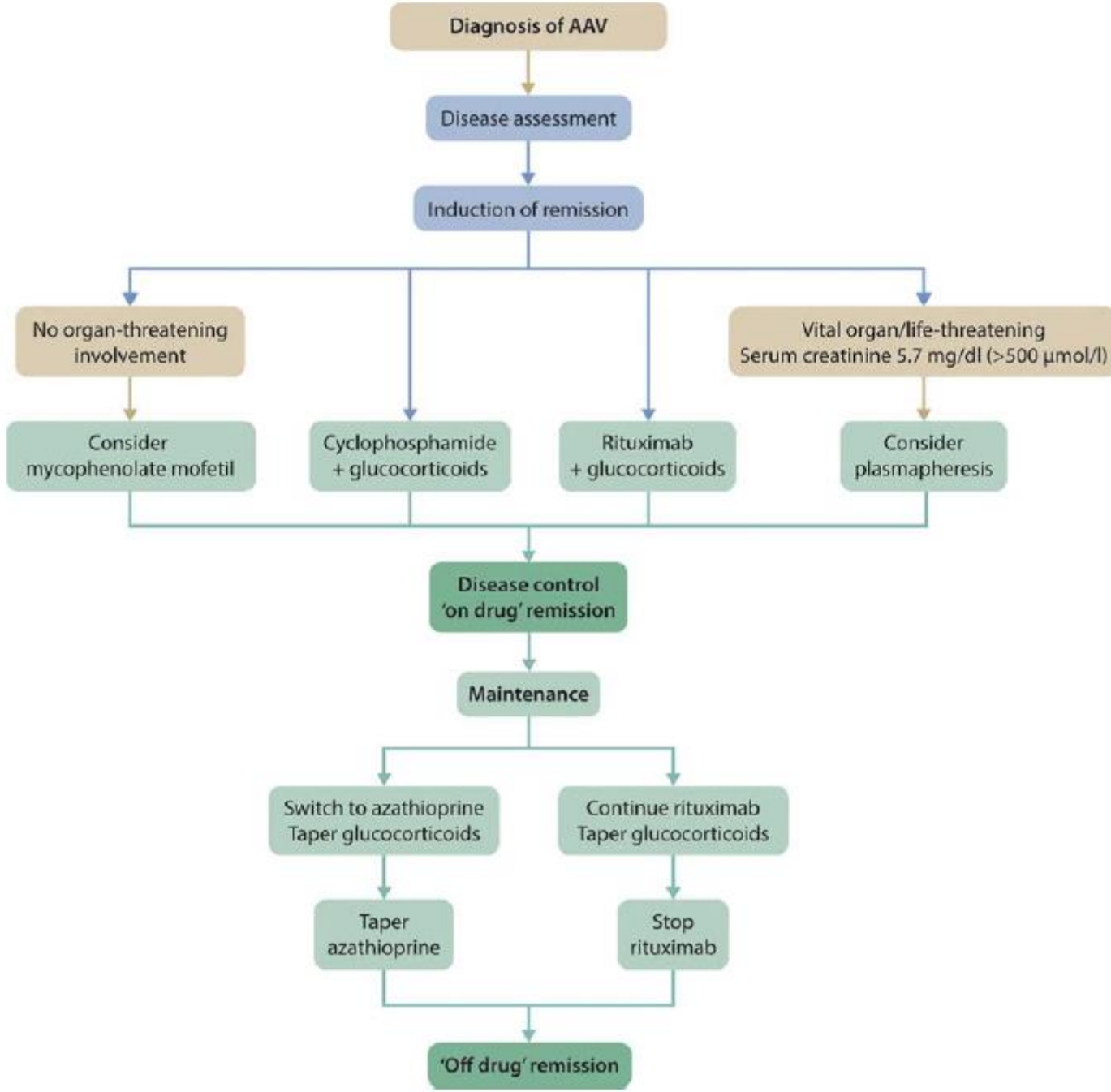
Practice Point 9.2.3.1: The persistence of ANCA positivity, an increase in ANCA levels, and a change in ANCA from negative to positive are only modestly predictive of future disease relapse and should not be used to guide treatment decisions.

9.3 Treatment

9.3.1 Induction

Recommendation 9.3.1.1: We recommend that glucocorticoids in combination with cyclophosphamide or rituximab be used as initial treatment of new-onset AAV *(1B)*.

Practice Point 9.3.1.1: A recommended treatment algorithm for AAV with kidney involvement is given in Figure 76.


Diagnosis of AAV
Disease assessment
Induction of remission
No organ-threatening involvement
Vital organ/life-threatening
Serum creatinine 5.7 mg/dl (>500 µmol/l)
Consider mycophenolate mofetil
Cyclophosphamide + glucocorticoids
Rituximab + glucocorticoids
Consider plasmapheresis
Disease control 'on drug' remission
Maintenance
Switch to azathioprine
Taper glucocorticoids
Continue rituximab
Taper glucocorticoids
Taper azathioprine
Stop rituximab
'Off drug' remission

Practice Point 9.3.1.2: In patients presenting with markedly reduced or rapidly declining GFR (SCr >4 mg/dl [>354 µmol/l]), there are limited data to support rituximab and glucocorticoids. Cyclophosphamide and glucocorticoids are preferred for induction therapy. The combination of rituximab and cyclophosphamide can also be considered in this setting.

Practice Point 9.3.1.3: Considerations for choosing between rituximab and cyclophosphamide for induction therapy are given in Figure 77.

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Pre-menopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l]), combination of two intravenous pulses of cyclophosphamide with rituximab can be considered

Practice Point 9.3.1.4: Considerations for choosing the route of administration of cyclophosphamide are given in Figure 78.

Intravenous cyclophosphamide	Oral cyclophosphamide
• Patients who already have a moderate cumulative dose of cyclophosphamide • Patients with lower white blood cell counts • Ready access to an infusion center • Adherence may be an issue	• Cost is an important factor • Access to an infusion center difficult • Adherence is not an issue

Figure 78| Considerations for the route of administration of cyclophosphamide for AAV. AAV, ANCA-associated vasculitis.

Practice Point 9.3.1.5: Discontinue immunosuppressive therapy after 3 months in patients who remain on dialysis and who do not have any extrarenal manifestations of disease.

Practice Point 9.3.1.8: Consider plasma exchange for patients with SCr >5.7 mg/dl (500 µmol/l) requiring dialysis or with rapidly increasing SCr, and in patients with diffuse alveolar hemorrhage who have hypoxemia.

Practice Point 9.3.1.9: Add plasma exchange for patients with an overlap syndrome of ANCA vasculitis and anti-GBM.

9.3.2 Maintenance therapy

Recommendation 9.3.2.1: We recommend maintenance therapy with either rituximab or azathioprine and low-dose glucocorticoids after induction of remission *(1C)*.

Practice Point 9.3.2.1: Following cyclophosphamide induction, either azathioprine plus low-dose glucocorticoids or rituximab without glucocorticoids should be used to prevent relapse.

Practice Point 9.3.2.2: Following rituximab induction, maintenance immunosuppressive therapy should be given to most patients.

Practice Point 9.3.2.3: The optimal duration of azathioprine plus low-dose glucocorticoids is not known but should be between 18 months and 4 years after induction of remission.

Practice Point 9.3.2.4: The optimal duration of rituximab maintenance is not known, but studies to date have evaluated a duration of 18 months after remission. There is no role for the routine use of an oral glucocorticoid or oral immunosuppressive with rituximab maintenance.

Practice Point 9.3.2.5: When considering withdrawal of maintenance therapy, the risk of relapse should be considered, and patients should be informed of the need for prompt attention if symptoms recur (Figure 82).

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Lower serum creatinine • More extensive disease • Ear, nose, and throat disease	• History of relapse • ANCA positive at the end of induction • Rise in ANCA	• Lower cyclophosphamide exposure • Immunosuppressive withdrawal • Glucocorticoid withdrawal

Practice Point 9.3.2.6: Consider methotrexate for maintenance therapy in patients, after induction with methotrexate or for those who are intolerant of azathioprine and MMF, but not if GFR is <60 ml/min per 1.73 m^2.

Practice Point 9.3.2.7: Considerations for choosing rituximab or azathioprine for maintenance therapy are presented in Figure 83.

Rituximab preferred	Azathioprine preferred
• Relapsing disease • PR3–ANCA disease • Frail older adults • Glucocorticoid-sparing especially important • Azathioprine allergy	• Low baseline IgG <300 mg/dl • Hepatitis B exposure (HBsAg positive) • Limited availability of rituximab

9.3.3 Relapsing disease

Practice Point 9.3.3.1: Patients with relapsing disease (life- or organ-threatening) should be reinduced (Recommendation 9.3.1.1.), preferably with rituximab.

9.4 Special situations

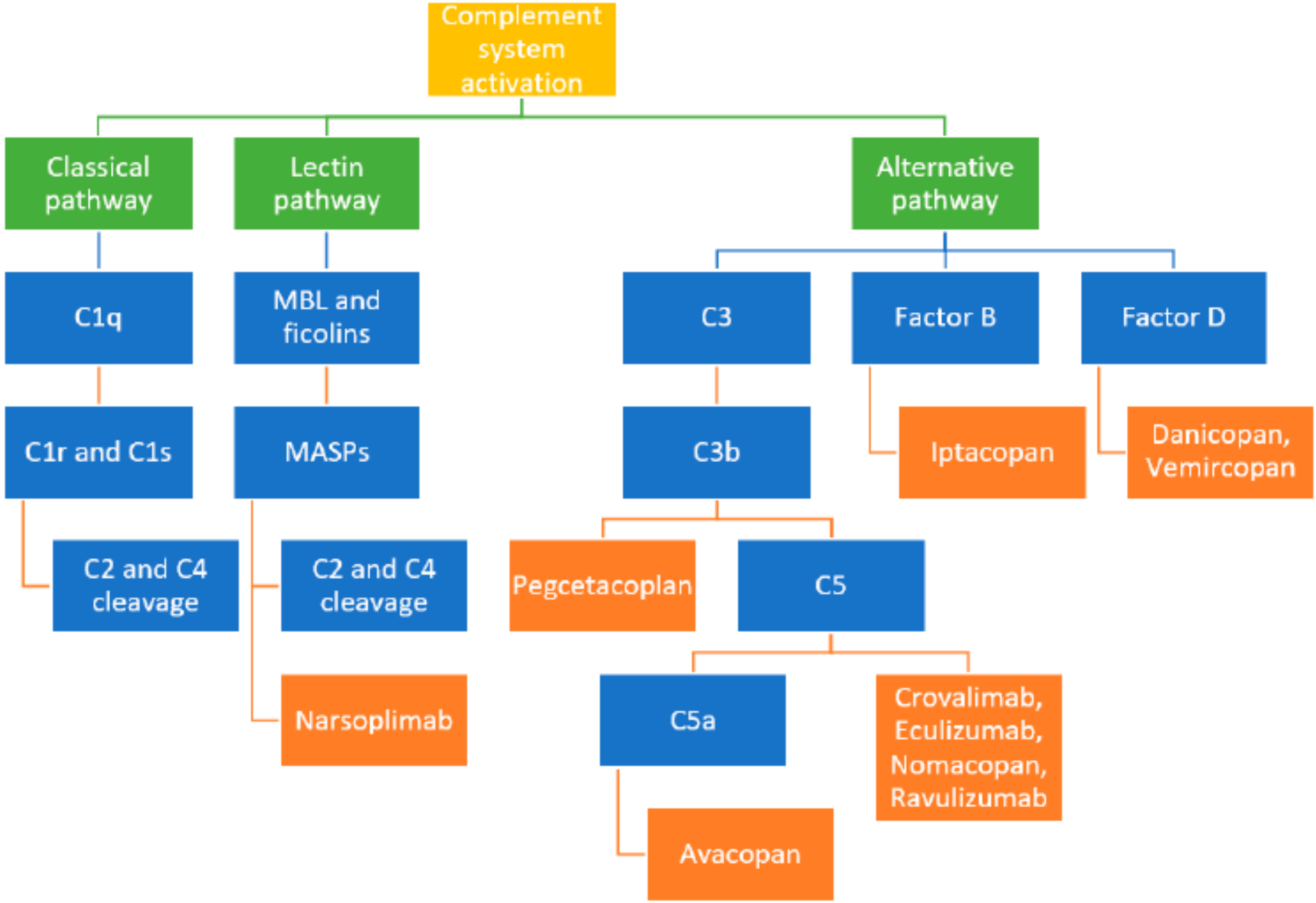
9.4.1 Refractory disease

Practice Point 9.4.1.1: Refractory disease can be treated by an increase in glucocorticoids (intravenous or oral), by the addition of rituximab if cyclophosphamide induction had been used previously, or vice versa. Plasma exchange can be considered.

Practice Point 9.4.1.2: In the setting of diffuse alveolar bleeding with hypoxemia, plasma exchange should be considered in addition to glucocorticoids with either cyclophosphamide or rituximab.

9.4.2 Transplantation

Practice Point 9.4.2.1: Delay transplantation until patients are in complete clinical remission for ≥6 months. Persistence of ANCA should not delay transplantation.


Complement system activation
Classical pathway
Lectin pathway
Alternative pathway
C1q
MBL and ficolins
C3
Factor B
Factor D
C1r and C1s
MASPs
C3b
Iptacopan
Danicopan, Vemircopan
C2 and C4 cleavage
C2 and C4 cleavage
Pegcetacoplan
C5
Narsoplimab
C5a
Crovalimab, Eculizumab, Nomacopan, Ravulizumab
Avacopan

Real-World Experience With Avacopan in Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis

Kidney International Reports (2024) 9, 1783–1791 1783

We found high rates of remission, no concerning safety signals, and successful use in previously unstudied patient populations, including those with low GFR and patients receiving dialysis.