KDIGO 2024 Guideline on ANCA-Associated Vasculitis (AAV)

DIAGNOSIS

BACKGROUND

Small vessel vasculitis is characterized by necrotizing inflammation of small vessels with little or no deposition of immune complexes in the vessel wall.

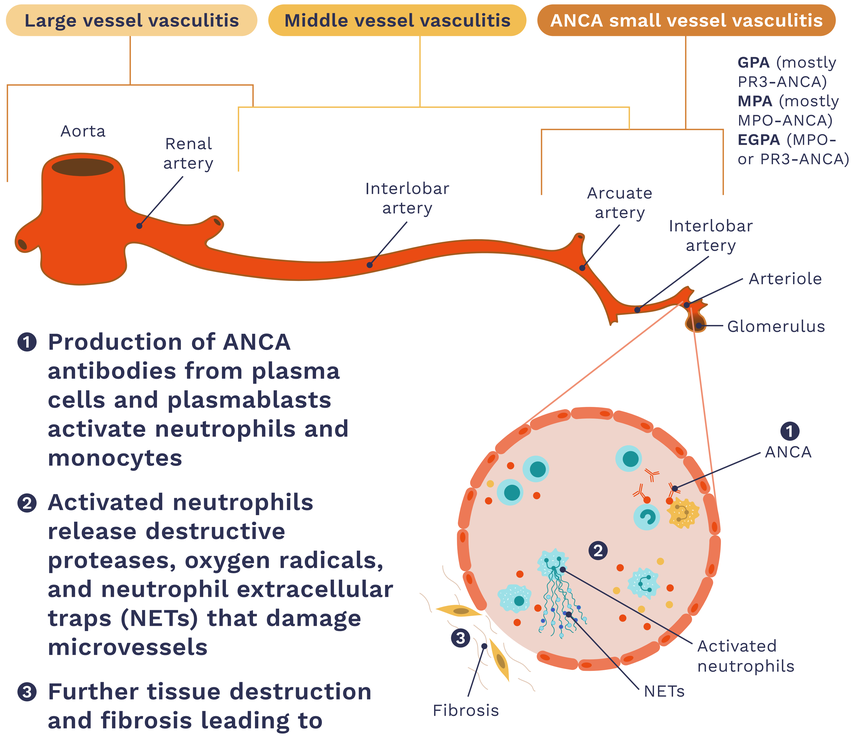
Such pauci-immune small vessel vasculitides include **granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA),** and **eosinophilic granulomatosis with polyangiitis (EGPA)**, as differentiated by serologic tests.

They are often associated with circulating antineutrophil cytoplasmic antibody (ANCA) and hence the above is collectively grouped as **ANCA-associated vasculitis (AAV) [Figure 1]**.

Kidney lesions associated with these conditions are known as **pauci-immune focal and segmental necrotizing and cresentic glomerulonephritis (NCGN)**.

AAV PATHOPHYSIOLOGY

Figure 1 **Renal vascular involvement in AAV***



❶ **Production of ANCA antibodies from plasma cells and plasmablasts activate neutrophils and monocytes**

❷ **Activated neutrophils release destructive proteases, oxygen radicals, and neutrophil extracellular traps (NETs) that damage microvessels**

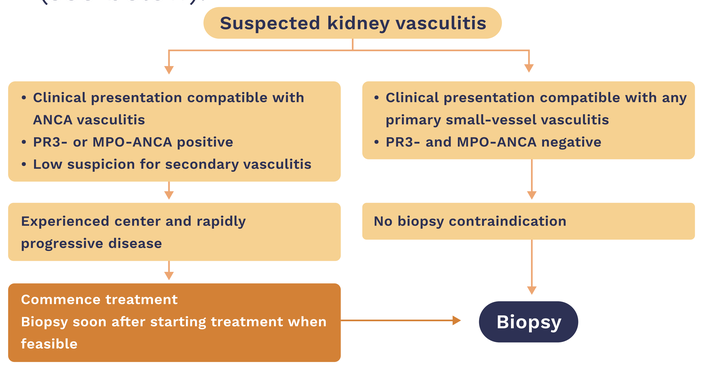
❸ **Further tissue destruction and fibrosis leading to organ dysfunction**

*Adapted from *Comprehensive Clinical Nephrology* 7th Edn (2024) and ANCA-associated Vasculitis, Nature Review Disease Primer (2020)

PRESENTATION

Patients with systemic vasculitis may present with extrarenal manifestations affecting one or several organ systems with or without kidney involvement. Clinical manifestations of kidney involvement include **microscopic hematuria with dysmorphic red blood cells and red cell casts, moderate proteinuria (1-3 g/d) and/or low eGFR**.

Kidney biopsy is the gold standard for diagnosis though if **clinical presentation is compatible with small-vessel vasculitis with positive MPO-ANCA or PR3-ANCA, an immediate biopsy may not be necessary and should not delay treatment initiation** (see below).



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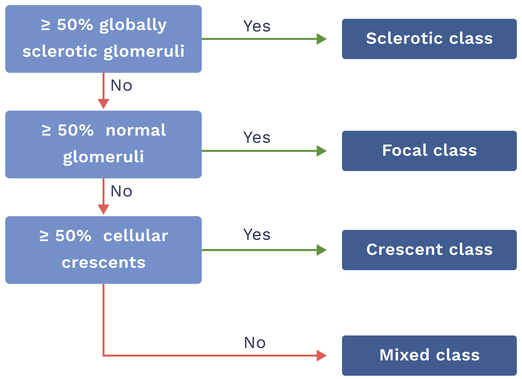
PROGNOSIS

PROGNOSIS

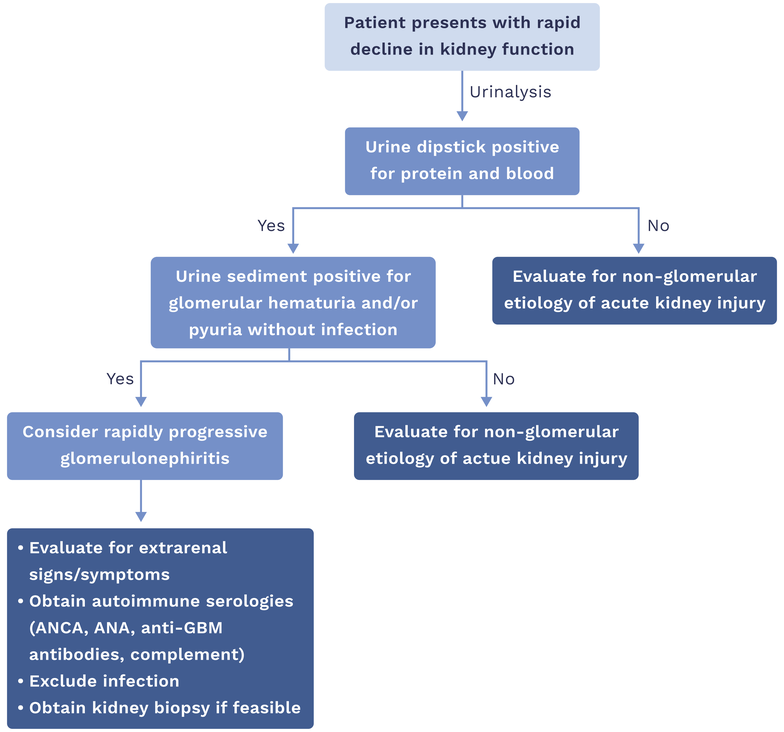
Pauci-immune NCGN is frequently associated with a **rapidly declining glomerular filtration rate (GFR) over days or weeks**. A suggested workup is presented in **Figure 2**.

Kidney histology is predictive of long-term risk of kidney failure. Histopathologic classification of ANCA-associated glomerulonephritis is presented below with **>50% normal glomeruli generally associated with a favorable outcome, while >50% sclerotic glomeruli is associated with a poor outcome**.

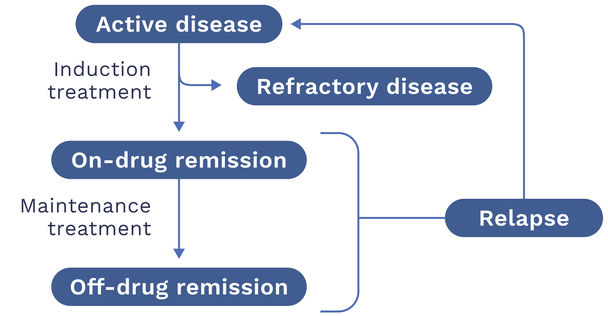


DIAGNOSTIC WORKUP

Figure 2 **Diagnostic strategy in rapidly progressive glomerulonephritis**



OVERARCHING TREATMENT MODEL FOR AAV



Without immunosuppressive therapy, AAV is associated with poor outcomes. **Remission** is defined as absence of manifestations of vasculitis and stable or improved GFR following treatment. **Relapse** is defined as the occurrence of increased disease activity (i.e., signs or symptoms attributed to active disease in any organ system) after a period of partial or complete remission. **Refractory disease** is defined as persistence of kidney or systemic manifestations of vasculitis despite treatment.

Adapted from: ANCA-associated Vasculitis, Nature Review Disease Primer (2020)

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TREATMENT: INDUCTION (1)

BACKGROUND

Treatment of AAV is generally divided into an initial phase commonly termed as **“induction,”** followed by a **“maintenance”** phase.

KDIGO recommends that glucocorticoids in combination with rituximab or cyclophosphamide be used as initial treatment of new-onset AAV **[Figure 3]**.

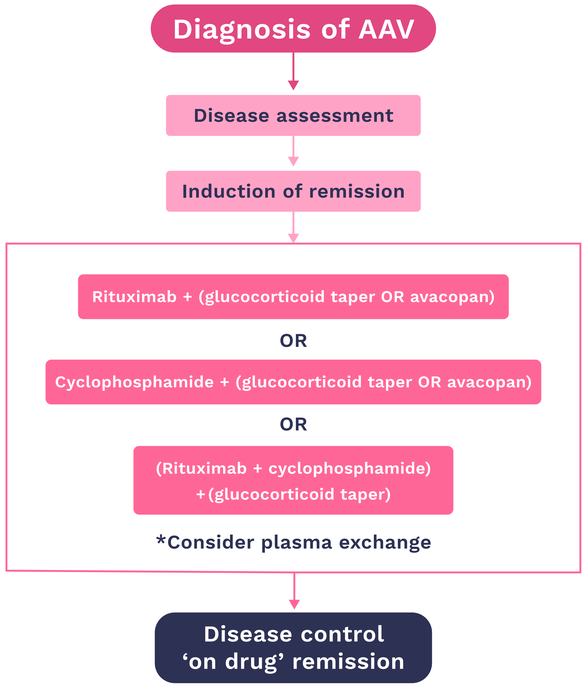
In patients with markedly reduced or rapidly declining GFR (serum creatinine >4 mg/dl [>354 µ mol/l]), a combination of rituximab and cyclophosphamide, or cyclophosphamide and glucocorticoids can be considered in this setting.

When oral glucocorticoids are used, a rapid tapering schedule is preferred as outlined in **Figure 4.**

Avacopan may be used as an alternative to glucocorticoids. In addition to its ability in controlling disease, it has been shown to improve patient quality of life. Patients at increased risk of glucocorticoid toxicity (e.g., infections, diabetes mellitus, osteoporosis) are likely to receive the most benefit from avacopan. Increased recovery of kidney function is also seen in patients with lower kidney function (eGFR <20 ml/min/1.73 m^2). Still, long-term safety data of avacopan are lacking.

TREATMENT ALGORITHM

Figure 3 **Practical treatment algorithm: Induction**



*Consider plasma exchange for patients with SCr >3.4 mg/dl (>300 µmol/l), patients requiring dialysis or with rapidly increasing SCr, or patients with diffuse alveolar hemorrhage who have hypoxemia.

GLUCOCORTICOID TAPERING REGIMEN

Figure 4 **Prednisolone tapering regimen**

Week	‘Reduced-corticosteroid dose’ in PEXIVAS trial		
	<50 kg	50-75 kg	>75 kg
1	50	60	75
2	25	30	40
3-4	20	25	30
5-6	15	20	25
7-8	12.5	15	20
9-10	10	12.5	15
11-12	7.5	10	12.5
13-14	6	7.5	10
15-16	5	5	7.5
17-18	5	5	7.5
19-20	5	5	5
21-22	5	5	5
23-52	5	5	5
>52	Investigators’ local practice		

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TREATMENT: INDUCTION (2)

INDICATIONS

Indications for rituximab vs. cyclophosphamide

Rituximab may be preferred in:

- Children and adolescents
- Premenopausal women and men who are concerned about fertility
- Frail older adults
- Patients who view glucocorticoid-sparing as especially important
- Patients with relapsing disease
- Patients with PR3-ANCA

Cyclophosphamide may preferred in instances where:

- Rituximab is difficult to access
- In the presence of severe glomerulonephritis (SCr >4 mg/dl [354 µ mol/l]*

IgG levels should be measured at baseline and every 6 months for patients treated with rituximab as hypogammaglobulinemia has been observed after prolonged rituximab administration.

*a combination of CYC in 2 IV pulses with RTX can be considered.

INTRAVENOUS VS. ORAL CYCLOPHOSPHAMIDE

Oral and i.v. cyclophosphamide resulted in similar outcomes. With i.v. cyclophosphamide, a reduction of the total cyclophosphamide dosage is achieved compared to the dosage needed with oral cyclophosphamide. However, patients treated with i.v. administration may have an increased risk of relapse. Frequent monitoring for treatment toxicity, in particular leukopenia, is important.

CONSIDERATIONS ON ROUTE OF ADMIN. FOR CYCLOPHOSPHAMIDE

Intravenous cyclophosphamide	Oral cyclophosphamide
• Patients who already have a moderate cumulative dose of cyclophosphamide • Patients with lower white blood cell counts • Patients with ready access to an infusion center • Patients who may have trouble adhering to an oral regimen	• Patients for whom cost is an important factor • Patients who do not have easy access to an infusion center • Patients for whom a self-administered oral regimen will not be difficult

INDICATIONS FOR PLASMA EXCHANGE

The routine use of plasma exchange is **not recommended** for patients presenting with a **GFR <50 ml/min per 1.73 m²**.

Plasma exchange may be considered in **patients with SCr >3.4 mg/dl (>300 µmol/l), patients requiring dialysis or with rapidly increasing SCr, or patients with diffuse alveolar hemorrhage who have hypoxemia**. Plasma exchange can also be considered in **refractory disease**. Volume replacement with fresh frozen plasma should be given to patients who are at risk of bleeding.

Plasma exchange is also indicated in patients with an **overlap syndrome of AAV and anti-glomerular basement membrane (anti-GBM)** as these patients bear more similarity to anti-GBM than AAV.

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TREATMENT: MAINTENANCE

INDICATIONS

KDIGO Work Group advises that maintenance therapy be given to all patients after induction of remission to **prevent relapses of disease**.

KDIGO recommends maintenance therapy with either rituximab, or azathioprine and low-dose glucocorticoids after induction of remission (**Figure 5**).

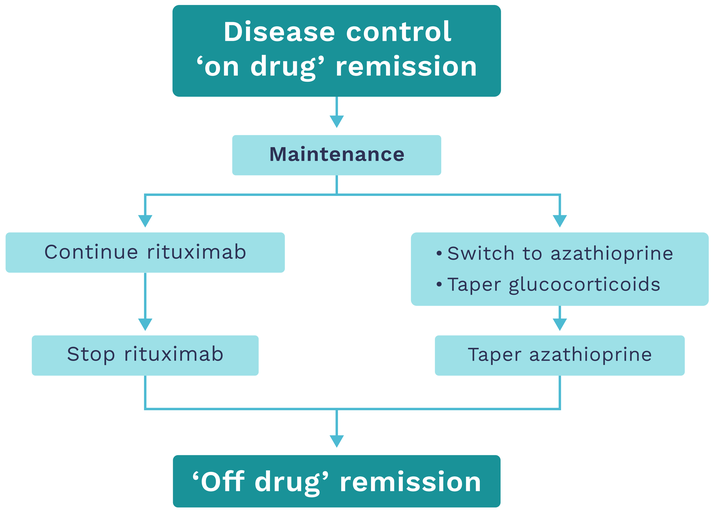
KDIGO prefers rituximab for maintenance therapy in patients with known relapsing disease, PR3-AAV, allergy to azathioprine, and post-rituximab induction. As a maintenance drug, rituximab can be dosed on a fixed schedule or upon reappearance of CD19+ B cells and/or ANCA.

Optimal duration of maintenance therapy is between **18 months and 4 years** after induction of remission.

Factors for selecting rituximab vs azathioprine for maintenance therapy is outlined in Figure 5. **Mycophenolate mofetil or methotrexate can be used as alternatives to azathioprine** though methotrexate should not be used in those with GFR <60 ml/min/1.73 m^2.

TREATMENT ALGORITHM

Figure 5 **Practical treatment algorithm: Maintenance**



Rituximab preferred	Azathioprine preferred
• Relapsing disease • PR3-ANCA disease • Frail older adults • Glucocorticoid-sparing especially important • Azathioprine allergy	• Low baseline lgG (<300 mg/dl) • Limited availability of rituximab

SPECIAL POPULATIONS

Relapsing disease: Risk factors include prior history of relapse and PR3-ANCA positivity. Patients with relapsing disease should be **reinduced**, preferably with rituximab, as relapses respond to immunosuppression with a remission rate similar to that of the initial presentation.

Given the lowered risk of relapse in **patients with MPO-ANCA**, maintenance therapy may sometimes be avoided when a complete remission is achieved if the patient can be monitored intensively with regular ANCA serologies. However, this is wholly based on expert opinion.

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

Transplantation: Delay transplantation until patients are in complete clinical remission for ≥6 months. The persistence of ANCA should not delay transplantation.

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