KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF ANTINEUTROPHIL CYTOPLASMIC ANTIBODY (ANCA)–ASSOCIATED VASCULITIS

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KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis

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FIGURES

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

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Reference keys

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1** or **Level 2**, and the certainty of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

	Implications		
Grade	**Patients**	**Clinicians**	**Policy**
Level 1 "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Grade	Certainty of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of the effect is very uncertain, and often it will be far from the true effect.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1-G5), and Albuminuria category (A1-A3), abbreviated as CGA.

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

	Conventional unit	Conversion factor	SI unit
Albumin	g/dl	10	g/l
Creatinine	mg/dl	88.4	μmol/l
Creatinine clearance	ml/min	0.01667	ml/s
Cyclosporine	ng/ml	0.832	nmol/l
Mycophenolic acid	μg/ml	3.12	μmol/l
PCR	mg/g	0.113	mg/mmol

PCR, protein–creatinine ratio; SI, International System of Units.
Note: Conventional unit × conversion factor = SI unit.

RELATIONSHIP AMONG CATEGORIES FOR ALBUMINURIA AND PROTEINURIA

	Categories		
Measure	Normal to mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)
AER (mg/d)	<30	30–300	>300
PER (mg/d)	<150	150–500	>500
ACR			
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
PCR			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; PCR, protein–creatinine ratio; PER, protein excretion rate.
Relationships among measurement methods within a category are not exact. For example, the relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is approximately 1.0 g/d or 10 mmol/d. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex, race, and diet; therefore, the relationship among these categories is approximate only. The relationship between urine reagent strip results and other measures depends on urine concentration.

Abbreviations and acronyms

AAV	ANCA-associated vasculitis
AKI	acute kidney injury
ANCA	antineutrophil cytoplasmic antibody
CI	confidence interval
eGFR	estimated glomerular filtration rate
EGPA	eosinophilic granulomatosis with polyangiitis
ERT	Evidence Review Team
GBM	glomerular basement membrane
GFR	glomerular filtration rate
GPA	granulomatosis with polyangiitis
HBV	hepatitis B virus
HCV	hepatitis C virus
IgG	immunoglobulin G
i.v.	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MPO	myeloperoxidase
NCGN	necrotizing and crescentic glomerulonephritis
OR	odds ratio
PR3	proteinase 3
RCT	randomized controlled trial
RR	relative risk
SCr	serum creatinine
TMP-SMX	trimethoprim-sulfamethoxazole

Notice

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in July 2022 and updated in April 2023. It is designed to assist decision-making. It is not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually, and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Disclosure section and is kept on file at KDIGO.

Foreword

Kidney International (2024) **105** (Suppl 3S), S71–S116; https://doi.org/10.1016/j.kint.2023.10.008

The mission of Kidney Disease: Improving Global Outcomes (KDIGO) is to "improve the care and outcomes of people with kidney disease worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines." Since its inception in 2003, KDIGO has published comprehensive guidelines on many distinct topics, including the Clinical Practice Guidelines for Glomerulonephritis in 2012 and for Glomerular Diseases in 2021. The latter guideline summarized recommendations for 11 diseases based on evidence available through June 2020. The current update, just 2 years later, reflects the unprecedented pace of scientific discovery in the field, and centers on guidance regarding the diagnosis, treatment, and monitoring of kidney involvement in ANCA-associated vasculitis.

KDIGO strives to maintain the highest standards of excellence and provide clinicians with the most relevant, evidence-based guidance, incorporating both recent advancements as well as widely accepted clinical standards. Thus, this ANCA-Associated Vasculitis Guideline update features a combination of both graded recommendations and practice points. Graded recommendations are based on a systematic review of the evidence and are graded for strength of the recommendation (Level 1, "we recommend" or Level 2, "we suggest") and certainty of the evidence (A, "high"; B, "moderate"; C, "low"; or D, "very low"). Practice points are ungraded, consensus-based statements representing the expert judgment of the Work Group. These practice points are issued when there has not been a systematic review. Some practice points aim at helping the reader in the implementation of graded recommendations and we often provide these in a graphical format. Readers should consider practice points as expert guidance or "good practice statements" and use them as they see fit to inform the care of patients.

We once again thank Jürgen Floege, MD, and Brad H. Rovin, MD, for leading this important initiative, and we very much appreciate the continued dedication of the Work Group members, David Jayne, MD, Jan-Stephan Sanders, MD, PhD, and Vladimír Tesar, MD, PhD. Each of these volunteers provided a considerable amount of time and expertise to the current ANCA-Associated Vasculitis guideline. The independent Evidence Review Team (ERT) from Brown University School of Public Health, led by Ethan Balk, MD, MPH and Craig Gordon, MD, MS, updated the evidence reviews that informed this latest version of the guideline.

To ensure transparency and rigorous public review during guideline development, the draft guideline update was made publicly available for comment in May 2023, per KDIGO policy. We very much appreciate the feedback received from the scientific community. All Work Group members have revised and approved the update for formal release.

In summary, we are pleased to present this latest Clinical Practice Guideline for the Management of ANCA-Associated Vasculitis, reflecting the most recent and up-to-date global evidence for the care of people with ANCA-associated vasculitis throughout the world. We are thrilled at the pace of scientific advancement and we are exceptionally grateful to the Work Group Co-Chairs, Work Group members, and other contributors to this very important KDIGO activity.

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Abstract

The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis represents a focused update of the ANCA-Associated Vasculitis chapter from the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. The aim is to assist clinicians caring for people with ANCA-associated vasculitis. The update takes into consideration evidence from randomized controlled trials published since February 2022. As in 2021, the chapter follows the same template providing guidance related to diagnosis, prognosis, treatment, and special situations. Based on the evidence, this update is mostly focused on guidance related to treatment of ANCA-associated vasculitis. Development of this guideline followed an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the certainty of the evidence and the strength of recommendations followed the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach. Limitations of the evidence are discussed and areas of future research are also presented.

Keywords: ANCA; antineutrophil cytoplasmic antibody-associated vasculitis; evidence-based; glomerular diseases; glomerulonephritis; guideline; KDIGO; nephrotic syndrome; systematic review

CITATION

In citing this document, the following format should be used: Kidney Disease: Improving Global Outcomes (KDIGO) ANCA Vasculitis Work Group. KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis. *Kidney Int.* 2024;105(3S):S71–S116.

Summary of recommendation statements and practice points

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 1).

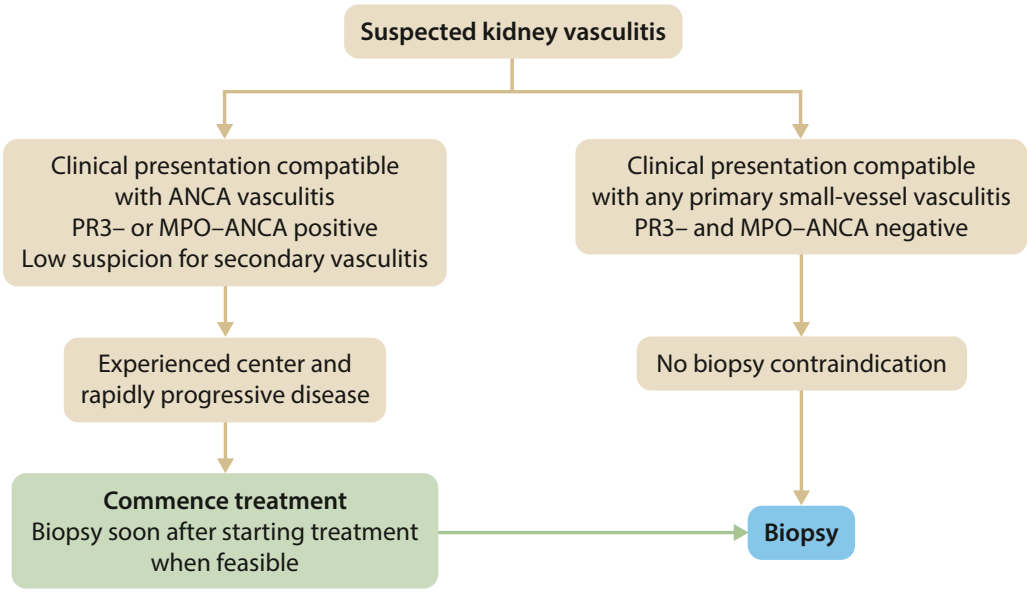

Figure 1 | Biopsy strategy in suspected kidney vasculitis. ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

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

9.2 Prognosis

9.2.1 Survival

[No recommendations or practice points]

9.2.2 Kidney prognosis and remission

[No recommendations or practice points]

9.2.3 Relapses

Practice Point 9.2.3.1: The persistence of ANCA positivity, an increase in ANCA levels, or a change in ANCA from negative to positive may be predictive of future disease relapse and should be considered when making treatment decisions.

9.3 Treatment

9.3.1 Induction

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

Practice Point 9.3.1.1: A practical treatment algorithm for AAV with kidney involvement is given in Figure 6.

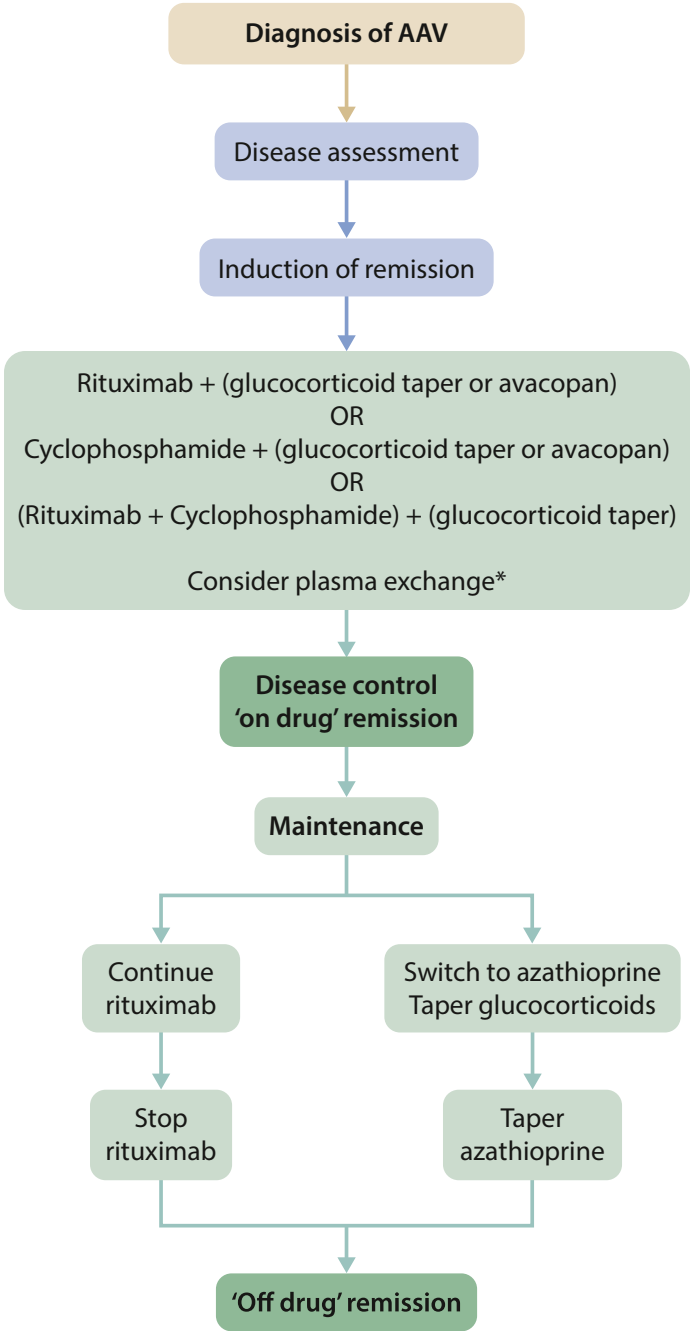

Figure 6| Practical treatment regimen for AAV. *Please see Practice Point 9.3.1.9 for details. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody.

Practice Point 9.3.1.2: In patients presenting with markedly reduced or rapidly declining glomerular filtration rate (GFR) (serum creatinine [SCr] >4 mg/dl [>354 μmol/l]), there are limited data to support rituximab and glucocorticoids. Both cyclophosphamide and glucocorticoids, and the combination of rituximab and cyclophosphamide can 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 7.

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])*

Figure 7| Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV. *A combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis; PR3, proteinase 3; SCr, serum creatinine.

Practice Point 9.3.1.4: Considerations for choosing the route of administration of cyclophosphamide are given in Figure 8.

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

Figure 8| Considerations for the route of administration of cyclophosphamide for AAV. AAV, ANCA-associated vasculitis. ANCA, antineutrophil cytoplasmic antibody.

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

Practice Point 9.3.1.6: Recommendations for oral glucocorticoid tapering are given in Figure 9.

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		

Figure 9| Prednisolone tapering regimen for AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; PEXIVAS, Plasma Exchange and Glucocorticoids for the Treatment of ANCA-Associated Vasculitis.

Practice Point 9.3.1.7: Avacopan may be used as an alternative to glucocorticoids. Patients with an increased risk of glucocorticoids toxicity are likely to receive the most benefit from avacopan. Patients with lower GFR may benefit from greater GFR recovery.

Practice Point 9.3.1.8: Recommendations for immunosuppressive dosing are given in Figure 10.

Oral cyclophosphamide	Intravenous cyclophosphamide	Rituximab	Rituximab and i.v. cyclophosphamide	MMF	Avacopan
2 mg/kg/d for 3 months, continue for ongoing activity to a maximum of 6 months	15 mg/kg at weeks 0, 2, 4, 7, 10, 13 (16, 19, 21, 24 if required)	375 mg/m^2/week × 4 weeks OR 1 g at weeks 0 and 2	Rituximab 375 mg/m^2/week × 4 weeks, with i.v. cyclophosphamide 15 mg/kg at weeks 0 and 2 OR Rituximab 1 g at 0 and 2 weeks with i.v. cyclophosphamide 500 mg/2 weeks × 6	2000 mg/d (divided doses), may be increased to 3000 mg/d for poor treatment response	30 mg twice daily as alternative to glucocorticoids, in combination with rituximab or cyclophosphamide induction
Reduction for age: • 60 yr, 1.5 mg/kg/d • 70 yr, 1.0 mg/kg/d Reduce by 0.5 mg/kg/day for GFR <30 ml/min/1.73 m^2	Reduction for age: • 60 yr 12.5 mg/kg • 70 yr, 10 mg/kg Reduce by 2.5 mg/kg for GFR <30 ml/min/1.73 m^2				

Figure 10| Immunosuppressive drug dosing for AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GFR, glomerular filtration rate; i.v., intravenous; MMF, mycophenolate mofetil.

Practice Point 9.3.1.9: 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.

Practice Point 9.3.1.10: Add plasma exchange for patients with an overlap syndrome of ANCA-associated vasculitis and anti-glomerular basement membrane (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 rituximab induction, maintenance immunosuppressive therapy should be given to most patients.

Practice Point 9.3.2.2: The optimal duration of remission therapy is between 18 months and 4 years after induction of remission.

Practice Point 9.3.2.3: 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 12).

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Higher 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

Figure 12 | Factors that increase relapse risk for AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; PR3, proteinase 3.

Practice Point 9.3.2.4: Consider mycophenolate mofetil (MMF) or methotrexate as alternatives to azathioprine for maintenance therapy in patients intolerant of azathioprine. Methotrexate should not be used for patients with a GFR <60 ml/min per 1.73 m^2.

Practice Point 9.3.2.5: Considerations for choosing rituximab or azathioprine for maintenance therapy are presented in Figure 13.

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

Figure 13 | Considerations for using rituximab or azathioprine for AAV maintenance therapy. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; IgG, immunoglobulin G; PR3, proteinase 3.

Practice Point 9.3.2.6: Recommendations for dosing and duration of maintenance therapy are given in Figure 14.

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: **1.** 500 mg × 2 at complete remission, and 500 mg at mo 6, 12, and 18 thereafter (MAINRITSAN scheme) OR **2.** 1000 mg infusion after induction of remission, and at mo 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme)	1.5–2 mg/kg/d at complete remission until 1 yr after diagnosis then decrease by 25 mg every 3 mo	2000 mg/d (divided doses) at complete remission for 2 yr
	Extend azathioprine at complete remission until 4 yr after diagnosis; start at 1.5–2 mg/kg/d for 18–24 mo, then decrease to a dose of 1 mg/kg/d until 4 yr after diagnosis, then taper by 25 mg every 3 mo. Glucocorticoids should also be continued at 5–7.5 mg/d for 2 yr and then slowly reduced by 1 mg every 2 mo	

Figure 14| Immunosuppressive dosing and duration of AAV maintenance therapy. MAINRITSAN, MAINtenance of Remission Using RITuximab in Systemic ANCA-associated Vasculitis; MMF, mycophenolate mofetil; RITAZAREM, Rituximab versus azathioprine as therapy for maintenance of remission for antineutrophil cytoplasm antibody-associated vasculitis (AAV). *RITAZAREM was in relapsing AAV.

9.3.3 Relapsing disease

Practice Point 9.3.3.1: Patients with relapsing disease 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 can 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. The persistence of ANCA should not delay transplantation.

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis

9.1 Diagnosis

Small-vessel vasculitis encompasses a group of diseases characterized by necrotizing inflammation of small vessels (i.e., arterioles, capillaries, and venules) and little or no deposition of immune complexes in the vessel wall (pauci-immune). Medium or large vessels may occasionally also be involved. Pauci-immune small-vessel vasculitides include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[1] The kidney lesion associated with these conditions is a pauci-immune focal and segmental necrotizing and crescentic glomerulonephritis (NCGN). Active pauci-immune small-vessel vasculitis is typically associated with circulating antineutrophil cytoplasmic antibody (ANCA), and GPA, MPA, and EGPA were grouped under the term "ANCA-associated vasculitis" (AAV) in the 2012 Chapel Hill definitions of primary systemic vasculitis.[1] NCGN may occur with or without extrarenal manifestations of disease.

Patients with systemic vasculitis may present with extrarenal manifestations affecting one or several organ systems, with or without kidney involvement. Commonly involved systems are the upper and lower respiratory tract, skin, eyes, and the nervous system. Pulmonary hemorrhage affects 10% of patients with AAV and is associated with an increased risk of death.[2] The need to treat extrarenal vasculitis may influence treatment choices for kidney vasculitis.

The clinical manifestations associated with NCGN include microscopic hematuria with dysmorphic red blood cells and red cell casts, and proteinuria that is usually moderate (1–3 g/d). Pauci-immune NCGN is frequently associated with a rapidly declining glomerular filtration rate (GFR) over days or weeks. A slowly progressive course has also been described when active vasculitic lesions may be hard to find on histology, and some patients with kidney vasculitis, especially if presenting with extrarenal disease, are diagnosed when the GFR is still normal.

Acute kidney injury (AKI) can present together with alveolar hemorrhage and is often referred to as a "pulmonary–renal syndrome." Although several diseases can manifest as a pulmonary–renal syndrome, simultaneous lung and kidney injury should raise concern for vasculitis. In this situation, serologic testing and interpretation are of great diagnostic importance. A positive test for anti-glomerular basement membrane (GBM) antibodies suggests anti-GBM disease (formerly Goodpasture's syndrome) and a need for urgent plasma exchange without waiting for a positive diagnostic biopsy (Figure 1), whereas a positive test for myeloperoxidase (MPO)- or proteinase 3 (PR3)-ANCA supports a diagnosis of AAV. Some patients are positive for

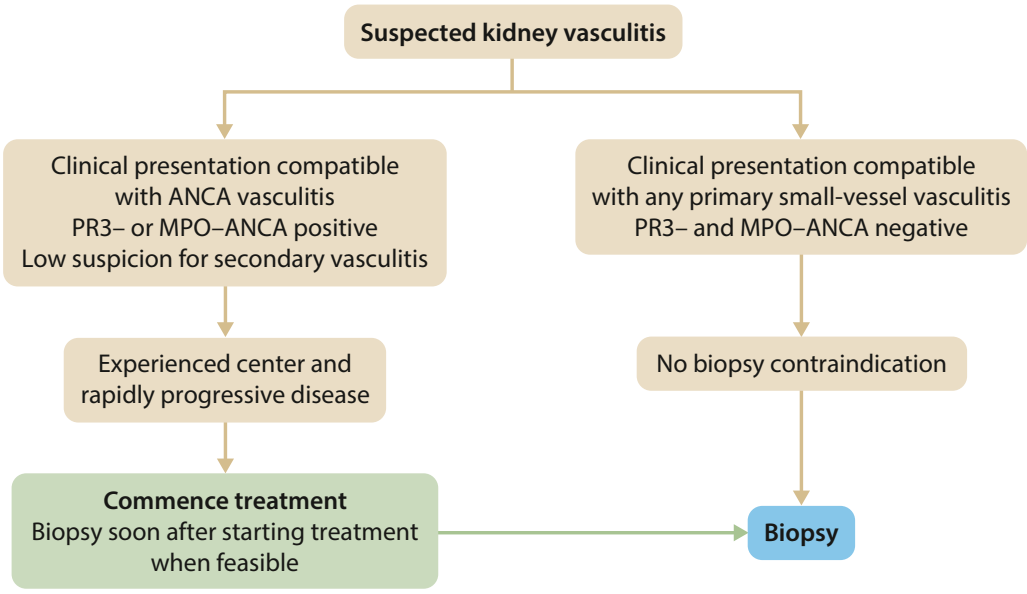

Figure 1 | Biopsy strategy in suspected kidney vasculitis. ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3.

both ANCA and anti-GBM antibodies. The diagnosis of AAV relies on the combination of clinical findings and results of imaging studies and laboratory tests (such as C-reactive protein level, complete blood count, kidney parameters, and urine sediment analysis).

About 90% of patients with small-vessel vasculitis or NCGN have ANCA, directed primarily to the neutrophil granule proteins MPO or PR3, but ANCA negativity does not exclude this diagnosis.[3] The 2017 revised international consensus on testing of ANCA in GPA and MPA states that high-quality antigen-specific immunoassays are the preferred screening method for MPO- and PR3-ANCA.[4]

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 1).

In AAV, a kidney biopsy is important for both the primary diagnosis and recurrent disease. This also relates to recurrent disease after kidney transplantation (Figures 2 and 3). Biopsy remains the gold standard, and in GPA, the diagnostic yield of a kidney biopsy can be as high as 91.5%.[5] The kidney biopsy provides prognostic information through assessment of glomerular, tubulointerstitial, and vascular histopathology.[6] Therefore, a kidney biopsy should always be considered in patients suspected of having active kidney involvement, but in the context of positive MPO- or PR3-ANCA serology and a clinical picture compatible with small-vessel vasculitis with low suspicion for secondary vasculitis, an immediate biopsy may not be necessary and should not delay the initiation of treatment.

The treatment recommendations in this guideline derive from studies of patients with AAV and/or NCGN. About 10% of patients presenting with signs and symptoms of MPA, GPA, or NCGN are persistently ANCA-negative. These patients are treated similarly to patients who are ANCA-positive, although no study has focused specifically on the treatment of patients who are ANCA-negative. When considering patients who are ANCA-negative, an important point to note is that several non-vasculitic diseases may closely mimic small-vessel vasculitis. These include systemic rheumatic diseases, such as systemic lupus erythematosus, infections, and malignancies (Figure 4[7]).

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

A center with experience in AAV management is equipped with adequate facilities for rapid diagnosis and management. For diagnosis, adequate serologic and histologic tests should be available. All treatment modalities should be available, including rituximab and plasma exchange. The center should have experience with these treatment modalities and their complications. Finally, a center should have access to an intensive care unit and an acute hemodialysis facility.

9.2 Prognosis

9.2.1 Survival

Factors influencing remission (no disease activity or Birmingham Vasculitis Activity Score [BVAS] = 0; Figure 2), relapse, and kidney and overall survival in AAV have been described.[8–10] Important factors associated with survival are age and kidney function and/or kidney involvement at diagnosis. Without immunosuppressive therapy, AAV is associated with poor outcomes. Consequently, immunosuppressive treatment is pivotal to improving survival of individual patients with active systemic AAV, including older adults (>75 years of age) for whom immunosuppressive treatment has been associated with improved survival.[11]

Disease activity of ANCA-associated vasculitis represents signs or symptoms attributable to active disease in any organ system.

Remission is defined as the absence of manifestations of vasculitis and GN (BVAS=0). For GN, it is defined as a stable or improved glomerular filtration rate. While hematuria and proteinuria are present at times of active disease and can resolve completely, their persistence does not necessarily imply active disease.

Relapse is defined as the occurrence of increased disease activity after a period of partial or complete remission. A return or increase of hematuria with proteinuria may indicate a kidney relapse. Relapse can be divided into major or minor, with major relapses defined as life- or organ-threatening. Examples of major relapse include diffuse alveolar hemorrhage, subglottic stenosis, GN or vasculitis threatening vision.

Treatment-resistant disease is defined as the persistence of or appearance of kidney and/or systemic manifestations of vasculitis, while receiving treatment equal in intensity to initial immunosuppressive therapy.

Figure 2 | Definition of disease activity, remission, relapse, and treatment-resistant disease in AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; GN, glomerulonephritis.

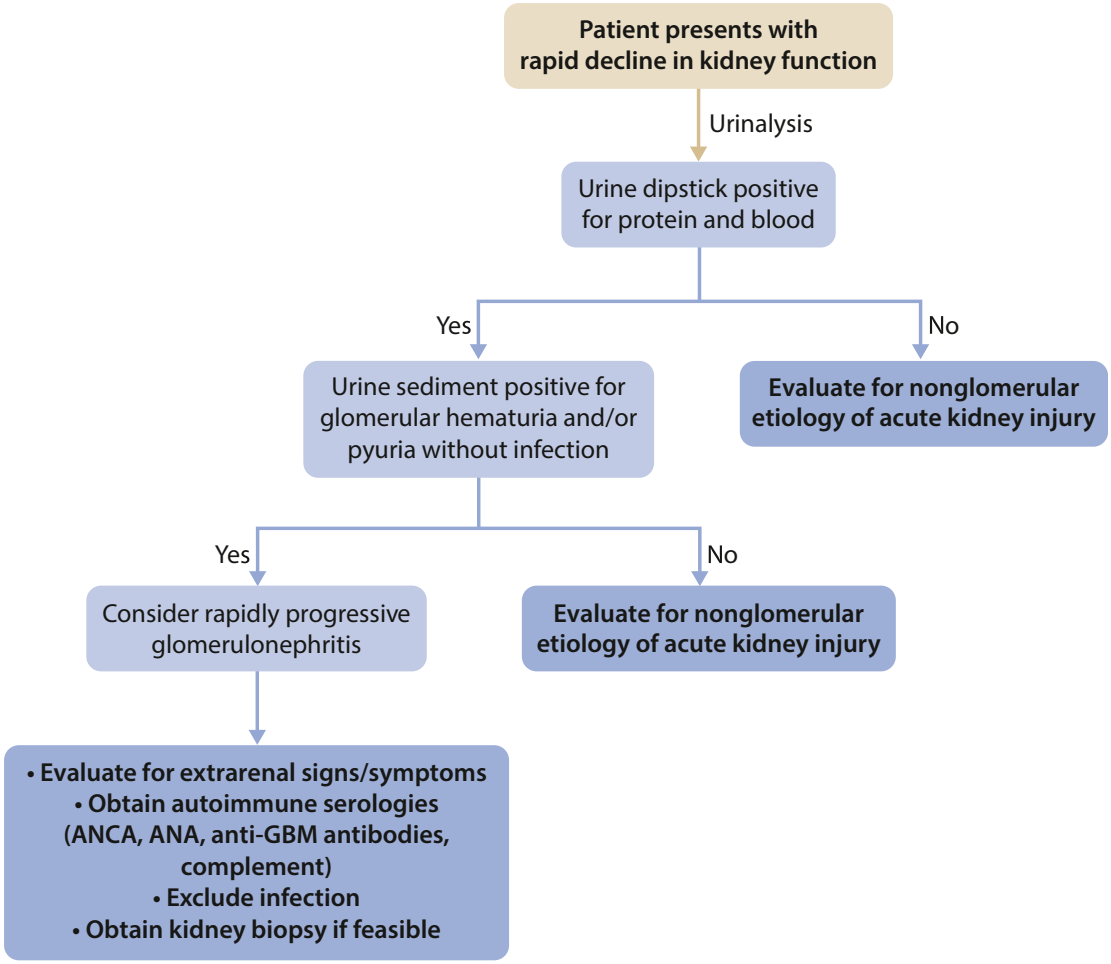

Figure 3| Diagnostic strategy in rapidly progressive glomerulonephritis. ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

9.2.2 Kidney prognosis and remission

Kidney histology is predictive of long-term risk of kidney failure; prognostic scores based on kidney histology have been developed (e.g., by Berden *et al.*[6] and Brix *et al.*[12]; Figure 5[6]).

In validation studies of the histopathologic classification by Berden *et al.*, >50% normal glomeruli in the focal class were associated with a favorable outcome, whereas >50% sclerotic glomeruli were associated with a poor outcome.[13] Also, in the kidney risk score developed by Brix *et al.*, a higher percentage of normal glomeruli (>25%) was associated with favorable kidney outcomes.[12] However, regarding the crescentic class (>50% cellular crescents) and the mixed class, discrepancies in outcome have been reported.

Organ system	Microscopic polyangiitis (MPA) (%)	Granulomatosis with polyangiitis (GPA) (%)	Eosinophilic granulomatosis with polyangiitis (EGPA) (%)
Cutaneous	40	40	60
Kidney	90	80	45
Pulmonary	50	90	70
Ear, nose, and throat	35	90	50
Musculoskeletal	60	60	50
Neurologic	30	50	70
Gastrointestinal	50	50	50

Figure 4| Frequency of organ involvement in AAV. Reproduced from *The New England Journal of Medicine*, Jennette JC, Falk RJ. Small vessel vasculitis, Volume 337, Pages 1512–1523.[7] Copyright © 1997 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody.

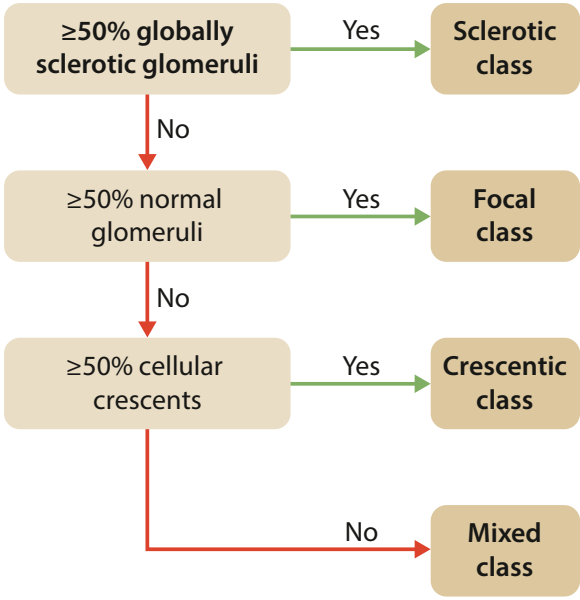

Figure 5 | Histopathologic classification of ANCA-associated glomerulonephritis. Biopsies should be scored for glomerular lesions in the following order: globally sclerotic glomeruli, normal glomeruli, and glomeruli with cellular crescents. Biopsies that do not fit into a category based upon a predominant glomerular phenotype will be included in the mixed category.[6] ANCA, antineutrophil cytoplasmic antibody.

Importantly, kidney recovery can be seen in the face of advanced kidney damage, and induction treatment should not be withheld on the basis of unfavorable histologic findings.

Assessing the remission of kidney vasculitis can be difficult in the presence of persistent hematuria and proteinuria, which are seen in 50% of patients. A stable or falling serum creatinine (SCr) level is a guide; control of extrarenal disease and normalization of inflammatory markers (e.g., C-reactive protein) are also helpful but do not exclude ongoing kidney activity. Also, other causes of AKI, not related to AAV, should be considered; therefore, a kidney biopsy should be considered at presentation and during follow-up in case of poor treatment response (Figure 1).

Histologic activity is unlikely in the absence of hematuria. Persisting proteinuria can reflect disease activity or chronic parenchymal damage from preceding inflammation. Such chronic damage confers an adverse long-term kidney prognosis. The significance of persisting hematuria is unclear. In a retrospective study, no difference was found in the occurrence of kidney failure between patients with versus without persisting hematuria, but more patients with hematuria experienced a relapse of kidney disease.[14] More importantly, a return of hematuria after initial resolution may indicate kidney relapse.

9.2.3 Relapses

Practice Point 9.2.3.1: The persistence of ANCA positivity, an increase in ANCA levels, or a change in ANCA from negative to positive may be predictive of future disease relapse and should be considered when making treatment decisions.

PR3- and MPO-AAV are characterized by the occurrence of relapses. Patients who are PR3-ANCA–positive experience more relapses than those who are MPO-ANCA–positive.[15] The achievement of ANCA-negativity after induction treatment is associated with a lower risk of relapse.[16,17] Both a rise in ANCA and persistence of ANCA are only modestly predictive of future disease relapse.[18] Also, a change in ANCA status from negative to positive has been associated with a higher incidence of relapse, and more frequent clinical assessments should be considered. However, regarding the relapsing phenotype of AAV, ANCA measurements should not guide treatment decisions in individual patients.

9.3 Treatment

Treatment of AAV is generally divided into an initial phase, commonly termed "induction," followed by a "maintenance" phase.

9.3.1 Induction

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

The best evidence is available for patients with new-onset AAV. In patients with severe kidney disease (SCr >4 mg/dl [>354 μmol/l]), limited data for induction therapy with rituximab are available.

Key information

Balance of benefits and harms. Cyclophosphamide, in combination with glucocorticoids, has been used as induction

therapy in several randomized controlled trials (RCTs). In 2 RCTs, rituximab alone or in combination with 2 cyclophosphamide pulses was shown to be equally effective as cyclophosphamide, with a similar rate of infectious complications (Supplementary Table S4[19–22]). However, *post hoc* analysis of the Rituximab in ANCA-Associated Vasculitis (RAVE) trial found a superior remission rate for the PR3-ANCA subgroup at 6 months treated with rituximab, with an odds ratio (OR) of 2.11 (95% confidence interval [CI]: 1.04–4.30) in analyses adjusted for age, sex, and new-onset versus relapsing disease at baseline.[23] In patients with PR3-AAV and relapsing disease, more patients achieved remission at 6 and 12 months with rituximab, with an OR of 3.57 (95% CI: 1.43–8.93) at 6 months and an OR of 4.32 (95% CI: 1.53–12.15) at 12 months.[23] No association between treatment drug and remission was observed in patients with MPO-AAV (RAVE trial; Supplementary Table S5[20,22]).

Regarding the route of cyclophosphamide administration, oral and intravenous (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. In the Pulse Versus Continuous Cyclophosphamide for Induction of Remission in ANCA-Associated Vasculitides (CYCLOPS) study, this resulted in a lower rate of leukopenia (Supplementary Table S6[22,24]). Nevertheless, more patients tended to experience relapses after receiving i.v. cyclophosphamide during long-term follow-up.

In patients with non-life-threatening disease, excluding those with rapidly progressive kidney disease, mycophenolate mofetil (MMF) might be an alternative to cyclophosphamide for the MPO-ANCA subgroup. MMF had a similar remission rate to that of cyclophosphamide for patients with both PR3- and MPO-ANCA (Supplementary Table S7[25–28]), but a much-increased relapse risk in those with PR3-ANCA in the Clinical Trial of Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis (MYCYC).[27]

Methotrexate, with glucocorticoids, has been used for AAV without kidney disease in the absence of irreversible tissue damage but is associated with a higher relapse rate and higher late accrual of damage compared to cyclophosphamide (Supplementary Table S8[22,29,30]).

Glucocorticoids are major contributors to adverse events. Intravenous methylprednisolone (doses of 1–3 g) is widely used for more severe presentations but has not been tested in an RCT. Oral prednisolone or prednisone starting at 1.0 mg/kg/d has been used in most RCTs, again without direct RCT support. The rate of reduction of glucocorticoids varies among studies, with some aiming for withdrawal by month 5, whereas others continue 5–10 mg/d after 6 months.[31] The Plasma Exchange and Glucocorticoids for the Treatment of ANCA-Associated Vasculitis (PEXIVAS) trial demonstrated that for patients with GFR <50 ml/min per 1.73 m^2, a more rapid reduction was as effective as, but safer than, a "standard" glucocorticoid-tapering regimen.[32] The Low-Dose Glucocorticoid Vasculitis Induction Study (LoVAS) compared reduced-dose versus high-dose glucocorticoids added to rituximab on remission induction in AAV.[33] Patients with severe glomerulonephritis (estimated glomerular filtration rate [eGFR] <15 ml/min per 1.73 m^2) and alveolar hemorrhage (oxygen >2 l/min) were excluded. Patients were randomized to receive reduced-dose prednisolone (0.5 mg/kg/d) or high-dose prednisolone (1 mg/kg/d) plus 4 doses of 375 mg/m^2 per week rituximab. Reduced-dose glucocorticoids (0.5 mg/kg/d) were noninferior in achieving remission, and the infections that occurred were less severe. As the included population was of Japanese origin, with a predominance of MPO-ANCA vasculitis, the wider applicability of this regimen in other populations remains to be determined. In the RAVE trial, the rituximab group had a lower glucocorticoid exposure, and observational studies have supported early glucocorticoid removal when rituximab is used.

Complement-targeted therapy might be another strategy to reduce glucocorticoid exposure. An oral C5a receptor antagonist, avacopan, has been shown in A Phase 3 Clinical Trial of CCX168 (Avacopan) in Patients with ANCA-Associated Vasculitis (ADVOCATE) to be an effective alternative to glucocorticoid treatment in AAV, with potential to improve kidney outcomes.[34] In this RCT, avacopan was dosed at 30 mg twice daily. Patients with more severe end-organ manifestations, such as eGFR <15 ml/min per 1.73 m^2 and alveolar hemorrhage requiring mechanical ventilation, were excluded from this trial. Remission at week 26 was observed in 72.3% of patients in the avacopan arm and 70.1% in the prednisolone arm, achieving noninferiority. In a *post hoc* analysis of the ADVOCATE trial, avacopan led to an earlier reduction in albuminuria and an improvement of kidney function compared to prednisolone, especially in patients with an eGFR <20 ml/min per 1.73 m^2.[35]

Certainty of evidence. The overall certainty of evidence is moderate. The RCTs that compared rituximab with cyclophosphamide reported important outcomes of remission and relapse, and the certainty of the evidence was rated as moderate for these outcomes because of serious imprecision (Supplementary Table S4[19–22]). The critical outcome, all-cause mortality, was included; however, no cases of kidney failure were reported in the 2 trials. Only the RAVE trial was blinded for both participants and personnel, and it is regarded by the panel as the best evidence available. Effects on remission at 6 months, relapse rate, and serious adverse events are graded as having moderate certainty of evidence. In a secondary paper, remission in ANCA subgroups was reported; this is graded as having low certainty of evidence due to imprecision (only 1 study). There were no differences in kidney outcomes, and those with SCr >4 mg/dl (>354 μmol/l) were excluded. Finally, follow-up was short, at 18 months.

The studies comparing continuous oral versus i.v. pulse cyclophosphamide were not blinded (participants and study personnel; Supplementary Table S9[22,36–38]). Overall, the certainty of evidence on the important endpoints of remission and leukopenia is graded as moderate because of study limitations. Other outcomes exhibited low certainty of evidence because of serious imprecision due to very few events (relapse, all-cause mortality). The Work Group

considers the CYCLOPS study the best available study on this topic because of the addition of azathioprine to both treatment arms; consequently, it was evaluated separately (Supplementary Table S6[22,24]). The certainty of the evidence was low for all critical outcomes, due to imprecision, as there was only 1 study.

The RCTs comparing MMF versus cyclophosphamide had few events for many critical and important outcomes (all-cause mortality, kidney failure, malignancy, serious adverse events), and hence, the certainty of the evidence was low (Supplementary Table S7[25–28]). However, for the outcomes of infection and relapse, the certainty of the evidence was rated as moderate due to study limitations from some studies (unclear blinding of outcome assessors). The MYCYC[27] and Tuin *et al.*[28] studies had an independent, blinded adjudication committee assess the primary endpoint of remission at 6 months, but the other studies had concerns regarding blinding, and hence, the certainty of the evidence for this outcome has been rated as moderate.

Neither of the 2 RCTs comparing standard and reduced-dose glucocorticoids were blinded. Only one RCT (LoVAS) studied a lower glucocorticoid starting dose. The other RCT (PEXIVAS) started glucocorticoids at the same dose but tapered the dose more quickly in the reduced-dose group. The certainty of evidence on sustained remission was graded as moderate; for other endpoints, including adverse events and serious infection, the certainty of evidence was graded as low, primarily due to imprecise summary estimates (Supplementary Table S10[32,33]).

Two placebo-controlled RCTs studied avacopan in AAV; one of the RCTs (ADVOCATE) had no serious methodological concerns, but the other RCT (Clinical ANCA Vasculitis Safety and Efficacy Study of Inhibitor of C5aR [CLASSIC]) had a high dropout rate and changed their *a priori* primary outcome. The certainty of the evidence on sustained remission and severe adverse events was graded as moderate, but the evidence for infections and discontinuation due to adverse events was graded as low (Supplementary Table S11[34,39]]. The CLASSIC study included 2 dosages, but in this phase 2 study, the number of randomized patients was small, and therefore, the certainty of the evidence on different dosages is very low (Supplementary Table S12[39]). In the ADVOCATE study, patients with an eGFR <15 ml/min per 1.73 m^2 were excluded.

Values and preferences. This Work Group places a relatively high value on achieving remission of disease, which was the primary outcome of most evaluated studies. However, extended immunosuppressive therapy should be associated with a minimum of adverse events. In subgroups of patients for whom fertility is a concern, and in relapsing patients, rituximab may be preferred.

Intravenously pulsed versus oral continuous cyclophosphamide results in a similar outcome. However, the cumulative dosage of cyclophosphamide is lower with i.v. cyclophosphamide. Patients treated with i.v. pulse cyclophosphamide may have an increased risk of relapse, as reported in the CYCLOPS study.

Glucocorticoids are disliked by patients and are major causes of adverse events. Use of rituximab or the combination of rituximab with cyclophosphamide may be associated with a lower glucocorticoid requirement, which is particularly desirable in those at higher risk of glucocorticoid toxicity.[20,40] C5a receptor inhibition with avacopan is a potential alternative to glucocorticoid treatment, which in addition to having efficacy in controlling disease, has been shown to improve patient quality of life as compared to prednisone in AAV.[34]

Resource use and costs. Rituximab is typically more expensive than cyclophosphamide, although secondary costs for cyclophosphamide (infusions and monitoring) and the reduced cost of generic rituximab can make the total costs similar. Ease of administration, simpler monitoring, glucocorticoid sparing, and reduced early toxicity associated with rituximab compared to cyclophosphamide are additional factors that influence cost and resource use.

Regarding i.v. versus oral cyclophosphamide, a reduction of the total cyclophosphamide dosage is achieved with i.v., compared to oral, cyclophosphamide. However, oral cyclophosphamide is less expensive. In patients treated with either i.v. or oral cyclophosphamide, frequent monitoring for treatment toxicity, in particular leukopenia, is important.

Regarding avacopan, high cost, limited availability, and lack of long-term safety data are currently barriers to its wider application.

Considerations for implementation. The choice of treatment regimen depends on patient comorbidity, age, and preference, as well as local availability and cost.

Rationale

Cyclophosphamide, in combination with glucocorticoids, has been applied as induction therapy in multiple RCTs. In 2 RCTs, rituximab has been shown to be equally effective in inducing remission as cyclophosphamide.[19,20] Rituximab compared to cyclophosphamide probably makes little or no difference in relapse rate, at 1–6 months (relative risk [RR]: 0.63; 95% CI: 0.35–1.14). Rituximab and cyclophosphamide have similar rates of severe adverse events, including infections. However, risks of long-term comorbidities, such as malignancy, hepatitis B virus (HBV) and hepatitis C virus (HCV) reactivation, and secondary immunodeficiency, appear to differ between rituximab and cyclophosphamide and may influence choice.[41,42]

In the RAVE study, patients with relapsing disease more often achieved remission at 6 and 12 months in the rituximab group compared to the cyclophosphamide–azathioprine group.[23,43] Analysis of the data according to ANCA status showed that patients with PR3-AAV were significantly more often in remission at 6 months under rituximab than patients treated with cyclophosphamide–azathioprine.[23]

An important consideration when interpreting the RAVE trial is that it excluded patients with severe kidney disease (SCr >4 mg/dl [>354 μmol/l]). A recent single-center retrospective study found that rituximab was comparable to cyclophosphamide in remission induction at 6 months.[44] However, no prospective data on the efficacy of remission induction of

rituximab in severe kidney disease are available. In contrast, the Rituximab versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) study included such patients and showed that rituximab combined with 2 cyclophosphamide pulses and glucocorticoids was comparable to cyclophosphamide for remission induction and number of adverse events.[19]

Regarding the administration route of cyclophosphamide, 4 RCTs compared induction therapy with i.v. pulse versus continuous oral cyclophosphamide.[22,24,36–38] Intravenous cyclophosphamide and oral cyclophosphamide resulted in a similar rate of remission, but less leukopenia was seen in patients given i.v. cyclophosphamide. In the CYCLOPS study, a higher rate of relapse was reported with i.v. pulse cyclophosphamide.[24] This finding reflects the 50% reduction in cyclophosphamide exposure seen with i.v. regimens; shorter-course oral cyclophosphamide regimens are also associated with higher relapse risk.

In patients with nonsevere disease, MMF and methotrexate have been compared to cyclophosphamide. Regarding MMF versus cyclophosphamide, no significant differences were found, but cyclophosphamide tended to show better efficacy and fewer relapses.[22,25–28] Compared to cyclophosphamide, methotrexate was associated with a higher relapse rate (RR: 1.50; 95% CI: 1.03–2.17).[22,29,30,45] Effects on other critical and important outcomes are unclear, as they either were not reported or occurred infrequently.

Glucocorticoids are part of induction therapy. In the PEXIVAS study, all patients received oral prednisone/prednisolone at 1 mg/kg/d for the first week, followed by rapid or slow tapering schedules. This led to an approximately 50% difference in oral glucocorticoid exposure during the first 6 months The lower-dose regimen was noninferior for efficacy and is safer, and therefore, it is preferred.[32,46] All patients in the PEXIVAS trial received an initial dose of i.v. methylprednisolone of 1–3 g; the optimal dose is yet to be determined. A point that should be noted is that the majority of patients in the PEXIVAS study were treated with cyclophosphamide.

Avacopan is an alternative for glucocorticoids for induction of remission in combination with either rituximab or cyclophosphamide. However, financial considerations and lack of long-term data limit the applicability. Patient subgroups that might benefit the most are those at increased risk of glucocorticoid toxicity, including those with high infection risk, preexisting diabetes mellitus, psychiatric disorders, and osteoporosis. Patients with lower kidney function (eGFR $<$20 ml/min per 1.73 m^2) also might benefit, as an increased recovery of kidney function was observed in these patients.[35] Cyclophosphamide dose should be reduced for kidney impairment and age, as these patients are at increased risk for infection.

Low-dose trimethoprim-sulfamethoxazole (TMP-SMX), or alternative, is advised for pneumocystis pneumonia prophylaxis for the duration of the cyclophosphamide course or for 6 months following rituximab induction. Longer-term use may be considered in those receiving repeated rituximab infusions, those with structural lung disease, and those requiring ongoing immunosuppressive or glucocorticoid therapy.

In a retrospective study, the immunoglobulin G (IgG) level before rituximab correlated with hypogammaglobulinemia post-rituximab.[47] Therefore, IgG levels should be measured at baseline and every 6 months for patients treated with rituximab. A low level at baseline (defined as IgG $<$3 g/l) may predict a greater risk of secondary immunodeficiency with rituximab.[47]

Practice Point 9.3.1.1: A practical treatment algorithm for AAV with kidney involvement is given in Figure 6.

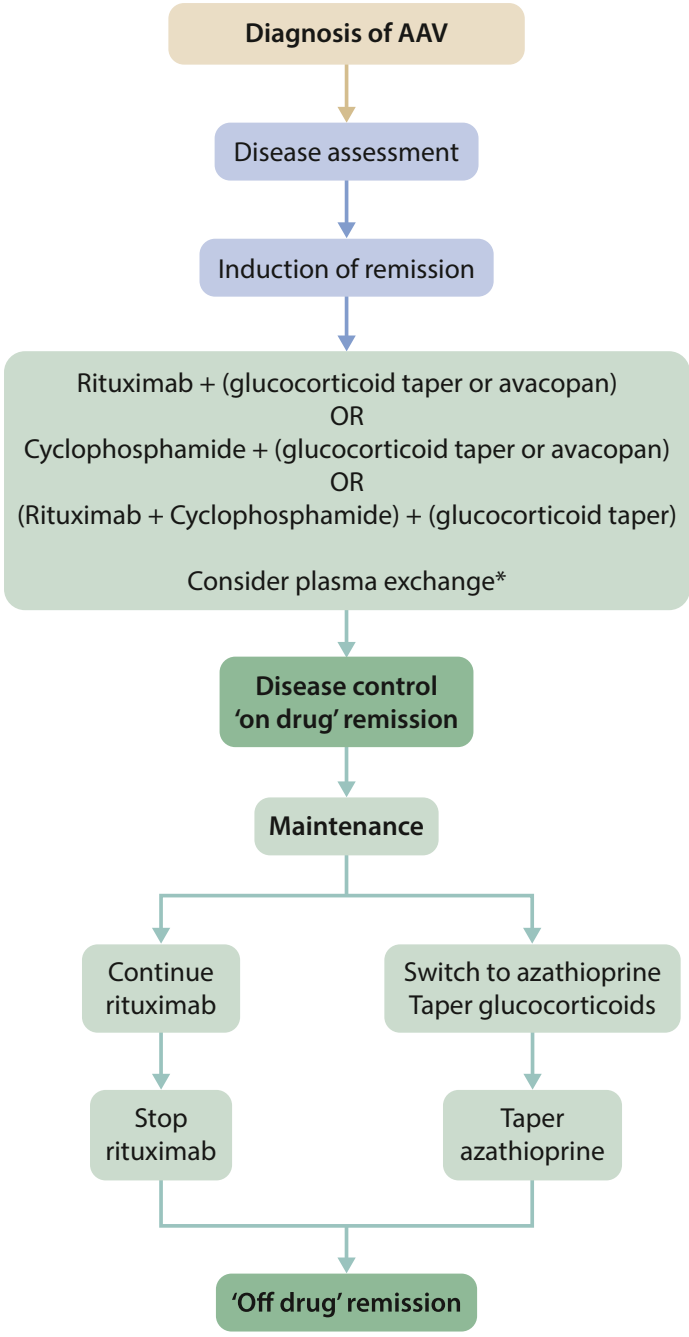

Figure 6| Practical treatment regimen for AAV. *Please see Practice Point 9.3.1.9 for details. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody.

Practice Point 9.3.1.2: In patients presenting with markedly reduced or rapidly declining glomerular filtration rate (GFR) (serum creatinine [SCr] >4 mg/dl [>354 µmol/l]), there are limited data to support rituximab and glucocorticoids. Both cyclophosphamide and glucocorticoids, and the combination of rituximab and cyclophosphamide can be considered in this setting.

No patients with a SCr >4 mg/dl (>354 µmol/l) were included in the RAVE trial, and therefore, in severe kidney disease, limited data for induction therapy with rituximab in combination with glucocorticoids are available, and cyclophosphamide is still the preferred agent for induction of remission. In severe kidney disease, combining 4 weekly infusions of rituximab and 2 i.v. cyclophosphamide pulses with glucocorticoids might be an alternative to i.v. cyclophosphamide for 3–6 months. In the RITUXVAS trial, this regimen resulted in a similar rate of remission and adverse events as cyclophosphamide.[19]

Practice Point 9.3.1.3: Considerations for choosing between rituximab and cyclophosphamide for induction therapy are given in Figure 7.

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])*

Figure 7| Factors for consideration when choosing between rituximab and cyclophosphamide for induction therapy of AAV. *A combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GN, glomerulonephritis; PR3, proteinase 3; SCr, serum creatinine.

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

Figure 8| Considerations for the route of administration of cyclophosphamide for AAV. AAV, ANCA-associated vasculitis. ANCA, antineutrophil cytoplasmic antibody.

Practice Point 9.3.1.4: Considerations for choosing the route of administration of cyclophosphamide are given in Figure 8.

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

Practice Point 9.3.1.6: Recommendations for oral glucocorticoid tapering are given in Figure 9.

Oral glucocorticoids with rapid tapering are preferred over slower tapering, as the 2 approaches probably make little or no difference in induction of sustained remission.

Following cyclophosphamide induction, oral prednisolone should be reduced to a dose of 5 mg/d by 6 months. Following rituximab induction, prednisolone can be withdrawn by 6 months.

The dose of oral prednisolone is 1 mg/kg/d for the first week, and then a programmed reduction is followed (Figure 9). Intravenous methylprednisolone is widely used initially for patients with more severe presentations, at a dose of 1–3 g in total. This approach is not evidence-based and is likely to contribute to glucocorticoid toxicity.

Practice Point 9.3.1.7: Avacopan may be used as an alternative to glucocorticoids. Patients with an increased risk of glucocorticoids toxicity are likely to receive the most benefit from avacopan. Patients with lower GFR may benefit from greater GFR recovery.

	'Reduced-corticosteroid dose' in PEXIVAS trial		
Week	<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		

Figure 9| Prednisolone tapering regimen for AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; PEXIVAS, Plasma Exchange and Glucocorticoids for the Treatment of ANCA-Associated Vasculitis.

Oral cyclophosphamide	Intravenous cyclophosphamide	Rituximab	Rituximab and i.v. cyclophosphamide	MMF	Avacopan
2 mg/kg/d for 3 months, continue for ongoing activity to a maximum of 6 months	15 mg/kg at weeks 0, 2, 4, 7, 10, 13 (16, 19, 21, 24 if required)	375 mg/m²/week × 4 weeks OR 1 g at weeks 0 and 2	Rituximab 375 mg/m²/week × 4 weeks, with i.v. cyclophosphamide 15 mg/kg at weeks 0 and 2 OR Rituximab 1 g at 0 and 2 weeks with i.v. cyclophosphamide 500 mg/2 weeks × 6	2000 mg/d (divided doses), may be increased to 3000 mg/d for poor treatment response	30 mg twice daily as alternative to glucocorticoids, in combination with rituximab or cyclophosphamide induction
Reduction for age: • 60 yr, 1.5 mg/kg/d • 70 yr, 1.0 mg/kg/d Reduce by 0.5 mg/kg/day for GFR <30 ml/min/1.73 m²	Reduction for age: • 60 yr 12.5 mg/kg • 70 yr, 10 mg/kg Reduce by 2.5 mg/kg for GFR <30 ml/min/1.73 m²				

Figure 10 | Immunosuppressive drug dosing for AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GFR, glomerular filtration rate; i.v., intravenous; MMF, mycophenolate mofetil.

Practice Point 9.3.1.8: Recommendations for immunosuppressive dosing are given in Figure 10.

Practice Point 9.3.1.9: 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.

The Methylprednisolone Versus Plasma Exchange for Renal Vasculitis (MEPEX) trial showed improved kidney outcomes in patients with severe kidney disease (SCr >5.7 mg/dl [>500 μmol/l]) who were treated with plasma exchange.[48] Also, a meta-analysis that looked at the addition of plasma exchange showed a reduction in the occurrence of kidney failure at 3 and 12 months after diagnosis (Supplementary Table S13[19,22,32,48–54]). However, the PEXIVAS trial failed to demonstrate that plasma exchange delayed the time to kidney failure or death for patients with AAV presenting with GFR <50 ml/min per 1.73 m^2 or alveolar hemorrhage over a median follow-up of 2.9 years.[32]

A meta-analysis has confirmed a reduction of kidney failure risk at 12 months with plasma exchange, but at a concomitant increase in the risk of serious infections.[55] The relative risk reduction in kidney failure at 12 months was comparable between subgroups with SCr <5.7 mg/dl (500 μmol/l) and those with an SCr level of ≥5.7 mg/dl (500 μmol/l) or dialysis at baseline. The absolute risk reduction of kidney failure by 12 months was 4.6% (95% CI: 1.2%-6.8%) in patients with SCr between 3.4 mg/dl (300 μmol/l) and 5.7 mg/dl (500 μmol/l) and absolute risk reduction of 6% in patients with SCr over 5.7 mg/dl (500 μmol/l).[55] Therefore, plasma exchange should be considered in patients with SCr over 3.4 mg/dl (300 μmol/l), or in those with alveolar hemorrhage and hypoxemia in whom early mortality is high.

Practice Point 9.3.1.10: Add plasma exchange for patients with an overlap syndrome of ANCA-associated vasculitis and anti-glomerular basement membrane (GBM).

In a single-center study, 5% of patients who were ANCA-positive were also positive for anti-GBM antibodies, and 32% of patients who were anti-GBM-positive had detectable ANCA.[56] Thus, double-positivity for both ANCA and anti-GBM antibodies is common. These patients behave more like those with anti-GBM disease than like those with AAV, supporting the initiation of plasma exchange (Figure 11). However, unlike those with pure anti-GBM disease, these patients have a tendency to relapse and should receive maintenance therapy.

ANCA vasculitis with severe kidney disease	Vasculitis with diffuse pulmonary hemorrhage	Vasculitis in association with anti-GBM antibodies
Seven treatments over a maximum of 14 days, 60 ml/kg volume replacement, albumin substitution	Daily until bleeding stops, replace albumin with fresh, frozen plasma	Daily for 14 days or until anti-GBM antibodies are undetectable

Figure 11 | Plasma exchange dosing and frequency for AAV. If a patient is at risk of bleeding, volume replacement should be with fresh, frozen plasma. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

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)*.

This recommendation places a higher value on prevention of relapses and a relatively lower value on adverse events related to immunosuppressive drugs.

Key information

Balance of benefits and harms. To date, most maintenance studies have been done after induction of remission with cyclophosphamide plus glucocorticoids. Maintenance regimens have evolved over time, and several immunosuppressive medications have been evaluated. Azathioprine, given after ≥3 months of cyclophosphamide induction, was found to be equally effective for relapse prevention with less leukopenia as extending cyclophosphamide for 12 months (Supplementary Table S14[22,57]). Compared to azathioprine, MMF maintenance was less effective in relapse prevention and did not have a superior infection profile (Supplementary Table S15[22,58]). In contrast, methotrexate and azathioprine were found to be equally effective in relapse prevention, with similar toxicity and long-term outcomes (Supplementary Table S16[22,59]). Overall, azathioprine has been the standard immunosuppressive used for maintenance of remission in AAV over the past several years.

The duration of azathioprine maintenance has been examined. Compared to tapering maintenance azathioprine after 12 months of treatment, tapering after 4 years of therapy decreased the relapse rate and the incidence of kidney failure.[30,60] The benefits of longer-duration azathioprine maintenance therapy did not differ between PR3- or MPO-ANCA patients, or between patients who remained ANCA-positive versus became ANCA-negative after 12 months. In these studies, no differences occurred in all-cause mortality, infection, or serious adverse events between treatment arms, but the certainty of the evidence was very low (Supplementary Table S17[22,30,60]).

After rituximab was found to be effective for induction of remission in AAV, it was tested as a maintenance medication. In new-onset disease, after cyclophosphamide induction, maintenance with rituximab decreased major, but not minor, relapses compared to azathioprine (MAINtenance of Remission Using RITuximab in Systemic ANCA-associated Vasculitis [MAINRITSAN]; Supplementary Table S18[22,61]). However, after rituximab induction for relapsing AAV, rituximab maintenance decreased major and minor disease relapses compared to azathioprine (Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis [RITAZAREM]).[62] No difference in infection rate was found between azathioprine and rituximab (Supplementary Table S19[22,62,63]).

As a maintenance drug, rituximab can be dosed on a fixed schedule or upon reappearance of CD19+ B cells and/or ANCA. Although the 2 regimens prevented relapse equally well, dosing based on reappearance of B cells required fewer rituximab infusions. No differences in adverse events were reported (MAINRITSAN2; Supplementary Table S18[22,61]). In MAINRITSAN3, after 18 months of maintenance therapy, patients were randomized to continuation of biannual rituximab or placebo. Rituximab maintenance decreased the number of relapses compared to placebo (RR: 0.16; 95% CI: 0.04–0.66), but the evidence for infection and other outcomes was imprecise due to the small size of the study (Supplementary Table S20[61]).

Addition of TMP-SMX (160/800 mg) compared with placebo in maintenance therapy may make little or no difference in terms of remission at 1 or 2 years (Supplementary Table S21[22,64,65]).

Certainty of evidence. The overall certainty of the evidence was rated as low due to the lower certainty of the evidence for rituximab as maintenance therapy, which is based on fewer RCTs compared with that for azathioprine. All comparisons, apart from azathioprine duration, included data from single studies with relatively low numbers of patients and limited follow-up, resulting in wide CIs and serious imprecision, in particular for the critical outcomes of all-cause mortality and kidney failure. The certainty of the evidence for azathioprine as maintenance therapy was moderate for relapse, in RCTs that compared azathioprine with cyclophosphamide (Supplementary Table S14[22,57]), methotrexate (Supplementary Table S16[22,59]), and MMF (Supplementary Table S15[22,58]), and RCTs that compared extended with standard azathioprine therapy (Supplementary Table S17[22,30,60]). The certainty of the evidence was downgraded because of imprecision, as there was only 1 study for each comparison. However, the comparison of MMF with azathioprine exhibited low certainty of evidence for infection because of very wide CIs that indicated less certainty in the effect. The certainty of evidence for continuation of rituximab beyond 18 months was graded as very low due to serious imprecision.

Currently, only limited evidence is available for maintenance therapy after induction therapy with rituximab and glucocorticoids. The certainty of the evidence was low from RCTs that compared rituximab with azathioprine for major relapse, because of a lack of blinding of outcome assessors, and serious imprecision, as 2 RCTs examined this comparison (Supplementary Tables S18[22,61] and S19[22,60,63]). The RCT that compared tailored rituximab therapy based on the reappearance of $CD19^+$ B cells and ANCA-levels exhibited low certainty of evidence for major relapse and adverse events, including all-cause mortality, infection, and malignancy (Supplementary Table S18[22,61]). The certainty of the evidence was downgraded from this RCT because of very serious imprecision, as it was from only 1 study, and outcomes exhibited very wide CIs, indicating less certainty regarding the treatment effect. A single study provided very low-certainty evidence regarding the comparison of

maintenance rituximab versus placebo for most outcomes due to a high level of imprecision related to the small study sample size; however, the study was graded as having low-certainty evidence for relapse, for which the effect was strong and statistically significant (Supplementary Table S20[61]).

Data are also limited regarding the continuation of glucocorticoids during maintenance. In most RCTs, glucocorticoids were withdrawn within or shortly after the induction window. However, in the Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis (REMAIN) trial, low-dose glucocorticoids were combined with azathioprine maintenance.[30] In a meta-analysis of observational studies and RCTs, a longer course of glucocorticoids in AAV was associated with fewer relapses.[66]

Values and preferences. This Work Group places a relatively high value on the prevention of relapses of disease, which are associated with morbidity, and advises that maintenance therapy be given to all patients after induction of remission. However, extended immunosuppressive therapy should be associated with a minimum of adverse events, and relapse risk may influence maintenance initiation, choice of medication, and duration.

Several AAV relapse risk factors have been identified, including a prior history of relapse and having a PR3-ANCA rather than an MPO-ANCA.[15,67] In the RAVE study, patients did not receive maintenance therapy after induction with rituximab, and a high relapse rate was seen in both the rituximab and cyclophosphamide–azathioprine groups, but glucocorticoids were withdrawn before 6 months.[23] Current practice, and therefore expert opinion, varies on whether maintenance therapy can be avoided in patients with MPO-AAV after induction of remission with rituximab. Opinion also varies on the use and duration of glucocorticoids in maintenance regimens. In the REMAIN trial, which studied patients with a history of renal vasculitis, no difference in relapse risk with ANCA serotype was seen. If maintenance therapy is not used, such patients should be considered at higher risk of relapse and should be monitored accordingly.[30]

In the subgroup of patients with MPO-AAV presenting with kidney failure without extrarenal disease manifestations, the risk of relapse is low, so the risk of adverse infectious events from immunosuppression might outweigh the benefits of relapse prevention.[68] Therefore, in patients with MPO-ANCA who are treated with dialysis and have no extrarenal manifestations of disease, despite thorough review including chest computed tomography (CT) scanning, the risks of maintenance therapy could outweigh the benefit. Further, when a complete clinical remission is achieved in the subgroup of patients with MPO-ANCA disease and abnormal kidney function, these patients may not need maintenance immunosuppression, but instead could be closely monitored with regular ANCA serologies.

In summary, the best evidence for effective relapse prevention is available for rituximab maintenance or prolonged azathioprine in combination with low-dose glucocorticoids. However, rituximab may have an advantage over azathioprine. In the MAINRITSAN study, health-related quality of life was compared between patients treated with rituximab and azathioprine. Mean improvements of Health Assessment Questionnaire (HAQ) scores from baseline to 24 months were significantly better for the rituximab group as compared to the azathioprine group.[69]

Therefore, this Work Group prefers rituximab for maintenance therapy, particularly for patients with known relapsing disease, PR3-AAV, and azathioprine allergy, and after rituximab induction (RITAZAREM). However, some caution should be exercised, as only a paucity of data is available on the long-term effects of rituximab maintenance treatment. Although significant falls in IgG were not seen after rituximab treatment in the RCTs, longer-term observational data suggest an increased risk of secondary immunodeficiency in this population.

Resource use and costs. Rituximab is relatively expensive and is not available worldwide; however, biosimilars will potentially generate global access to this drug. Additionally, prevention of relapses reduces the costs of both hospitalization and induction therapy with its frequent hospital visits. Use of rituximab also permits the withdrawal of glucocorticoids.

Considerations for implementation. Even in patients on kidney replacement therapy, extrarenal AAV can and does relapse, and a remission should be consolidated with maintenance therapy. In patients with kidney failure, anti-MPO positivity, and no extrarenal symptoms, long-term maintenance may not be necessary. The need for (and length of) maintenance treatment should in this situation be assessed at an individual level.

Rationale

This Work Group advises maintenance therapy be given to all patients with AAV after induction of remission with either cyclophosphamide or rituximab. The aim of this maintenance therapy is to prevent relapse of disease after induction of remission. Remission is defined as the absence of manifestations of vasculitis. To score the absence of clinical features of active disease, a validated scoring system such as the BVAS can be used.[70] During follow-up, a structured clinical assessment in combination with inflammatory markers and kidney function should be conducted in all patients.

Rituximab maintenance after cyclophosphamide induction has been shown to be superior to azathioprine for preventing relapses in 1 RCT. It probably decreases major relapses; no difference in adverse events was reported (MAINRITSAN).[61] Extending rituximab maintenance beyond 18 months after induction of remission was associated with a lower relapse rate as compared to placebo.[71] Azathioprine maintenance up to 18 months after induction of remission with cyclophosphamide has been shown to be equally effective as

continuing cyclophosphamide (Cyclophosphamide versus Azathioprine for Early Remission Phase of Vasculitis [CYCAZAREM]) for 1 year and then switching to azathioprine.[57] MMF has not been shown to be more effective than azathioprine.[58]

The evidence for the minimum duration of maintenance is weak; longer maintenance reduces the relapse rate but could be associated with more adverse events. Azathioprine prolongation (REMAIN trial; Extended versus standard azathioprine maintenance therapy in newly diagnosed proteinase 3 anti-neutrophil cytoplasmic antibody-associated vasculitis patients who remain cytoplasmic anti-neutrophil cytoplasmic antibody-positive after induction of remission: a randomized clinical trial [AZA-ANCA]) limits relapse rate after 4 versus 2 years.[30,60]

As the aim of maintenance therapy is the prevention of relapse, the risk of relapse should be considered in choosing both the immunosuppressive agent and the duration of maintenance therapy.

Reported risk factors for relapse are PR3-ANCA versus MPO-ANCA, and cardiovascular or lung involvement.[15,67] Persistent ANCA-positivity after induction of remission has also been reported.[30,72] The RCT that tested extended azathioprine for 4 years versus azathioprine for 2 years in patients with PR3-AAV who remained ANCA-positive showed a nonsignificant difference (at 4 years, relapse rates 48% standard vs. 24% extended) but was underpowered.[60]

Comparison with other guidelines. Considering other guidelines, the European Alliance of Associations for Rheumatology (EULAR) also prefers rituximab over azathioprine and glucocorticoids for remission maintenance.[31] The EULAR guideline advises maintenance therapy for at least 24–48 months following induction. This panel advises an interval of 18 months to 4 years following induction of remission, tailored according to an individual's risk of relapse and the drug used for maintenance. Additionally, in MPO-AAV after induction of remission with rituximab, maintenance therapy may sometimes be avoided if the patient can be monitored intensively. However, this point is based on expert opinion; little evidence is available and no consensus was reached, even among experts.

Practice Point 9.3.2.1: Following rituximab induction, maintenance immunosuppressive therapy should be given to most patients.

The preference of this Work Group, based upon observational reports and unpublished data from the RITAZAREM study, is for rituximab maintenance. The RITAZAREM study also showed that after rituximab induction for relapsing AAV, rituximab maintenance decreased major and minor disease relapses compared to azathioprine maintenance (RITAZAREM).[62] However, azathioprine combined with glucocorticoids can be considered as an alternative.

In the RAVE study, no maintenance was given following induction of remission in AAV. The relapse rate was lower in MPO-AAV compared to PR3-AAV. This finding led some experts to opine that patients with MPO-AAV in complete clinical remission after induction therapy with rituximab with a low relapse risk may not need maintenance therapy, but instead could be closely monitored with regular ANCA serologies and home urine checks. Consensus regarding no maintenance therapy was, however, not reached within the KDIGO Work Group.

Practice Point 9.3.2.2: The optimal duration of remission therapy is between 18 months and 4 years after induction of remission.

Practice Point 9.3.2.3: 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 12).

Practice Point 9.3.2.4: Consider mycophenolate mofetil (MMF) or methotrexate as alternatives to azathioprine for maintenance therapy in patients intolerant of azathioprine. Methotrexate should not be used for patients with a GFR <60 ml/min per 1.73 m^2.

Baseline factors	Factors after diagnosis	Treatment factors
• Diagnosis of granulomatosis with polyangiitis • PR3–ANCA subgroup • Higher 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

Figure 12| Factors that increase relapse risk for AAV. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; PR3, proteinase 3.

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

Figure 13| Considerations for using rituximab or azathioprine for AAV maintenance therapy. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; IgG, immunoglobulin G; PR3, proteinase 3.

Practice Point 9.3.2.5: Considerations for choosing rituximab or azathioprine for maintenance therapy are presented in Figure 13.

Practice Point 9.3.2.6: Recommendations for dosing and duration of maintenance therapy are given in Figure 14.

9.3.3 Relapsing disease

Practice Point 9.3.3.1: Patients with relapsing disease should be reinduced (Recommendation 9.3.1.1.), preferably with rituximab.

Relapses respond to immunosuppression with a remission rate similar to that of the initial presentation, and severe relapses should be treated by reintroducing induction therapy. When deciding whether to use cyclophosphamide again, the cumulative dose of cyclophosphamide already given should be taken into account. Cumulative dosages above 36 g have been associated with the occurrence of malignancies.[73] In a *post hoc* analysis of the RAVE trial, higher remission rates were seen in relapsing patients treated with rituximab compared to cyclophosphamide, especially for patients with PR3-AAV.[23] Rituximab is therefore preferred for relapsing AAV. The RITAZAREM trial studied the effect of rituximab induction in 187 patients with relapsing GPA/MPA—there was a high rate of remission, >90% by 4 months.[74]

In patients with nonsevere relapses, immunosuppression should be increased while avoiding cyclophosphamide. Apart from MMF, which has been tested in combination with glucocorticoids in RCTs for induction therapy in relapsing patients, no strong evidence supports other regimens.[27,28] However, if nonsevere relapses are treated with MMF, the

Rituximab	Azathioprine	MMF
Scheduled dosing protocol: **1.** 500 mg × 2 at complete remission, and 500 mg at mo 6, 12, and 18 thereafter (MAINRITSAN scheme) OR **2.** 1000 mg infusion after induction of remission, and at mo 4, 8, 12, and 16 after the first infusion (RITAZAREM* scheme)	1.5–2 mg/kg/d at complete remission until 1 yr after diagnosis then decrease by 25 mg every 3 mo	2000 mg/d (divided doses) at complete remission for 2 yr
	Extend azathioprine at complete remission until 4 yr after diagnosis; start at 1.5–2 mg/kg/d for 18–24 mo, then decrease to a dose of 1 mg/kg/d until 4 yr after diagnosis, then taper by 25 mg every 3 mo. Glucocorticoids should also be continued at 5–7.5 mg/d for 2 yr and then slowly reduced by 1 mg every 2 mo	

Figure 14| Immunosuppressive dosing and duration of AAV maintenance therapy. MAINRITSAN, MAINtenance of Remission Using RITuximab in Systemic ANCA-associated Vasculitis; MMF, mycophenolate mofetil; RITAZAREM, Rituximab versus azathioprine as therapy for maintenance of remission for antineutrophil cytoplasm antibody-associated vasculitis (AAV). *RITAZAREM was in relapsing AAV.

rate of future relapse is increased, and glucocorticoid exposure will be increased accordingly; therefore, in the current guideline, rituximab is preferred.

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.

The causes of refractory disease include drug intolerance, nonadherence, concomitant morbidities complicating treatment, a secondary drive for vasculitis, such as malignancy, drugs, or infection, and true treatment failure. Progression of kidney failure can reflect chronic damage and does not necessarily imply active disease; a kidney biopsy can be considered to assess ongoing kidney disease activity. Several small series suggest a role for rituximab in resistant ANCA-associated vasculitis.

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

In the absence of hypoxemia, diffuse alveolar hemorrhage has a benign prognosis and responds as extrapulmonary disease is controlled. Alveolar hemorrhage with hypoxemia has a high early mortality risk, and plasma exchange should be considered in addition to glucocorticoids with either cyclophosphamide or rituximab. Patients in the intensive care unit, such as those receiving assisted ventilation, have a particularly high risk of infection and death. Leukopenia should be avoided, with glucocorticoid use minimized. Plasma exchange and high-dose i.v. immunoglobulins can be considered in this setting.

9.4.2 Transplantation

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

AAV can recur after kidney transplantation. The frequency of disease recurrence in AAV has been assessed in several retrospective studies and is about 0.02–0.03 per patient-year.[75,76] This relapse rate was not influenced by remission duration or ANCA status before transplantation.[75]

Research recommendations

- RCTs are needed to incorporate patient-reported outcomes, to assess long-term outcomes, to define the use of rituximab in severe AAV, and to assess therapies in ethnically diverse populations
- Biomarker studies to identify early markers of disease relapse, markers to guide the choice of therapy, including plasma exchange, markers to predict optimal dosing and dosing interval for rituximab, and surrogate markers of remission

Methods for guideline development

Aim

This is an update of the ANCA-Associated Vasculitis chapter of the *KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases* published in 2021.[77] Based on the recently published data in the field, it was decided that a guideline update was required.

The objective of this project was to update the evidence-based Clinical Practice Guideline for the Management of ANCA-Associated Vasculitis. The guideline development methods are described below.

Overview of the process

This guideline adhered to international best practices for guideline development (Appendix B: Supplementary Tables S2 and S3).[78] This guideline has been developed and reported in accordance with the AGREE II reporting checklist.[79]

The processes undertaken for the development of the KDIGO 2024 Clinical Practice Guideline for the Management of ANCA-Associated Vasculitis included:

- Appointing Work Group members and the ERT
- Defining scope of the guideline update
- Implementing literature search strategies to update the evidence base for the guideline
- Selecting studies according to predefined inclusion criteria
- Conducting data extraction and critical appraisal of the updated literature
- Updating the evidence synthesis and meta-analysis to include newly identified studies
- Updating the certainty of the evidence for each outcome
- Finalizing guideline recommendations and supporting rationale
- Grading the strength of the recommendations, based on the certainty of the evidence and other considerations
- Convening a public review of the guideline draft in May 2023
- Amending the guideline based on the external review feedback and updating the literature search
- Finalizing and publishing the guideline

Commissioning of Work Group and ERT. The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group, to include content experts in adult nephrology, epidemiology, and public health. The Work Group was responsible for writing the recommendations and practice points and underlying rationale, as well as grading the strength of each recommendation.

For the 2024 update, the Brown University School of Public Health Center for Evidence Synthesis in Health was contracted to update the systematic evidence review and provide expertise in guideline development methodology. The Brown ERT consisted of a senior physician–methodologist who led the ERT for the KDIGO 2012 Clinical Practice Guideline for Glomerulonephritis, an adult nephrologist, and a librarian–methodologist, all with expertise in evidence synthesis and guideline development, including for KDIGO guidelines. Cochrane Kidney and Transplant was contracted to conduct systematic evidence review and provide expertise in guideline development methodology for the 2021 guideline.

Defining scope and topics and formulating key clinical questions. Due to resourcing and the probability of practice-changing studies, clinical questions on effectiveness and safety of interventions included in the guideline update were limited to RCTs. Guideline topics and clinical questions focusing on nonrandomized studies were not included in the guideline update (Supplementary Table S1). The guideline Work Group, with assistance from the ERT, determined the overall scope of the guideline. A preliminary list of topics and key clinical questions was informed by the previous KDIGO guideline.[77] The majority of clinical questions for this guideline were based upon RCTs to avoid bias by design. Clinical questions adhered to the population, intervention, comparator, outcomes, and study design (PICOD) format (a list of critical and important outcomes was compiled after voting from the Work Group [Table 1]). Clinical questions were mapped to existing Cochrane Kidney and Transplant systematic reviews. These systematic reviews were updated accordingly. For clinical questions that did not map to any Cochrane Kidney and Transplant systematic reviews, *de novo* systematic reviews were undertaken. The previous guideline was reviewed to ensure all identified studies were included in the evidence review.[77] Details of the PICOD questions and associated Cochrane Kidney and Transplant systematic reviews are provided in Table 2.[80]

All evidence reviews were conducted in accordance with the Cochrane Handbook,[81] and guideline development adhered to the standards of GRADE (Grading of Recommendations, Assessment, Development, and Evaluation).[82]

Table 1 | Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	• All-cause mortality • Kidney failure • ≥50% loss of GFR • Infection • Glucocorticoid-related adverse events • Malignancy
Important outcomes	• Remission/relapse • Annual GFR loss (minimum 3 years follow-up)

GFR, glomerular filtration rate.
The critical and important outcomes were voted on by the Work Group using an adapted Delphi process (1–9 Likert scale). Critical outcomes were rated 7–9, and important outcomes were rated 4–6 on the 9-point scale.

Table 2 | Clinical questions and systematic review topics in PICOD format

PICOD criteria	Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
Clinical question	**In adults with AAV, what immunosuppressive agents compared to no treatment, placebo, or other immunosuppressive therapies improve clinical efficacy outcomes and reduce adverse effects?**
Population	Adults with AAV
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, or other immunosuppressive therapy
Outcomes	Outcomes listed in Table 1
Study design	RCTs
Cochrane systematic reviews	Walters *et al.* Interventions for renal vasculitis in adults (Review). Cochrane Database of Systematic Reviews. 2020:1;CD003232.[22]
SoF tables	Supplementary Tables S4–S32

PICOD, population, intervention, comparator, outcomes, study design; RCT, randomized controlled trial; SoF, summary of findings.

Literature searches and article selection. For the KDIGO 2024 Clinical Practice Guideline for the Management of ANCA-Associated Vasculitis, updated literature searches were conducted in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials. The searches were restricted to records entered into the databases since January 1, 2020. This was done to provide a 6-month overlap with the prior searches. The searches were conducted on July 7, 2022 and were further updated on April 25, 2023. These search updates included terms for both ANCA and lupus nephritis (LN; which underwent updating concurrently with the chapter on ANCA).

The titles and abstracts resulting from the searches were screened by 2 members of the ERT who independently assessed retrieved abstracts, and if necessary, the full text, to determine which studies satisfied the inclusion criteria. Disagreement about inclusion was resolved by discussion with a third member of the ERT.

For the KDIGO 2021 guideline, a total of 25,925 citations were screened. Of these, 479 RCTs and 102 observational studies were included in the evidence review for all diseases (Figure 15). For the 2024 update, a total of 1556 citations were screened (for both ANCA and LN). From these, we found 9 new eligible articles on ANCA that addressed 6 new RCTs.

Data extraction. For the KDIGO 2024 Clinical Practice Guideline for the Management of ANCA-Associated Vasculitis, data extraction was performed by 1 member of the Brown ERT and confirmed by the 2 other members of the ERT. The Brown ERT extracted data into the forms designed by the Cochrane ERT. The Cochrane ERT designed data extraction forms to capture data on study design, study participant characteristics, intervention and comparator characteristics, and critical and important outcomes. Any differences in extraction between members of the ERT were resolved through discussion. A third reviewer was included if consensus could not be achieved.

Critical appraisal of studies. The majority of reviews undertaken were interventional reviews that included RCTs. For these reviews, the Cochrane Risk of Bias tool was used to assess individual study limitations based on the following items[83]:

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

All critical appraisal was conducted independently by 2 members of the ERT, with disagreements regarding the risk of bias adjudications resolved by consultation with a third review author.

Evidence synthesis and meta-analysis. *Measures of treatment effect.* Dichotomous outcome (all-cause mortality, kidney failure, ≥50% loss of GFR, infection, malignancy, remission/relapse) results were expressed as RR with 95% CI. When continuous scales of measurement were used to assess the effects of treatment, such as annual GFR loss, the mean difference (MD) with 95% CI was used.

Data synthesis. Data were pooled using the Mantel-Haenszel random-effects model for dichotomous outcomes and the inverse variance random-effects model for continuous outcomes. The random-effects model was chosen because it provides a conservative estimate of effect in the presence of known and unknown heterogeneity.[81]

Assessment of heterogeneity. Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes, and of risk ratios, and by χ^2 tests. A P value of <0.1 was used to denote statistical heterogeneity, and an I^2 was calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.[81] We used conventions of interpretation as defined by Higgins *et al.*[84]

Assessment of publication bias. We made every attempt to minimize publication bias by including unpublished studies (for example, by searching online trial registries). To assess publication bias, we used funnel plots of the log odds ratio (effect vs. standard error of the effect size) when a sufficient number of studies were available (i.e., >10 studies).[81] Other reasons for the asymmetry of funnel plots were considered.

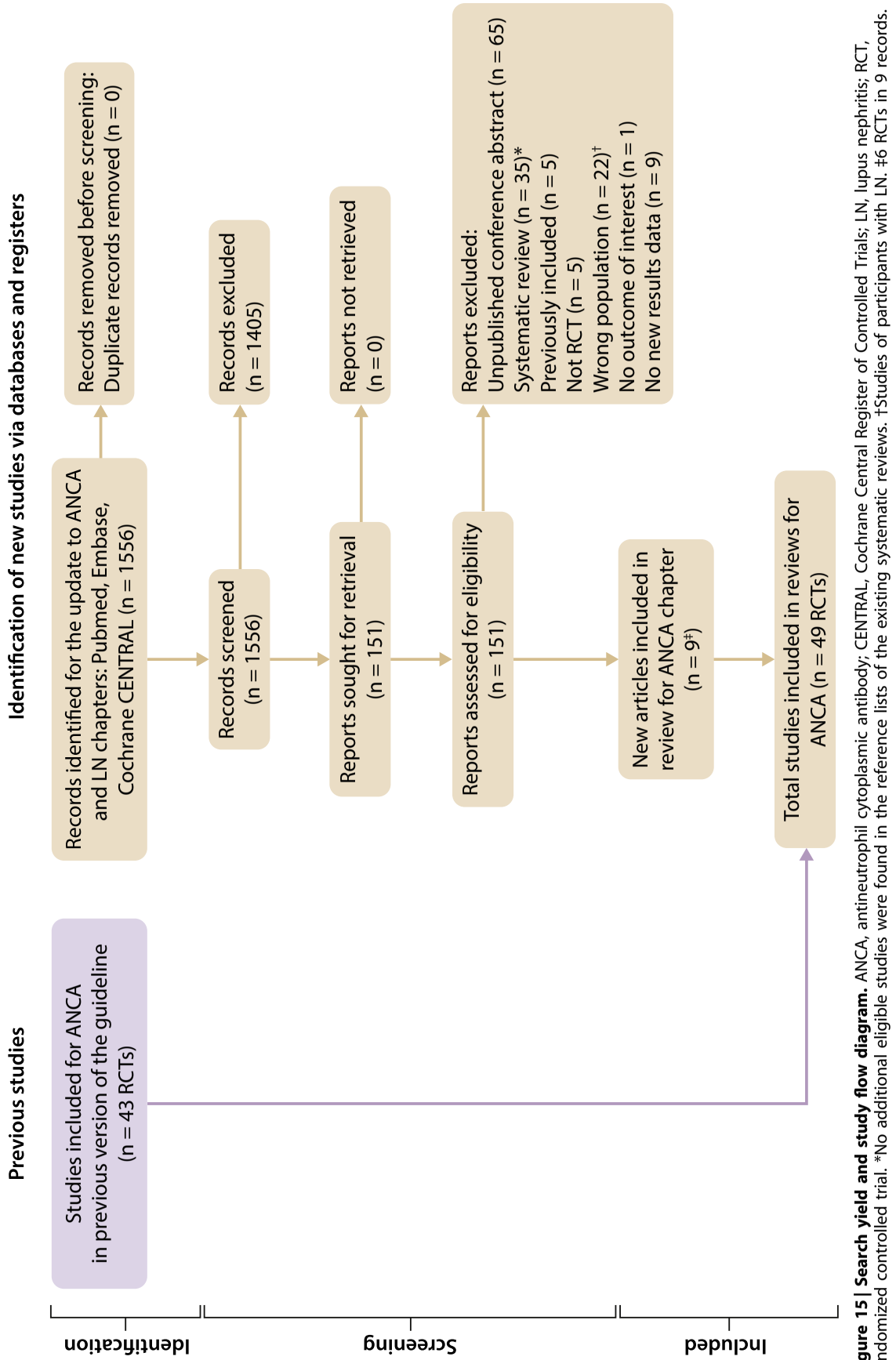

Figure 15| Search yield and study flow diagram. ANCA, antineutrophil cytoplasmic antibody; CENTRAL, Cochrane Central Register of Controlled Trials; LN, lupus nephritis; RCT, randomized controlled trial. *No additional eligible studies were found in the reference lists of the existing systematic reviews. †Studies of participants with LN. ‡6 RCTs in 9 records.

Table 3 | Grading the certainty of the evidence

Grade	Certainty of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of the effect is very uncertain, and often it will be far from the true effect.

Subgroup analysis and investigation of heterogeneity. Subgroup analysis was undertaken to explore whether there were clinical differences among the studies that may have systematically influenced the differences that were observed in the critical and important outcomes. However, subgroup analyses are hypothesis-forming rather than hypothesis-testing and should be interpreted with caution. The following subgroups were considered: baseline kidney function (GFR, proteinuria, presence of albuminuria, presence of macroscopic hematuria), histopathologic class of disease, primary versus secondary forms of disease, sex, and adult versus pediatric. The test of subgroup differences used the I^2 statistic and a P value of 0.10 (noting that this is a weak test).[81]

Sensitivity analysis. The following sensitivity analyses were considered:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis, taking account of the risk of bias, as specified
- Repeating the analysis excluding any very long or large studies, to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry vs. other), and country in which the study was conducted.

For the 2024 guideline update, sensitivity analyses were considered only to assess the impact of potential outlier studies. However, the available data were insufficient to determine the influence of these factors on the effect size of critical and important outcomes.

Grading the certainty of the evidence and the strength of a guideline recommendation. *GRADING the certainty of the evidence for each outcome across studies.* The overall certainty of the evidence related to each critical and important outcome was assessed using the GRADE approach,[82,85] which assesses the certainty of the evidence for each outcome. For outcomes that are based on data from RCTs, the initial grade for the certainty of the evidence is considered to be high. For observational studies, the initial certainty of the evidence is low. The certainty of the evidence is lowered in the event of study limitations; important inconsistencies in results across studies; indirectness of the results, including uncertainty about the population, intervention, and outcomes measured in trials and their applicability to the clinical question of interest; imprecision in the evidence review results; and concerns about publication bias. For imprecision, data were benchmarked against optimal information size, low event rates in either arm, CIs that indicate appreciable benefit and harm (25% decrease and 25% increase in the outcome of interest), and sparse data (only 1 study), all indicating concerns about the precision of the results.[85] The final grade for the certainty of the evidence for an outcome could be high, moderate, low, or very low (Table 3). For observational studies and other study types, it is possible for the certainty of the evidence to be upgraded from a rating of low certainty, according to the specified criteria. For further details on the GRADE approach for rating certainty of the evidence, see Table 4.

Table 4 | GRADE system for grading certainty of evidence

Study design	Starting grade for the certainty of evidence	Step 2—lower grade	Step 3—raise grade for observational evidence
RCTs	High	Study limitations: −1, serious −2, very serious	Strength of association +1, large effect size (e.g., <0.5 or >2) +2, very large effect size (e.g., <0.2 or >5)
	Moderate	Inconsistency: −1, serious −2, very serious	Evidence of a dose–response gradient
Observational studies	Low	Indirectness: −1, serious −2, very serious	All plausible confounding would reduce the demonstrated effect
	Very low	Imprecision: −1, serious −2, very serious	
		Publication bias: −1, serious −2, very serious	

RCT, randomized controlled trial; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

Table 5 | KDIGO nomenclature and description for grading recommendations

Grade	Implications		
	Patients	Clinicians	Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Summary of findings (SoF) tables. The SoF tables were developed to include a description of the population, intervention, and comparator. In addition, the SoF tables included results from the data synthesis as relative and absolute effect estimates. The grading of the certainty of evidence for each critical and important outcome is also provided in the SoF tables. For the 2024 update, the SoF tables were updated or created manually. The SoF tables are available in the Data Supplement: Appendix C and Appendix D (https://kdigo.org/guidelines/gd/).

Developing the recommendations. For the KDIGO 2024 Clinical Practice Guideline for the Management of ANCA-Associated Vasculitis, the existing recommendations were reviewed and revised, as necessary, and new recommendations were drafted by the Work Group and Co-Chairs. Recommendations were revised in a multistep process by email and by teleconferences. The Brown ERT participated in these discussions to ensure consistency with the evidence base and to provide additional feedback.

The final draft was sent for external public review, and reviewers provided open-ended responses. Based on the external stakeholder feedback, the draft was further revised by the Work Group. All Work Group members provided feedback on initial and final drafts of the guideline statements and text and approved the final version of the guideline. The ERT also provided a descriptive summary of the evidence certainty in support of the recommendations.

Grading the strength of the recommendations. The strength of a recommendation is graded as Level 1, "we recommend" or Level 2, "we suggest" (Table 5). The strength of a recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall certainty of the evidence, patient values and preferences, resource use and costs, and considerations for implementation (Table 6).

Balance of benefits and harms. The Work Group and ERT determined the anticipated net health benefit on the basis of expected benefits and harms across all critical and important outcomes from the underlying evidence review.

The overall certainty of the evidence. The overall certainty of the evidence was based on the certainty of the evidence for all critical and important outcomes, taking into account the relative importance of each outcome to the population of interest. The overall certainty of the evidence was graded (A, B, C, or D—Table 3).

Patient values and preferences. No patients or caregivers were involved in the Work Group. The Work Group, from their experience in managing patients with AAV and their understanding of the best available scientific literature, made judgments on the values and preferences of patients. Formal qualitative evidence synthesis on patient priorities and preferences was undertaken, but there was limited evidence available to inform the formulation of guideline recommendations (Appendix D).

Table 6 | Determinants of the strength of recommendation

Factors	Comment
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is provided. The narrower the gradient, the more likely a weak recommendation is warranted.
Certainty of evidence	The higher the certainty of evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low certainty of the evidence will warrant a strong recommendation.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature, when possible, or were assessed by the judgment of the Work Group when robust evidence was not identified.
Resource use and costs	The higher the costs of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Resources and other costs. Healthcare and non-healthcare resources, including all inputs in the treatment management pathway,[86] were considered in grading the strength of a recommendation. The following resources were considered: direct healthcare costs; non-healthcare resources, such as transportation and social services; informal caregiver resources (e.g., time of family and caregivers); and changes in productivity. Economic evaluations, including cost-effectiveness analysis, were not conducted for any of the guideline topics.

Practice points

In addition to graded recommendations, KDIGO guidelines now include "practice points" to help clinicians better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care, and they supplement recommendations for which a larger quantity of evidence was identified. They are issued when a clinical question was not supported by a systematic review, often to help readers implement the guidance from graded recommendation. Practice points represent the expert judgment of the guideline Work Group, but they also may be based on limited evidence. For example, practice points were provided on monitoring, frequency of testing, dosing adjustments for the stage of chronic kidney disease, and use of therapies in specific subgroup populations. Practice points were sometimes formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

Format for guideline recommendations

Each guideline recommendation provides an assessment of the strength of the recommendation (Level 1 or Level 2) and the certainty of the evidence (A, B, C, D). The recommendation statements are followed by Key information (Balance of benefits and harms, Certainty of the evidence, Values and preferences, Resource use and costs, Considerations for implementation), and Rationale. Each recommendation is linked to relevant SoF tables. An underlying rationale may support a practice point.

Limitations of the guideline development process

The evidence review prioritized RCTs as the primary source of evidence. In the development of these guidelines, no scoping exercise with patients, limited searches of the qualitative literature, or formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, although resource implications were considered in the formulation of recommendations, formal economic evaluations were not undertaken for all topics.

Biographic and disclosure information

Jürgen Floege, MD (Work Group Co-Chair), is senior professor in the Division of Nephrology and Immunology at the University of Aachen, Aachen, Germany.

Professor Floege is a former executive council member of the International Society of Nephrology (ISN), European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), and Kidney Disease: Improving Global Outcomes (KDIGO). He is a Distinguished Fellow of the ERA-EDTA and recipient of the 2018 ERA-EDTA Award for Outstanding Clinical Contributions to Nephrology, past President of the German Society of Nephrology, as well as an honorary member of the Japanese, Polish, Portuguese, Serbian, and Slovakian Societies of Nephrology. Together with Professors Richard Johnson, Marcello Tonelli, and John Feehally, he edits the best-selling textbook *Comprehensive Clinical Nephrology*. He is associate editor of *Kidney International*, editor-in-chief of *Clinical Kidney Journal*, and a member of the editorial board of *Journal of the American Society of Nephrology (JASN)*, *Journal of Nephrology*, and other journals. Until 2017, he served as associate editor of *Nephrology Dialysis Transplantation (NDT)*.

His research interests encompass progression of kidney disease, particularly kidney fibrosis, immune-mediated kidney disease, particularly IgA nephropathy, as well as chronic kidney disease-mineral and bone disorders (CKD-MBD) and cardiovascular disease in uremic patients.

His scientific work encompasses about 700 original papers, reviews, and editorials, and 40 book chapters.

JF reports receiving consultancy fees and/or speaker honoraria from AstraZeneca, Bayer, Calliditas, Chinook, GlaxoSmithKline, Novartis, Omeros, Otsuka, Stadapharm, and Travere; and serving on data safety monitoring boards for Novo Nordisk and Visterra.

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BHR reports receiving consultancy fees from Alexion, AstraZeneca, Aurinia, Bristol Myers Squibb, Exagen, Genentech, GlaxoSmithKline, Kezar Life Sciences, Kyverna, Novartis, and Otsuka; and grant/research support from Biogen.*
**Monies paid to institution.*

David R.W. Jayne, MD, FMedSci, is a professor of clinical autoimmunity at the University of Cambridge, Cambridge, UK, and director of the Vasculitis and Lupus Service at Addenbrooke's Hospital, Cambridge, UK. He trained at the Universities of Cambridge and London, Cambridge and London, UK, and in nephrology at Harvard Medical School, Boston, Massachusetts, USA. Dr. Jayne was a research fellow at Imperial College, London, UK, and the University of Cambridge and was appointed as a senior lecturer in Nephrology at St George's Hospital, London, UK. He is a co-founder and the current president of the European Vasculitis Society, and his research focus has been ANCA vasculitis, having led a sequence of international randomized controlled trials over the past 25 years. His research group conducted the first studies on disease trials of newer immunosuppressives and biologics in vasculitis and lupus. He has published over 400 peer-reviewed papers and has contributed to numerous guideline statements. The clinical service in Cambridge cares for over 2000 patients with complex multisystem autoimmunity and receives tertiary referrals from throughout the UK and beyond.

DRWJ reports receiving consultancy fees from AstraZeneca, GlaxoSmithKline, Novartis, Takeda, and Vifor; grant/research support from GlaxoSmithKline, Roche*, and Vifor*; funding for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Otsuka and Vifor; serving on a Data Safety Monitoring Board or Advisory Board for Chinook and GlaxoSmithKline; receiving funding for a leadership or fiduciary role at Aurinia; and receiving stock or stock options from Aurinia.*
**Monies paid to institution.*

Jan-Stephan F. Sanders, MD, PhD, is Associate Professor of Nephrology and Head of the Division of Nephrology at the University Medical Center Groningen (UMCG), Groningen, The Netherlands. Dr. Sanders received his MD degree in 2002 at the University of Groningen. He did a research fellowship at

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J-SFS declared no competing interests.

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VT reports receiving funding for a leadership or fiduciary role at Calliditas, Novartis, Omeros, Otsuka, and Travere.

KDIGO Chairs

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Dr. Jadoul has coauthored over 350 scientific papers, most of them published in major nephrology journals. He is currently serving as an associate editor of *Nephrology Dialysis Transplantation*, and he is also a country co-investigator for the Dialysis Outcomes and Practice Patterns Study (DOPPS) (2001–present). In 2008, he received the International Distinguished Medal from the U.S. National Kidney Foundation (NKF). He was previously a member of the European Renal Association Council (2013–2016). Presently, Dr. Jadoul is a Kidney Disease: Improving Global Outcomes (KDIGO) Co-Chair.

MJ reports receiving consultancy fees from Astellas, AstraZeneca*, Bayer*, Boehringer Ingelheim*, Cardiorenal*, CSL Vifor*, Fresenius Medical Care Asia Pacific*, GlaxoSmithKline*, Mundipharma*, and Vertex*; grants/research support from Amgen and AstraZeneca*; speaker honoraria from AstraZeneca*, Bayer*, and Boehringer Ingelheim*; fees for providing expert testimony from Astellas* and Stada-Eurogenerics*; travel support from AstraZeneca*.*

**Monies paid to institution.*

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MG declared no competing interests.

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MAT reports receiving payment for providing expert testimony from Gilead Sciences (not related to the guideline topic).

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EMB declared no competing interests.

Craig E. Gordon, MD, MS, is Associate Professor of Medicine at Tufts University Medical Center in Boston, Massachusetts, USA. Dr. Gordon graduated from New York University School of Medicine and received a master's degree in clinical care research from the Tufts University School of Graduate Biomedical Sciences. Dr. Gordon previously served as the assistant project director of the ERT for the 2020 KDIGO Clinical Practice Guideline for the Evaluation and Management of Candidates for Kidney Transplantation and associate director of the ERT, and assistant project director for the 2018 and the 2022 KDIGO Clinical Practice Guideline for HCV in CKD.

Dr. Gordon provided methodologic expertise to the Work Group during the guideline development process and assisted in the collection, evaluation, grading, and synthesis of evidence for the guideline, as well as providing guidance to Work Group members in the areas of topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research and clinical interests are in the management of HCV in patients with CKD, polycystic kidney disease, and thrombotic microangiopathies, as well as evidence-based medicine and systematic review related to other areas of nephrology.

CEG reports receiving consultancy fees from Alexion; serving in the speaker bureau for Alexion; and receiving funding for travel and/or accommodation from Alexion.

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GPA declared no competing interests.

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References

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65:1–11.
2. Mohammad AJ, Mortensen KH, Babar J, et al. Pulmonary involvement in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: the influence of ANCA subtype. *J Rheumatol*. 2017;44:1458–1467.
3. Damoiseaux J, Csernok E, Rasmussen N, et al. Detection of antineutrophil cytoplasmic antibodies (ANCAs): a multicentre European Vasculitis Study Group (EUVAS) evaluation of the value of indirect immunofluorescence (IIF) versus antigen-specific immunoassays. *Ann Rheum Dis*. 2017;76:647–653.
4. Bossuyt X, Cohen Tervaert JW, Arimura Y, et al. Position paper: revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. *Nat Rev Rheumatol*. 2017;13:683–692.
5. Aasarod K, Bostad L, Hammerstrom J, et al. Renal histopathology and clinical course in 94 patients with Wegener's granulomatosis. *Nephrol Dial Transplant*. 2001;16:953–960.
6. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol*. 2010;21:1628–1636.
7. Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med*. 1997;337:1512–1523.
8. Flossmann O, Berden A, de Groot K, et al. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis*. 2011;70:488–494.
9. Heijl C, Mohammad AJ, Westman K, et al. Long-term patient survival in a Swedish population-based cohort of patients with ANCA-associated vasculitis. *RMD Open*. 2017;3:e000435.
10. Mukhtyar C, Flossmann O, Hellmich B, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism Systemic Vasculitis Task Force. *Ann Rheum Dis*. 2008;67:1004–1010.
11. Weiner M, Goh SM, Mohammad AJ, et al. Outcome and treatment of elderly patients with ANCA-associated vasculitis. *Clin J Am Soc Nephrol*. 2015;10:1128–1135.
12. Brix SR, Noriega M, Tennstedt P, et al. Development and validation of a renal risk score in ANCA-associated glomerulonephritis. *Kidney Int*. 2018;94:1177–1188.
13. Berden AE, Wester Trejo MAC, Bajema IM. Investigations in systemic vasculitis—the role of renal pathology. *Best Pract Res Clin Rheumatol*. 2018;32:83–93.
14. Vandenbussche C, Bitton L, Bataille P, et al. Prognostic value of microscopic hematuria after induction of remission in antineutrophil cytoplasmic antibodies-associated vasculitis. *Am J Nephrol*. 2019;49:479–486.
15. Walsh M, Flossmann O, Berden A, et al. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2012;64:542–548.
16. McClure ME, Wason J, Gopaluni S, et al. Evaluation of PR3-ANCA status after rituximab for ANCA-associated vasculitis. *J Clin Rheumatol*. 2019;25:217–223.
17. Sanders JS, Huitma MG, Kallenberg CG, et al. Prediction of relapses in PR3-ANCA-associated vasculitis by assessing responses of ANCA titres to treatment. *Rheumatology (Oxford)*. 2006;45:724–729.
18. Tomasson G, Grayson PC, Mahr AD, et al. Value of ANCA measurements during remission to predict a relapse of ANCA-associated vasculitis—a meta-analysis. *Rheumatology (Oxford)*. 2012;51:100–109.
19. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*. 2010;363:211–220.
20. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363:221–232.
21. Walters G, Willis NS, Craig JC. Interventions for renal vasculitis in adults. *Cochrane Database Syst Rev*. 2015;9:CD003232.
22. Walters GD, Willis NS, Cooper TE, et al. Interventions for renal vasculitis in adults. *Cochrane Database Syst Rev*. 2020;1:CD003232.
23. Unizony S, Villarreal M, Miloslavsky EM, et al. Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type. *Ann Rheum Dis*. 2016;75:1166–1169.
24. de Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med*. 2009;150:670–680.
25. Han F, Liu G, Zhang X, et al. Effects of mycophenolate mofetil combined with corticosteroids for induction therapy of microscopic polyangiitis. *Am J Nephrol*. 2011;33:185–192.
26. Hu W, Liu C, Xie H, et al. Mycophenolate mofetil versus cyclophosphamide for inducing remission of ANCA vasculitis with moderate renal involvement. *Nephrol Dial Transplant*. 2008;23:1307–1312.
27. Jones RB, Hiemstra TF, Ballarin J, et al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. *Ann Rheum Dis*. 2019;78:399–405.
28. Tuin J, Stassen PM, Bogdan DI, et al. Mycophenolate mofetil versus cyclophosphamide for the induction of remission in nonlife-threatening relapses of antineutrophil cytoplasmic antibody-associated vasculitis: randomized, controlled trial. *Clin J Am Soc Nephrol*. 2019;14:1021–1028.
29. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2005;52:2461–2469.
30. Karras A, Pagnoux C, Haubitz M, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. *Ann Rheum Dis*. 2017;76:1662–1668.
31. Hellmich B, Sanchez-Alamo B, Schirmer JH, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheum Dis*. 2024;83:30–47.
32. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med*. 2020;382:622–631.
33. Furuta S, Nakagomi D, Kobayashi Y, et al. Effect of reduced-dose vs high-dose glucocorticoids added to rituximab on remission induction in ANCA-associated vasculitis: a randomized clinical trial. *JAMA*. 2021;325:2178–2187.
34. Jayne DRW, Merkel PA, Schall TJ, et al. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med*. 2021;384:599–609.
35. Cortazar FB, Niles JL, Jayne DRW, et al. Renal recovery for patients with ANCA-associated vasculitis and low eGFR in the ADVOCATE trial of avacopan. *Kidney Int Rep*. 2023;8:860–870.
36. Adu D, Pall A, Luqmani RA, et al. Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis. *QJM*. 1997;90:401–409.
37. Guillevin L, Cordier JF, Lhote F, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum*. 1997;40:2187–2198.
38. Haubitz M, Schellong S, Gobel U, et al. Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. *Arthritis Rheum*. 1998;41:1835–1844.
39. Merkel PA, Niles J, Jimenez R, et al. Adjunctive treatment with avacopan, an oral C5a receptor inhibitor, in patients with antineutrophil cytoplasmic antibody-associated vasculitis. *ACR Open Rheumatol*. 2020;2:662–671.
40. Pepper RJ, McAdoo SP, Moran SM, et al. A novel glucocorticoid-free maintenance regimen for anti-neutrophil cytoplasm antibody-associated vasculitis. *Rheumatology (Oxford)*. 2019;58:260–268.
41. McClure M, Gopaluni S, Jayne D, et al. B cell therapy in ANCA-associated vasculitis: current and emerging treatment options. *Nat Rev Rheumatol*. 2018;14:580–591.
42. van Daalen EE, Rizzo R, Kronbichler A, et al. Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis. *Ann Rheum Dis*. 2017;76:1064–1069.

43. Specks U, Merkel PA, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med*. 2013;369:417–427.
44. Casal Moura M, Irazabal MV, Eirin A, et al. Efficacy of rituximab and plasma exchange in antineutrophil cytoplasmic antibody-associated vasculitis with severe kidney disease. *J Am Soc Nephrol*. 2020;31:2688–2704.
45. Maritati F, Alberici F, Oliva E, et al. Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: a randomised trial. *PLoS One*. 2017;12:e0185880.
46. US National Library of Medicine. Plasma exchange and glucocorticoids for treatment of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (PEXIVAS). Accessed May 5, 2023. https://clinicaltrials.gov/study/NCT00987389
47. Roberts DM, Jones RB, Smith RM, et al. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. *J Autoimmun*. 2015;57:60–65.
48. Jayne DR, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol*. 2007;18:2180–2188.
49. Cole E, Cattran D, Magil A, et al. A prospective randomized trial of plasma exchange as additive therapy in idiopathic crescentic glomerulonephritis. The Canadian Apheresis Study Group. *Am J Kidney Dis*. 1992;20:261–269.
50. Glockner WM, Sieberth HG, Wichmann HE, et al. Plasma exchange and immunosuppression in rapidly progressive glomerulonephritis: a controlled, multi-center study. *Clin Nephrol*. 1988;29:1–8.
51. Mauri JM, Gonzalez MT, Poveda R. Therapeutic plasma exchange in the treatment of rapidly progressive glomerulonephritis. *Plasma Ther Transfus Technol*. 1985;6:587–591.
52. Pusey CD, Rees AJ, Evans DJ, et al. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. *Kidney Int*. 1991;40:757–763.
53. Rifle G, Chalopin JM, Zech P, et al. Treatment of idiopathic acute crescentic glomerulonephritis by immunodepression and plasma-exchanges. A prospective randomised study. *Proc Eur Dial Transplant Assoc*. 1981;18:493–502.
54. Szpirt WM, Heaf JG, Petersen J. Plasma exchange for induction and cyclosporine A for maintenance of remission in Wegener's granulomatosis—a clinical randomized controlled trial. *Nephrol Dial Transplant*. 2011;26:206–213.
55. Walsh M, Collister D, Zeng L, et al. The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. *BMJ*. 2022;376:e064604.
56. Levy JB, Hammad T, Coulthart A, et al. Clinical features and outcome of patients with both ANCA and anti-GBM antibodies. *Kidney Int*. 2004;66:1535–1540.
57. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med*. 2003;349:36–44.
58. Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA*. 2010;304:2381–2388.
59. Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med*. 2008;359:2790–2803.
60. Sanders JS, de Joode AA, DeSevaux RG, et al. Extended versus standard azathioprine maintenance therapy in newly diagnosed proteinase-3 anti-neutrophil cytoplasmic antibody-associated vasculitis patients who remain cytoplasmic anti-neutrophil cytoplasmic antibody-positive after induction of remission: a randomized clinical trial. *Nephrol Dial Transplant*. 2016;31:1453–1459.
61. Charles P, Terrier B, Perrodeau E, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). *Ann Rheum Dis*. 2018;77:1143–1149.
62. Smith RM, Jones RB, Specks U, et al. Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial. *Ann Rheum Dis*. 2023;82:937–944.
63. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med*. 2014;371:1771–1780.
64. Stegeman CA, Tervaert JW, de Jong PE, et al. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. *N Engl J Med*. 1996;335:16–20.
65. Zycinska K, Wardyn KA, Zielonka TM, et al. Co-trimoxazole and prevention of relapses of PR3-ANCA positive vasculitis with pulmonary involvement. *Eur J Med Res*. 2009;14(suppl 4):265–267.
66. Walsh M, Merkel PA, Mahr A, et al. Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis. *Arthritis Care Res (Hoboken)*. 2010;62:1166–1173.
67. Pagnoux C, Hogan SL, Chin H, et al. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. *Arthritis Rheum*. 2008;58:2908–2918.
68. Romeu M, Couchoud C, Delaroziere JC, et al. Survival of patients with ANCA-associated vasculitis on chronic dialysis: data from the French REIN registry from 2002 to 2011. *QJM*. 2014;107:545–555.
69. Pugnet G, Pagnoux C, Terrier B, et al. Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life. *Clin Exp Rheumatol*. 2016;34:S54–S59.
70. Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis*. 2009;68:1827–1832.
71. Charles P, Perrodeau E, Samson M, et al. Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med*. 2020;173:179–187.
72. Slot MC, Tervaert JW, Boomsma MM, et al. Positive classic antineutrophil cytoplasmic antibody (C-ANCA) titer at switch to azathioprine therapy associated with relapse in proteinase 3-related vasculitis. *Arthritis Rheum*. 2004;51:269–273.
73. Faurschou M, Sorensen IJ, Mellemkjaer L, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. *J Rheumatol*. 2008;35:100–105.
74. Smith RM, Jones RB, Specks U, et al. Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. *Ann Rheum Dis*. 2020;79:1243–1249.
75. Geetha D, Eirin A, True K, et al. Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis: a multicenter experience. *Transplantation*. 2011;91:1370–1375.
76. Goceroglu A, Rahmattulla C, Berden AE, et al. The Dutch Transplantation in Vasculitis (DUTRAVAS) Study: outcome of renal transplantation in antineutrophil cytoplasmic antibody-associated glomerulonephritis. *Transplantation*. 2016;100:916–924.
77. Kidney Disease: Improving Global Outcomes Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4S):S1–S276.
78. Institute of Medicine (IOM). Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. In: Graham R, Mancher M, Miller Wolman D, et al., eds. *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press; 2011.
79. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *J Clin Epidemiol*. 2010;63:1308–1311.
80. Tunnicliffe DJ, Palmer SC, Henderson L, et al. Immunosuppressive treatment for proliferative lupus nephritis. *Cochrane Database Syst Rev*. 2018;6:CD002922.
81. Higgins JPT, Thomas J, Chandler J, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley; 2019.
82. Guyatt GH, Oxman AD, Schunemann HJ, et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol*. 2011;64:380–382.
83. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
84. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
85. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. *J Clin Epidemiol*. 2011;64:1283–1293.
86. Brunetti M, Shemilt I, Pregno S, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. *J Clin Epidemiol*. 2013;66:140–150.