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The 2025 Turkish Society for Rheumatology management recommendations for ANCA-associated vasculitides

Türkiye Romatoloji Derneği ANCA ilişkili (asosiye) vaskülitler hastalık yönetimi kılavuzu

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) manifest with involvement of the ear, nose, and throat; the skin; and the nervous system, together with constitutional symptoms, and can also be potentially life-threatening with cardiac renal, and pulmonary involvement leading to organ dysfunction. Early diagnosis is critical, necessitating increased awareness among clinicians. In patients presenting with systemic features suggestive of AAV, such as cutaneous vasculitis, chronic upper and lower respiratory tract diseases, rapidly progressive renal impairment, or peripheral neuropathy, high-quality antigen-specific assays for proteinase-3

Özet

Anti-nötrofil sitoplazmik antikor (ANCA) asosiye vaskülitlerde (AAV), üst solunum yolu, deri, nörolojik sistem ve konstitüsyonel bulgularla birlikte kardiyak, renal ve pulmoner sistemleri tutan ve organ fonksiyon kaybı ya da yaşamı tehdit eden klinik tablolar gelişebilir. Bu nedenle erken tanı için hekimler arasında farkındalığın artırılması gerekmektedir. AAV şüphesi bulunan ve kutanöz vaskülit, kronik üst ve alt solunum yolu hastalıkları, hızlı ilerleyen böbrek fonksiyon bozukluğu, periferik nöropati gibi AAV tanısını düşündüren sistemik bulguları olan hastalarda, birincil tanı yöntemi olarak yüksek kaliteli antijen-spesifik yöntemle proteinaz-3 ANCA ve

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Abstract

and myeloperoxidase should be performed as primary diagnostic tests. Management by multidisciplinary teams experienced in the management of vasculitis is recommended. Advances in technology have facilitated the use of various laboratory, imaging, and interventional methods for diagnosis, differential diagnosis, and disease monitoring; composite indices are employed to assess disease activity and organ damage. AAV treatment is divided into remission induction and maintenance phases; induction therapy for organ- or life-threatening disease typically includes glucocorticoids combined with rituximab- or cyclophosphamide-based regimens. Maintenance therapy, often with rituximab, follows remission to prevent relapse. While glucocorticoids remain a cornerstone of induction therapy, studies demonstrate that reduced-dose steroid regimens offer comparable efficacy to standard doses, with a lower risk of infection. Additionally, the introduction of biologics such as rituximab and mepolizumab has significantly decreased treatment-related damage associated with glucocorticoids and other immunosuppressants. During follow-up, patients should be monitored regularly for treatment-related adverse effects and comorbidities, including hypertension, osteoporosis, and cardiovascular disease-and appropriate lifestyle modifications should be recommended to optimize long-term outcomes.

Keywords: Vasculitis, granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), immunosuppressive therapy, cyclophosphamide, rituximab, plasma exchange, glucocorticoids, infections

Özet

miyeloperoksidaz ANCA bakılmalıdır. AAV hastalarının vaskülitler konusunda deneyimli merkezler tarafından multidisipliner bir ekiple değerlendirilmesi akılcı yaklaşımdır. Teknolojik gelişmelerle birlikte tanı, ayırıcı tanı ve hastalık süresinin izleminde çeşitli laboratuvar, görüntüleme teknikleri ve girişimsel yöntemler kullanılmaktadır. Hastalık aktivitesinin ve organ hasarının değerlendirilmesinde çeşitli hastalık kompozit indekslerinden yararlanılmaktadır. AAV tedavisi, remisyon indüksiyonu ve idame tedavisi olmak üzere iki aşamada planlanmaktadır. Organ veya yaşamı tehdit eden olgularda, indüksiyon tedavisinde glukokortikoidlere ek olarak rituksimab veya siklofosfamid temelli rejimler önerilmektedir. Remisyon sağlandıktan sonra, nüksleri önlemek amacıyla idame tedavisine geçilir ve bu dönemde en sık tercih edilen ajan rituksimabdır. Glukokortikoidler, indüksiyon tedavisinin temel bileşenlerinden biri olmasına karşın, yapılan çalışmalar düşük doz glukokortikoid rejimlerinin standart dozlara benzer etkinlik gösterdiğini ve daha düşük enfeksiyon riski ile ilişkili olduğunu ortaya koymuştur. Ayrıca, rituksimab ve mepolizumab gibi biyolojik ilaçların kullanımıyla birlikte glukokortikoidler ve diğer immünsüpresiflere bağlı gelişen hasar gelişimi önemli oranda azalmıştır. Hastalar takipleri sırasında tedavi ilişkili yan etkiler ve komorbiditeler (hipertansiyon, osteoporoz, kardiyovasküler hastalıklar) açısından periyodik olarak taranmalı ve hastalara gerekli yaşam tarzı değişiklikleri önerilmelidir.

Anahtar Kelimeler: Vaskülit, granülomatöz polianjiitis (GPA), eozinofilik granülomatöz polianjiitis (EGPA), mikroskopik polianjiitis (MPA), immünosüpresif tedavi, siklofosfamid, rituksimab, plazma değişimi, glukokortikoid, komorbidite, enfeksiyonlar

Introduction and Objectives

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are rare, heterogeneous, and potentially llife-threatening diseases. Therefore, these diseases should be managed by a multidisciplinary team in centers with vasculitis expertise or with ready access to such expertise. Patients diagnosed with AAV should receive optimal and individualized care through shared decision-making between patients and physicians, taking into account efficacy, safety, and cost considerations. Disease activity and organ damage should be assessed using validated composite disease indices. Furthermore, patients should undergo regular monitoring for treatment-related adverse effects and comorbid conditions, with appropriate preventive measures implemented as needed. This guideline on AAV has been developed primarily for rheumatologists and is also intended for internists, nephrologists, pulmonologists, and otorhinolaryngologists who may be involved in the diagnosis or follow-up of such patients in secondary and tertiary care settings. The development process of this guideline was primarily informed by current scientific literature and expert consensus. In addition, recommendations from international organizations such as the European Alliance of Associations for Rheumatology (EULAR), Kidney Disease: Improving Global Outcomes, and the American College of Rheumatology (ACR) were incorporated.

Epidemiology

The annual incidence of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) varies by country and ethnicity, ranging from 0.4 to 11.9 per 1,000,000 for GPA, 0.5 to 24 per 1,000,000 for MPA, and 0.5 to 2.3 per 1,000,000 for EGPA. The prevalence of GPA has been reported to range from 2.3 to 146 per 1,000,000 individuals, whereas those of MPA and EGPA range from 9 to 94 and 2 to 22.3 per 1,000,000 individuals, respectively.[1] The age at disease onset ranges from 45 to 65 years for GPA, 55 to 75 years for MPA, and 38 to 54 years for EGPA, with an overall male-to-female ratio of approximately 1:1. According to data collected in our country by the Turkish Vasculitis Study Group (TRVaS), the age of onset of AAV tends to fall at the lower end of these ranges and does not exhibit a significant sex-based difference.[2]

Symptoms, Signs, and Characteristics of AAV-specific Disease Involvement

Patients with AAV may present with a wide spectrum of symptoms because of heterogeneous clinical manifestations and multisystem involvement. Supplementary Table 1 summarizes the frequency of organ and tissue involvement in patients with AAV at the time of diagnosis. The data presented in this table are derived from the international Diagnostic and Classification Criteria in Vasculitis Study and the TRVaS Prospective Database.[2,3]

GPA is typically characterized by an insidious onset and granulomatous inflammation affecting both the upper and lower respiratory tracts. In contrast, MPA usually presents with renal and pulmonary involvement accompanied by systemic vasculitic features and is often associated with a more acute clinical

course. EGPA, on the other hand, is defined by eosinophilia and granulomatous inflammation that develop during the disease course in patients with a history of asthma.

• Patients may present with constitutional symptoms such as fever, fatigue, and weight loss, which are nonspecific and often precede organ-specific manifestations.

• Skin lesions may include palpable purpura, livedoid changes, papules, nodules, urticarial lesions, and less commonly ulcers. These may occur concomitantly with systemic symptoms or represent the initial manifestation of the disease.

• Treatment-resistant oral ulcers and red, exophytic gingival hypertrophy (commonly referred to as strawberry gingivitis) may occur in cases of oral mucosal involvement.

• Patients may experience arthralgia, arthritis, or myalgia. Ear, nose, and throat (ENT) manifestations include epistaxis, nasal crusting, nasal polyps, septal perforation, saddle-nose deformity, chronic sinusitis, subglottic stenosis, hoarseness, and ear fullness.

• Symptoms may include hearing loss, otorrhea, otalgia, tinnitus, and dizziness, along with skull base involvement manifesting as facial nerve paralysis and hypertrophic pachymeningitis.

• Pulmonary involvement in AAV encompasses tracheobronchial inflammation and structural abnormalities, as well as parenchymal lesions such as nodules, masses, or cavitations. Severe complications may include diffuse alveolar hemorrhage (DAH) and interstitial lung disease (ILD).

• Acute kidney injury is common in patients with rapidly progressive glomerulonephritis (RPGN) secondary to AAV. Hematuria, proteinuria, edema, and hypertension are frequently observed.

• Ocular involvement may present as conjunctivitis, uveitis, proptosis, episcleritis/scleritis, or peripheral ulcerative keratitis. Less commonly, retinitis, optic neuritis, and vision loss may develop.

• The peripheral nervous system is most often affected, manifesting as mononeuritis multiplex, sensory neuropathy, or

Table 1. 2022 ACR/EULAR Classification Criteria for GPA, MPA, and EGPA

Entry criterion: A confirmed diagnosis of small- or medium-vessel vasculitis is required, and other medical conditions that may mimic vasculitis must be excluded.

	GPA	MPA	EGPA
Clinical criteria			
• Nasal involvement (bloody discharge, ulcers, crusting, congestion, obstruction, or septal defect/perforation)	+3	-3	
• Cartilaginous involvement (auricular or nasal cartilage, stridor, endobronchial involvement, or saddle-nose deformity)	+2		
• Conductive or sensorineural hearing loss	+1		
• Obstructive airway disease			+3
• Nasal polyps			+3
• Mononeuritis multiplex			+1
Laboratory criteria			
• PR3-ANCA (or cANCA) positivity	+5	-1	-3
• MPO-ANCA (or pANCA) positivity	-1	+6	
• Serum eosinophils ≥1000/μL	-4	-4	+5
• Hematuria			-1
Histological criteria			
• Granuloma, granulomatous inflammation, or giant cells	+2		
• Pauci-immune glomerulonephritis	+1	+3	
• Extravascular eosinophilic inflammation			+2
Radiological criteria			
• Pulmonary nodules, masses, or cavitation on chest imaging	+2		
• Fibrosis or interstitial lung disease on chest imaging		+3	
• Nasal/paranasal sinusitis or mastoiditis on imaging	+1		
Score required for classification	≥5	≥5	≥6

ACR: American College of Rheumatology, ANCA: Anti-neutrophil cytoplasmic antibodies, EGPA: Eosinophilic granulomatosis with polyangiitis, EULAR: European Alliance of Associations for Rheumatology, GPA: Granulomatosis with polyangiitis, MPA: Microscopic polyangiitis, MPO: Myeloperoxidase

polyneuropathy. Central nervous system (CNS) involvement is rare but may present with headache, cognitive decline, seizures, cranial nerve palsy, or cerebrovascular events.

• Mesenteric ischemia may occur, leading to abdominal pain, bloody diarrhea, or intestinal perforation. Other manifestations may include cholecystitis and pancreatitis.

• Cardiac manifestations include pericarditis, myocarditis, cardiomyopathy, and heart failure.

a. Pulmonary Involvement

Pulmonary involvement may range from asymptomatic findings detected incidentally on imaging to severe, symptomatic disease. Depending on the site and extent of involvement, patients may experience cough, dyspnea, hoarseness, stridor, sputum production, hemoptysis, or pleuritic chest pain. The most frequently observed thoracic manifestations of AAV are summarized below.[4]

1. Tracheobronchial involvement: Tracheobronchial inflammation, mucosal alterations, tracheo- and/or bronchomalacia, and subglottic stenosis (SGS)

2. Pulmonary nodules (solitary/multiple), masses, consolidation, and cavitation

3. DAH

4. ILD

A baseline chest computed tomography (CT) scan should be obtained before initiating immunosuppressive therapy, even in the absence of respiratory symptoms in newly diagnosed patients. Thoracic CT may demonstrate cavitating nodules, subpleural lesions, airway inflammation, or stenotic changes of the large airways, as well as small nodules that may not be visible on conventional chest radiography. In addition, thoracic CT provides a more comprehensive evaluation of ILD and DAH. Non-contrast CT is preferred when renal involvement is suspected, to avoid contrast-induced nephropathy. Furthermore, three-dimensional reconstructions of the tracheobronchial tree can be generated using thoracic CT for detailed anatomical assessment. Tracheobronchial involvement is common in GPA but occurs less frequently in MPA and EGPA. The segmental and focal distribution of mucosal lesions represents a key distinguishing feature. These lesions are characterized by erosions (mucosal ulcers) and inflammatory changes within the mucosa. When cartilaginous structures are affected, they may cause tracheomalacia, bronchomalacia, or airway stenosis. SGS is the most common manifestation of tracheobronchial involvement in GPA and is defined as a narrowing of the airway immediately below the vocal cords.[5] Prompt evaluation is warranted in patients presenting with dyspnea, hoarseness, or stridor, as severe cases may require tracheostomy for airway stabilization. Although endobronchial inflammation and stenosis are less common than subglottic involvement, they may present with similar clinical manifestations. Biopsy specimens from tracheobronchial lesions often demonstrate nonspecific mucosal inflammation, ulceration, and fibrosis, leading to secondary stenosis; however, histopathologic evidence of vasculitis is rarely observed.[6] Pulmonary nodules may occur in all forms of AAV, but they are most frequently seen in GPA. Consolidation, pulmonary infiltrates, and unilateral or bilateral nodules are present at disease onset in approximately 40-70% of patients, while cavitation develops in 20-50% of these lesions. The pulmonary lesions may be migratory and transient.[7,8] Nodular lesions are often located in subpleural regions and are commonly associated with adjacent blood vessels, a characteristic described as the “feeding vessel sign.” As these nodules enlarge, they may undergo cavitation, with diameters ranging from a few millimeters to 10 cm.

Cavitating lesions typically exhibit thick walls with irregular inner margins and lack calcification. A ground-glass halo surrounding the nodules—known as the “halo sign”—is frequently observed and suggests concomitant alveolar hemorrhage. In addition, the presence of air bronchograms within pulmonary nodules is a common radiologic finding.

AAV-ILD represents pulmonary involvement that may develop during the course of AAV, particularly in patients with myeloperoxidase (MPO)-ANCA–positive disease. ILD may be detected either during follow-up or prior to the diagnosis of AAV.

Thoracic CT may reveal ground-glass opacities, reticular patterns, consolidation, interlobular septal thickening, and honeycombing. The usual interstitial pneumonia (UIP) pattern is the most common radiologic subtype of ILD in patients with MPO-ANCA-positive AAV. Patterns of non-specific interstitial pneumonia and, less frequently, of desquamative interstitial pneumonia may also be observed. Furthermore, 5-10% of patients with idiopathic pulmonary fibrosis may have positive ANCA serology at diagnosis.[9]

DAH is defined as the extravasation of blood into the alveolar spaces resulting from increased capillary wall permeability secondary to capillaritis, leading to impaired gas exchange and hypoxemia. Early recognition and prompt treatment are crucial because of its significant contribution to morbidity and mortality. Notably, chest radiographs may appear normal in up to 50% of patients with suspected DAH. On thoracic CT, typical findings include bilateral alveolar opacities, interlobular and intralobular septal thickening, a cobblestone appearance, and ground-glass opacities. The gold standard for diagnosis is the identification of hemosiderin-laden macrophages in bronchoalveolar lavage (BAL) fluid. Moreover, BAL is valuable for excluding infectious etiologies that may mimic DAH.[6]

b. Asthma

Asthma occurs in more than 90% of patients with EGPA. It typically develops in adulthood and is frequently accompanied by upper respiratory tract symptoms. Chronic rhinosinusitis with eosinophilic nasal polyposis is common in the upper airways. The disease is often refractory to conventional therapy, and nasal polyps may recur despite surgical intervention.

Pulmonary parenchymal infiltrates, which are frequently observed in EGPA, are not typically present in cases of severe eosinophilic asthma without vasculitic involvement. In patients with asthma whose symptoms remain uncontrolled despite optimal therapy, or in those who require high-dose inhaled corticosteroids (ICS) to maintain control and who exhibit peripheral blood eosinophilia (≥1500/mm³), an evaluation for vasculitic manifestations should be undertaken. Furthermore, EGPA should be suspected in individuals presenting with chronic rhinosinusitis with eosinophilic nasal polyposis, severe eosinophilic asthma, and marked eosinophilia. Such patients warrant thorough assessment for evidence of systemic involvement.[10]

c. Renal Involvement

In patients with renal involvement, kidney function may deteriorate rapidly over days to weeks, leading to acute kidney injury consistent with RPGN. Hematuria—particularly dysmorphic erythrocytes or erythrocyte casts—and proteinuria are key urinalysis findings that should prompt clinical suspicion for renal vasculitis. Edema and hypertension may also accompany the presentation. Although uncommon, a more gradual decline in renal function has been reported in some cases. Despite appropriate treatment, end-stage renal disease (ESRD) develops in approximately 20-25% of patients.[11]

d. Neurological Involvement

Peripheral neuropathy in AAV typically presents with distal tingling or painful paresthesia in the lower extremities, often progressing to sensory loss in a mononeuritis multiplex pattern. When motor involvement is present, muscle weakness and atrophy may occur in the affected region; however, pure motor neuropathy is uncommon in AAV-related neuropathies. Electrophysiological studies typically reveal findings consistent with axonal neuropathy, characterized by reduced compound muscle and sensory nerve action potentials, while motor and sensory conduction velocities and distal motor latencies are generally preserved. Nerve biopsy demonstrates axonal degeneration affecting both myelinated and unmyelinated fibers, accompanied by inflammation of epineural vessels. However, due to the patchy distribution of mononeuritis multiplex, the biopsied nerve may not consistently demonstrate pathological involvement.

Meningeal involvement in AAV is rare but clinically significant, and it may occur early in the disease course. Magnetic resonance imaging (MRI) plays a critical role in establishing the diagnosis and assessing disease extent.

Laboratory and Histopathological Evaluation

a. Acute Phase Response and Serology

ANCAs are autoantibodies directed against specific antigens such as proteinase 3 (PR3) and MPO. ANCA can be detected by indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay. Based on the staining pattern observed on ethanol-fixed neutrophil slides, three types of ANCA are identified by the IIF technique:

- Cytoplasmic ANCA (c-ANCA)
- Perinuclear ANCA (p-ANCA)
- Atypical ANCA

Antigen-specific immunoassays demonstrate greater diagnostic accuracy than IIF for the detection of ANCA. The 2017 International Consensus on ANCA Testing recommends high-quality immunoassays targeting PR3 and MPO as the preferred initial screening method for the diagnosis of GPA and MPA.[12]

In patients presenting with clinical features suggestive of AAV, testing for both PR3-ANCA and MPO-ANCA using a high-quality, antigen-specific immunoassay is recommended as the primary diagnostic approach. If immunoassay results are negative but clinical suspicion for AAV remains high, a confirmatory test—using an alternative immunoassay or IIF—should be performed.

A negative ANCA result does not exclude the diagnosis of AAV, as a small subset of patients—particularly those with disease confined to the respiratory tract or isolated renal involvement—may be ANCA-negative.[13]

b. Pulmonary Function Tests

Simple spirometry may aid diagnosis by demonstrating an extrathoracic obstructive pattern in cases of SGS and an intrathoracic obstructive pattern in cases of tracheobronchial involvement. In patients with ILD, a reduction in the diffusing capacity for carbon monoxide (DLCO) is typically observed. A restrictive ventilatory pattern, often accompanied by reduced lung volumes, may also be evident.

For the follow-up of patients with ILD, spirometry, DLCO measurement, and the six-minute walk test can be employed to monitor disease progression and functional decline.

c. Bronchoscopic Evaluation

Bronchoscopic evaluation may be valuable in selected cases for the diagnosis and assessment of AAV. In GPA, bronchoscopy facilitates the direct evaluation of tracheobronchial

involvement. Biopsy specimens can be obtained from areas of mucosal abnormality or transbronchially from the lung parenchyma to support histopathologic confirmation. However, the small size of bronchoscopic biopsy specimens may limit the demonstration of granulomatous or vasculitic involvement. In patients with suspected DAH and active pulmonary bleeding, a progressively more hemorrhagic appearance in sequential BAL aliquots (20-50 mL each) obtained from the same bronchopulmonary segment supports the diagnosis of alveolar hemorrhage. The identification of hemosiderin-laden macrophages comprising ≥20% of total macrophages on cytological examination is considered the gold standard for confirming the diagnosis.[14] BAL is also valuable for the differential diagnosis of infection, and microbiological analyses should be performed accordingly.

d. Histopathology

In patients presenting with cutaneous manifestations, histopathological examination is recommended owing to the ease of tissue accessibility. Diagnostic features may include leukocytoclastic vasculitis, granulomatous inflammation, and variable degrees of eosinophilic infiltration.

Although the sensitivity of biopsy for detecting vasculitic changes is relatively low in cases with sinonasal involvement, tissue sampling may still be warranted to exclude invasive fungal infections, particularly those mimicking mucormycosis.

In patients with GPA who present with pulmonary nodules, masses, or consolidation, percutaneous or thoracoscopic lung biopsies may be performed for diagnostic confirmation. However, percutaneous approaches often yield limited tissue samples, which may be insufficient for definitive histopathologic evaluation. Nonetheless, image-guided biopsies—using CT or positron emission tomography/CT—targeting metabolically active lesions and avoiding necrotic areas can significantly enhance diagnostic yield.

Histopathological examination in GPA typically demonstrates necrotizing granulomatous inflammation. When biopsy is performed, special stains and microbiological investigations, including cultures for infectious agents capable of inducing granulomatous inflammation—such as tuberculosis—should be routinely conducted to facilitate differential diagnosis.

Renal biopsy plays a crucial role in both establishing the diagnosis and assessing the prognosis of AAV. It is recommended for patients with MPO-ANCA or PR3-ANCA positivity, or for those with organ involvement suggestive of small-vessel vasculitis, when renal impairment, hematuria, or proteinuria is present, provided no contraindications exist. In patients unresponsive to therapy, a repeat renal biopsy may be considered to assess chronic renal damage, identify alternative causes of acute kidney injury, or evaluate persistent disease activity. In circumstances where biopsy cannot be performed—such as patients receiving anticoagulant therapy or those at high risk of bleeding—treatment initiation should not be delayed. Renal biopsy provides critical information regarding glomerular, tubulointerstitial, and vascular involvement. The characteristic histopathologic pattern observed in AAV is pauci-immune necrotizing crescentic glomerulonephritis, with minimal or absent immunoglobulin and complement deposition. Furthermore, renal biopsy findings can be used to predict the risk of long-term renal failure and guide prognostic assessment. Several prognostic scoring systems have been developed based on histopathologic features observed at the time of renal biopsy. Among these, the most widely applied are the Berden classification, the Mayo Clinic/Renal Pathology Society (RPS) Chronicity Score, and the ANCA Renal Risk Score (Supplementary Table 2). These prognostic scoring systems differ in their assessment parameters. In the Berden classification, only glomerular lesions identified on renal biopsy are evaluated, and patients are categorized into four classes: focal, crescentic, mixed, and sclerotic. According to this system, the focal class is associated with the most favorable prognosis, whereas the sclerotic class carries the poorest prognosis. The crescentic and mixed classes exhibit intermediate or variable prognoses.[15] The Mayo Clinic/RPS Chronicity Score evaluates the extent of chronic histopathologic changes in the kidney. The degrees of glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis were graded as minimal, mild, moderate, or severe; these grades provide an overall measure of chronic renal damage (Supplementary Table 2). It has been demonstrated that patients with minimal or mild histopathologic changes exhibit greater improvement in renal function and more favorable long-term renal survival.[16] The ANCA Renal Risk Score is a prognostic model designed to predict renal survival in patients with AAV and renal involvement. In this system, the percentage of normal glomeruli, the extent of tubular atrophy and interstitial fibrosis, and the glomerular filtration rate (GFR) at diagnosis—categorized as ≥15 or <15 mL/min/1.73 m²—are incorporated, which distinguishes it from other histopathologic scoring models. Higher values are associated with an increased risk of progression to ESRD.[17]

Differential Diagnosis of AAV and the 2022 ACR/EULAR Classification Criteria

In evaluating a patient with suspected AAV, differential diagnoses that commonly cause symptoms, organ involvement, and laboratory findings associated with AAV are outlined below.[18]

• Infectious diseases (subacute bacterial endocarditis, hepatitis B, hepatitis C, human immunodeficiency virus infection, tuberculosis, fungal infections)

• Malignancies (lymphoma, leukemia, solid organ malignancies)

• Other autoimmune and autoinflammatory diseases (systemic lupus erythematosus, large- and medium-vessel vasculitides, IgG4-related disease, antiphospholipid antibody syndrome, etc.)

• Drug/substance-induced ANCA positivity (propylthiouracil, hydralazine, phenytoin, levamisole, cocaine, etc.)

After excluding secondary causes, the 2022 ACR/EULAR classification criteria for GPA, EGPA, and MPA—which are useful in differentiating patients primarily considered to have small- or medium-vessel vasculitis—can be applied. These are presented in Table 1.[19]

Disease Activity and Damage Assessments

It is recommended that patients with AAV undergo regular evaluations of disease activity and organ damage, with more frequent assessments during induction therapy. In routine clinical practice, follow-up visits may be scheduled at diagnosis and at weeks 2, 4, 8, 12, 18, and 24, depending on the clinical severity and treatment protocol. During these visits, multidisciplinary specialist assessments should be performed based on the affected organ systems (e.g., nephrology, otorhinolaryngology, ophthalmology, pulmonology). For affected organs, functional and radiologic evaluations—including paranasal sinus CT, chest CT, pulmonary function testing with DLCO, electrocardiography, cardiac MRI, and electromyography—may be planned based on the patient's clinical status, disease severity, and treatment-related factors, such as monitoring requirements, tolerability, and potential adverse effects.[20]

Renal function tests are the most critical parameters for assessing and monitoring renal remission in AAV. In addition, hematuria, proteinuria, and ANCA titers may be used as supplementary follow-up markers. The principal criteria for evaluating renal remission are serum creatinine and eGFR, which reflect overall kidney function. Stable or improving serum creatinine levels indicate renal remission. However, hematuria and/or proteinuria may persist in up to 50% of patients during long-term follow-up; therefore, their significance in defining remission, relapse, and renal survival remains controversial. An increase in hematuria, or its recurrence after resolution, may suggest renal relapse once other etiologies are excluded and warrants close monitoring. Persistent proteinuria may reflect either ongoing disease activity or chronic parenchymal injury secondary to previous inflammation. Importantly, proteinuria associated with chronic structural damage constitutes a negative prognostic factor for long-term renal function.[21-24]

In AAV, several standardized indices have been developed to objectively assess disease activity, guide treatment decisions, evaluate therapeutic response, and quantify vasculitis-related damage. In clinical practice, validated scoring systems such as the Birmingham Vasculitis Activity Score (BVAS, version 3) and the BVAS for Wegener's Granulomatosis (BVAS-WG) should be used—alongside structured clinical evaluation and inflammatory markers—to determine the presence of active disease.[20,25] When calculating BVAS and BVAS-WG scores, findings attributable

Table 2. Drugs and dosage regimens used in the treatment of AAV

Treatment	Dosage and administration
Pulse glucocorticoid	Intravenous methylprednisolone 500-1000 mg/day (or equivalent) for 3-5 days.
High-dose oral glucocorticoid	Prednisolone 1 mg/kg/day (up to a maximum of 75 mg/day) or an equivalent dose.
Induction therapy	
Methotrexate	Up to 20 mg weekly (oral or subcutaneous).
Azathioprine	2-3 mg/kg/day (oral).
Mycophenolate mofetil	2000 mg/day (oral, in two divided doses).
Cyclophosphamide	15 mg/kg IV, every 2 weeks for the first 3 doses, then every 3 weeks for the next 3 doses.
Rituximab	375 mg/m² IV weekly for 4 consecutive weeks or 1000 mg IV twice, 14 days apart.
Maintenance therapy	
Methotrexate, azathioprine, mycophenolate mofetil	Initiated at a dose similar to that used for remission induction, with gradual tapering during follow-up based on clinical response.
Rituximab	500 mg or 1000 mg every 4-6 months, depending on the clinical condition of the patient.
Drugs specific to EGPA	
Mepolizumab	100-300 mg subcutaneously every 4 weeks.
Benralizumab	30 mg subcutaneously every 4 weeks.

AAV: ANCA-associated vasculitis, ANCA: Anti-neutrophil cytoplasmic antibody, EGPA: Eosinophilic granulomatosis with polyangiitis, IV: Intravenous

to active vasculitis that have appeared or worsened within the preceding four weeks are classified as new or worsening disease, whereas findings that have persisted since the previous evaluation are recorded as persistent disease. These tools enhance clinical decision-making by allowing for the systematic documentation of treatment response (Supplementary Table 3).[13] The frequency of assessment should be individualized according to the patient's clinical status, disease severity, and the monitoring needs of ongoing therapy.

Refractory disease is defined as the persistence or progression of disease activity despite standard induction therapy. It is characterized by either the absence of clinical improvement or worsening of disease activity within the first four weeks of treatment, or by a reduction in the disease activity score (e.g., BVAS) of less than 50% by week six of therapy. Before confirming disease refractoriness, alternative explanations such as infection, poor treatment adherence, drug intolerance, secondary vasculitic processes, treatment-related toxicity, comorbid conditions, and non-inflammatory causes of organ dysfunction should be carefully excluded.[26] The Five-Factor Score (FFS) is not intended to assess disease activity but rather serves as a prognostic tool that assists in estimating patient outcomes and guiding treatment intensity.[27]

The Vasculitis Damage Index (VDI) is a standardized assessment tool designed to quantify damage resulting from both the disease process and its treatment in systemic vasculitides. Damage is defined as a pathologic change persisting for more than three months after the onset of vasculitis symptoms.[28] The VDI is a validated instrument for documenting irreversible disease- or therapy-related damage in ANCA-AAV and provides standardized definitions that assist in distinguishing permanent damage from active disease.[13]

Table 3. Reduced-dose glucocorticoid regimen in the treatment of AAV

Week	Body weight <50 kg	Body weight 50-75 kg	Body weight >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

*The glucocorticoid dose is expressed as the prednisolone equivalent (mg/day) and is based on the reduced-dose regimen used in the PEXIVAS trial, AAV: ANCA-associated vasculitis, ANCA: Anti-neutrophil cytoplasmic antibody

The ANCA-AAV patient-reported outcome measure was published in 2018 and has since been translated and validated for use in Turkish. It comprises 29 items that assess patients' overall experiences during the preceding four weeks, focusing on symptoms and problems attributed to vasculitis or its treatment.[29]

Treatment and Follow-up

a. Induction of Remission

The treatment of AAV consists of two main phases: induction of remission and maintenance therapy. In patients with AAV presenting with life- or organ-threatening involvement (such as glomerulonephritis, DAH, tracheal or subglottic stenosis, meningeal involvement, CNS involvement, retro-orbital disease, cardiac involvement, mesenteric involvement, or mononeuritis multiplex), remission induction therapy is recommended with either rituximab (RTX) or cyclophosphamide (CYC), combined with glucocorticoids.[13,20,25,27,30] The agents and their dosage ranges used in remission induction and maintenance therapy are summarized in Table 2.

Although intravenous (IV) pulse glucocorticoid therapy is often preferred during remission induction due to its rapid clinical efficacy, there is insufficient evidence to support its routine use. Considering the potential increased risk associated with glucocorticoid toxicity, including infections, methylprednisolone pulse therapy should be restricted to the treatment of severe clinical manifestations such as active glomerulonephritis with an eGFR <50 mL/min/1.73 m² or DAH. The cumulative dose should be limited to 1-3 grams, followed by oral glucocorticoid therapy.[13]

The initial dose of oral glucocorticoids is generally equivalent to 50-75 mg per day of prednisolone. Recent studies have demonstrated that reduced-dose glucocorticoid regimens show comparable efficacy to standard-dose therapy in improving overall survival and reducing the risk of ESRD. In addition, patients receiving reduced-dose glucocorticoid therapy demonstrated a lower incidence of serious infections, particularly during the first year of treatment.[31] In this regimen, prednisolone is initiated at 1 mg/kg/day during the first week and subsequently tapered according to the schedule in Table 3.[13,25] However, this tapering regimen may not be suitable for all patients. In cases of renal involvement, the tapering schedule should be individualized to take into account the patient's specific risk factors and clinical condition and may require a slower dose reduction.

In patients with renal involvement, dialysis dependence at diagnosis or severe histopathological findings on renal biopsy do not preclude the initiation of remission induction therapy. On the contrary, even in cases of advanced renal failure requiring dialysis, appropriate remission induction therapy may lead to recovery of renal function. Although RTX or CYC can be used as first-line agents, nephrology societies

recommend CYC as the initial therapy in patients with severe glomerulonephritis (serum creatinine >4.0 mg/dL).[25] In addition to severe renal involvement, CYC may also be preferred in cases presenting with systemic and life- or organ-threatening manifestations, such as DAH; tracheobronchial involvement in patients with AAV and concurrent anti-GBM antibody positivity; and granulomatous disease predominantly involving the orbit or pachymeninges.[20,30] On the other hand, RTX may be considered the first-line option in adult patients with fertility concerns, elderly and/or frail individuals, and those with PR3-ANCA positivity. Mycophenolate mofetil (MMF) may be considered an alternative remission induction option in patients who cannot receive CYC or RTX, particularly in the MPO-ANCA–positive subgroup. The combination of RTX and CYC is rarely used and is generally reserved for refractory and/or life-threatening cases. Studies have shown that the addition of low-dose CYC to RTX therapy may reduce the frequency of relapses. However, these findings are based on limited observational studies. Although avacopan is not yet available in Türkiye, it has been considered a potential alternative to steroid therapy and can be used in combination with other immunosuppressive agents.[25]

Other AAV manifestations that are not life- or organ-threatening (such as pulmonary nodules or localized upper respiratory tract involvement) can be treated with oral glucocorticoids in combination with methotrexate (MTX).[6] In cases where MTX is not tolerated or is deemed inappropriate, MMF, azathioprine (AZA), or RTX may be used as alternative therapies. The response rate of granulomatous pulmonary lesions to treatment varies considerably among patients. Therapy should be continued while the lesions regress under treatment.[32] The treatment of AAV patients with interstitial fibrosis should be managed according to therapeutic recommendations for vasculitis.

b. Renal and Respiratory Supportive Therapies, Plasma Exchange, and Intravenous Immunoglobulin

The management of AAV should, whenever possible, be conducted within a multidisciplinary framework. In patients with renal failure, renal replacement therapies should be coordinated with a nephrologist, while in cases requiring respiratory support (including noninvasive or invasive mechanical ventilation), treatment and follow-up should be planned in collaboration with intensive care specialists.

Plasma exchange enables the rapid and effective removal of pathogenic inflammatory mediators, including ANCA and complement components.[33] In patients with AAV, plasma exchange has not been shown to provide a significant survival benefit. However, it may reduce the risk of developing ESRD in cases of severe renal involvement but is associated with an increased risk of serious infections.[31] Therefore, plasma exchange is not routinely recommended as part of the induction regimen for patients with AAV.[30]

Plasma exchange may be considered in patients with RPGN due to AAV (such as those with serum creatinine levels >3.4 mg/dL, requiring dialysis, or exhibiting a rapid rise in serum creatinine despite immunosuppressive therapy), as well as in patients with DAH accompanied by hypoxemia. In addition, plasma exchange should be considered an effective therapeutic option for patients with AAV who are positive for anti-GBM antibodies.[25] A personalized approach that takes into account individual patient characteristics, as well as clinical and histological parameters, plays a crucial role in determining the potential benefit of plasma exchange.[34]

Although IV immunoglobulin (IVIG) is not a routine component of standard therapy in AAV, it may provide a rapid improvement in disease activity and biomarker levels in certain patients.[35] The parameters to be considered when determining the indication for IVIG are summarized below.[27,30,36]

- Degree of hypogammaglobulinemia
- Presence of severe, persistent, unusual, or recurrent infections
- Demonstration of a poor antibody response to polysaccharide antigens
- Inadequate response to antibiotic prophylaxis
- Individual comorbidities (such as bronchiectasis, neutropenia, and long-term corticosteroid use or concurrent use of additional immunosuppressive agents)

In patients with refractory AAV who do not respond to remission induction therapy, IVIG may be considered at immunomodulatory doses (2 g/kg per course). During remission maintenance with RTX, IVIG replacement therapy (0.4 g/kg monthly) may be administered to patients who develop hypogammaglobulinemia [immunoglobulin G (IgG) <4 g/L] and experience recurrent severe infections.[30]

c. Maintenance Treatment and Approach to Relapses

The duration of maintenance therapy, initiated once disease activity is controlled, should be individualized based on disease severity, ANCA antibody profile, and organ involvement. In patients with GPA and MPA, maintenance therapy is generally recommended for 24-48 months after remission is achieved.[13,25] It should be emphasized that maintenance therapy should be prolonged in patients who experience relapse or are considered at high risk of relapse. The agents currently used for maintenance treatment are summarized in Table 2. Before initiating RTX for maintenance, serum IgG levels should be measured, and in cases of hypogammaglobulinemia (serum IgG <7 g/L), IgG concentrations should be reassessed after 2-4 weeks to re-evaluate the treatment decision.

Relapse is defined as the reappearance of clinical signs or symptoms of active vasculitis in any organ system following the achievement of partial or complete remission. Relapses are classified as major or minor. Major relapse denotes life-threatening or organ-threatening disease activity. Risk factors for relapse include the PR3-ANCA subtype, ENT involvement, elevated serum creatinine at diagnosis, and extensive systemic disease. Persistent ANCA positivity, rising ANCA titers, or seroconversion from negative to positive may serve as partial predictors of future relapse, although their prognostic value remains limited.[25] Renal relapse is defined by the recurrence or worsening of glomerular inflammation, manifesting as increased hematuria, active urinary sediment, and/or new-onset impairment of renal function. Although disease flares most frequently occur in the organ initially affected, involvement of new organs is not uncommon. In cases where the diagnosis of recurrent vasculitis is uncertain, a tissue biopsy may be warranted to confirm disease reactivation and exclude alternative causes of renal dysfunction.[37,38]

Relapses generally respond to immunosuppressive therapy. In cases of severe relapse, treatment should follow a standard induction therapy protocol. In non-severe relapses, the dose of the current immunosuppressive agent may be increased, and CYC should be considered a second-line option.[25] During relapse, treatment choice should be guided by the previous induction and maintenance regimens. CYC may be administered to patients who relapse while receiving RTX, whereas RTX may be used in those who relapse during CYC therapy—both in combination with glucocorticoids. RTX is generally preferred as the first-line treatment option for relapsing disease.[13] Evidence regarding the efficacy of RTX in patients with serum creatinine levels exceeding 4.0 mg/dL remains limited. For patients receiving maintenance RTX therapy, a repeat course may be considered if 4-6 months have elapsed since the previous infusion.[30]

d. Treatment Approaches in Specific Clinical Conditions

In the management of sinonasal involvement in AAV, culture-directed systemic antibiotics and topical antibiotic irrigations, in conjunction with immunosuppressive therapy, are effective in controlling infection and relieving symptoms. High-volume saline irrigations are a valuable adjunct for reducing nasal obstruction and mucopurulent discharge by enhancing mucociliary clearance. In patients with a septal perforation, septal obturators may be used to alleviate crusting and airflow-related symptoms. Rhinoplasty may be considered for patients with saddle-nose deformity or septal perforation once sustained remission has been achieved.

The primary therapeutic objective in tracheal or subglottic stenosis is to prevent progression through early diagnosis and timely initiation of immunosuppressive therapy, thereby reducing the need for surgical intervention. In early or mild SGS, inhaled glucocorticoids and topical anti-inflammatory therapies may be sufficient to control local inflammation. When mechanical airway obstruction results from fibrotic scarring, interventional procedures such as laser ablation, intralesional corticosteroid injection, cryotherapy, balloon dilation, or surgical reconstruction may be required to restore airway patency.[6]

The efficacy of antifibrotic agents, such as nintedanib and pirfenidone, in AAV with interstitial pulmonary fibrosis remains uncertain. Therapeutic management is particularly challenging and controversial in patients with MPO-ANCA positivity and ILD exhibiting a UIP pattern, due to the limited availability of robust evidence.[39] According to the most recent international guideline on the management of progressive pulmonary fibrosis (PPF), antifibrotic therapy is recommended for PPF secondary to autoimmune ILD, including vasculitis-related forms. In this setting, nintedanib is recommended as the first-line antifibrotic agent.[40] Pirfenidone is considered a second-line option due to limited supporting evidence for its use.[41]

Asthma management in patients with EGPA should be maintained at the appropriate step based on disease severity and level of asthma control. At no stage of therapy should bronchodilators be used as monotherapy; ICSs must always be combined with bronchodilators. Patients should undergo monthly monitoring until adequate asthma control is achieved, then attend follow-up visits every 3-6 months.[42,43]

In patients with EGPA whose vasculitic manifestations are in remission, persistent exacerbations or uncontrolled asthma, despite optimized therapy with high-dose ICSs plus long-acting β_2-agonists, should prompt evaluation for biologic therapy targeting interleukin-5 (IL-5) or its receptor (IL-5Rα) for the management of severe eosinophilic asthma. Mepolizumab has been approved by both the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of EGPA at a dose of 300 mg every four weeks. However, observational studies have demonstrated that a 100 mg dose administered every four weeks may also be effective in patients with FFS=0 and without major organ involvement, particularly in those with predominant respiratory manifestations.[44-46] Therefore, in such patients, it is recommended to initiate mepolizumab at a dose of 100 mg every four weeks, with dose escalation to 300 mg if an adequate clinical response is not achieved by week 16. For patients with life-threatening or organ-threatening manifestations, maintenance therapy with mepolizumab at 300 mg every four weeks is recommended. For EGPA patients who are refractory to mepolizumab, benralizumab may be considered an alternative biologic therapy. In Türkiye, the use of benralizumab for EGPA currently requires an application for off-label use.

The management of AAV-associated neuropathy requires a multidisciplinary approach. For residual neuropathic pain, pharmacologic treatments such as gabapentinoids, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and sodium channel blockers may be used in collaboration with neurologists. Given that peripheral neuropathy can substantially impair quality of life, psychosocial support and patient education should be prioritized. During rehabilitation, involvement of physical and occupational therapists may provide functional benefits. In patients with motor deficits, such as foot drop, the use of lower-extremity orthoses may be required to improve mobility and prevent secondary complications.

e. Discontinuation of Therapy During Follow-up

In patients who remain dialysis-dependent for more than three months despite appropriate treatment and have not recovered renal function, reduction or discontinuation of immunosuppressive therapy should be considered, provided there are no indications for continued treatment due to extra-renal disease activity. The risk of relapse in patients on chronic dialysis is significantly lower than during the pre-dialysis period, although relapses may still occur. Conversely, among patients requiring chronic dialysis due to AAV, infections represent the leading cause of death, with a markedly increased incidence of severe infectious complications. Overall, patients who develop ESRD exhibit poorer survival outcomes compared with those who maintain renal function.[11,47-49]

Patients with GPA or MPA who progress to stage 5 chronic kidney disease should be evaluated for kidney transplantation. Candidates are required to be in complete clinical remission for 6-12 months before transplantation. Although persistent ANCA positivity at the time of transplantation is not, in itself, a contraindication, each patient should be individually assessed for residual disease activity. In the post-transplant period, the overall risk of relapse is low, and vasculitis recurrence in the renal allograft is rare. However, patients should continue to be monitored for extra-renal relapses. Following transplantation, both patient and graft survival are comparable to those in recipients transplanted for other causes, whereas overall patient survival is significantly improved compared with those maintained on dialysis.[50,51]

f. Prevention of Morbidity and Complications

In patients with AAV receiving RTX, CYC, and/or high-dose glucocorticoids, prophylaxis with trimethoprim–sulfamethoxazole (400/80 mg daily or 800/160 mg three times per week) is recommended to prevent *Pneumocystis jirovecii* pneumonia and other opportunistic infections.[52] In addition, appropriate vaccinations should be administered in accordance with national and international immunization guidelines to reduce the risk of infection.[53,54]

To minimize corticosteroid-related complications in patients with AAV, steroids should be used at the lowest effective dose and for the shortest possible duration. Regular monitoring of blood glucose, lipid profile, and blood pressure, along with bone mineral density screening to assess osteoporosis risk, is recommended.[55] In addition, supplementation with calcium (1000-1200 mg/day) and vitamin D (800-1500 IU/day) is recommended for patients receiving corticosteroids at any dose for ≥3 months.[56]

Patient Education, Pregnancy Planning, and Management of Surgical Needs

Patients should be thoroughly informed about AAV, including its impact, prognosis, warning symptoms, and the potential effects and complications of therapy. Key points to consider in the education of patients with AAV are as follows:

a. Patients should be informed about the course of the disease, the treatment process, and warning signs or symptoms that may indicate disease activity.

b. Among women of reproductive age, the need for contraception with certain medications used in treatment, the risks of premature menopause or infertility, and potential contraindications related to pregnancy and breastfeeding should be identified, and patients should be counselled appropriately.

c. Vaccination recommendations and plans for infection prevention should be implemented.

d. Patients should be educated about the possible side effects of corticosteroid therapy, the importance of treatment adherence, and necessary dietary and lifestyle modifications.[20]

Pregnancy is considered an independent risk factor for AAV flare, and pregnancies in women with AAV should be regarded as high-risk. If vasculitis develops during pregnancy or pregnancy occurs while a patient is receiving treatment for vasculitis, multidisciplinary collaboration among rheumatologists, perinatologists, and obstetricians is required to improve maternal and fetal outcomes, guide treatment, and ensure appropriate postpartum follow-up.[57] During pregnancy, the use of medications such as MTX, leflunomide, MMF, and CYC is contraindicated. These agents should be discontinued 3-6 months before conception. If disease activity persists during pregnancy, treatment options such as corticosteroids, AZA, and IVIG may be used. In life-threatening situations, plasma exchange, RTX, or CYC may be considered.[58]

In patients with AAV, urgent or elective surgical interventions may be performed, either alone or in combination with

immunosuppressive therapy, depending on disease activity and the patients' clinical condition. In elective cases, surgical intervention is recommended after remission has been sustained for 6-12 months.[59]

In conclusion, interdisciplinary collaboration is of paramount importance in the management of AAV, a multisystem disorder that may involve multiple organs and tissues across diverse medical specialties. This guideline was developed by consensus of experts in rheumatology, nephrology, pulmonology, allergy and clinical immunology, otorhinolaryngology, and hematology appointed by the Executive Board of the Turkish Society for Rheumatology. Additional recommendations have been formulated to address the different stages of disease management, from diagnosis to long-term follow-up. It is our sincere expectation that this guideline will advance clinical practice and enhance patient care for individuals with AAV throughout Türkiye.

Footnotes

Author Contributions

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Management of ANCA-associated vasculitis: Recommendations of the Turkish Society for Rheumatology	
General principles	
A	Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are heterogeneous diseases that may present with variable clinical features and be life- or organ-threatening. Therefore, management should be provided by a multidisciplinary team at centers experienced in vasculitis or at clinics with access to such centers.
B	The broad clinical spectrum of AAV highlights the need for educational meetings to enhance physicians' awareness of the disease. In addition, meetings that promote collaboration among specialities would help optimize disease management.
C	Patients diagnosed with AAV should be informed about the possible course of the disease, the treatment process, and warning signs or symptoms that may indicate disease activity.
D	Patients should be periodically screened for treatment-related adverse effects and comorbidities, including hypertension, osteoporosis, and cardiovascular diseases, and be advised on appropriate lifestyle modifications.
Recommendations	
1	In patients with symptoms and/or findings suggestive of AAV, both PR3-ANCA and myeloperoxidase-ANCA tests are recommended as the primary diagnostic approach, using high-quality antigen-specific assays.
2	Tissue biopsy, particularly from the kidney or lung, is the gold standard for the diagnosis of AAV. However, when biopsy cannot be performed or there is strong clinical suspicion of vasculitis before biopsy results are available, immunosuppressive therapy should not be delayed.
3	In patients with AAV, inflammatory markers and a structured clinical assessment tool [Birmingham Vasculitis Activity Score version 3 (BVAS v3)] are recommended for evaluating disease activity at diagnosis and during follow-up.
4	In life- or organ-threatening manifestations (such as glomerulonephritis, diffuse alveolar hemorrhage, tracheal or subglottic stenosis, meningeal involvement, central nervous system involvement, retro-orbital disease, cardiac involvement, mesenteric involvement, or mononeuritis multiplex), remission induction therapy with glucocorticoids in combination with either cyclophosphamide (CYC) or rituximab (RTX) is recommended.
5	In life- or organ-threatening situations, pulse glucocorticoid therapy may be administered. The initial oral glucocorticoid dose should be adjusted according to the severity of the clinical condition. During long-term corticosteroid use, a reduced-dose regimen is preferred whenever clinically feasible.
6	Other AAV manifestations, such as pulmonary nodules or localized upper respiratory tract involvement, should be treated with oral glucocorticoids in combination with methotrexate (MTX). Alternatively, mycophenolate mofetil (MMF), azathioprine, or rituximab (RTX) may be considered.
7	Plasma exchange is not routinely recommended as part of the induction regimen. It may be considered in patients with rapidly progressive glomerulonephritis (serum creatinine >3.4 mg/dL, requiring dialysis, or with rapidly rising serum creatinine despite immunosuppressive therapy) and/or in those with diffuse alveolar hemorrhage accompanied by hypoxemia.
8	In cases of refractory disease or relapse, referral of patients to centers with expertise in vasculitis may be considered.
9	Pulmonary exacerbations in eosinophilic granulomatosis with polyangiitis (EGPA) should be evaluated in collaboration with pulmonologists or allergy–immunology specialists and managed with a regimen containing an inhaled corticosteroid (ICS) to ensure adequate asthma control.
10	Patients with EGPA who have uncontrolled asthma (persistent exacerbations despite high-dose ICS plus long-acting β-agonist therapy) should be evaluated for treatment with anti–interleukin-5 (IL-5) (mepolizumab) or anti–IL-5Rα (benralizumab).
11	MTX, MMF, azathioprine, or RTX can be used as maintenance therapy in patients with AAV. Fewer relapses have been reported with RTX than with azathioprine. The duration of maintenance therapy may range from 24 to 48 months, depending on the patient's clinical condition.
12	In patients receiving RTX, CYC, and/or high-dose glucocorticoids, prophylaxis with trimethoprim–sulfamethoxazole (400/80 mg daily or 800/160 mg three times per week) is recommended to prevent *Pneumocystis jirovecii* pneumonia. In addition, annual influenza and age-appropriate pneumococcal vaccinations should be administered.
13	Serum immunoglobulin levels should be measured before starting RTX, before each subsequent cycle during treatment, and for at least one year after discontinuation of RTX to monitor for secondary immunodeficiency associated with RTX therapy.
14	Intravenous immunoglobulin (IVIG) is not a routine component of AAV therapy. Its administration should be considered for patients with comorbidities such as bronchiectasis, unusual or recurrent infections, neutropenia, or hypogammaglobulinemia (IgG <4 g/L).

Supplementary Link: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/f798b210-b702-4979-98f8-a7557990577b.pdf