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Review article

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Challenges in the diagnosis, classification and prognosis of ANCA-associated vasculitis

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) encompasses three rare yet interrelated diseases: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Despite increasing recognition, the diagnosis of AAV remains challenging, even in specialized medical centres, owing to its clinical heterogeneity, overlap with mimicking conditions, and the variable performance of ANCA testing. The assessment of a patient suspected of AAV requires a timely synthesis of symptoms, physical examination, laboratory tests, histopathology and imaging data to substantiate the diagnosis, exclude alternative diagnoses, assess disease activity and extent, and enable rapid initiation of appropriate therapies. Classification is similarly complex, and evolving classification systems are based on clinical phenotype, ANCA specificity or a combination of both, each with implications for disease monitoring, therapeutic decisions and trial design. Assessing disease severity and predicting prognosis are fundamental but complicated by the diverse patterns of organ involvement, relapsing–remitting course and co-morbidities. Although validated tools exist for measuring disease activity, organ damage and prognosis, many limitations remain, particularly in identifying smouldering disease, irreversible damage and risk of relapse. Emerging therapies have improved outcomes, with recovery of kidney function, better overall survival and improved glucocorticoid-related toxicity, but patients with AAV continue to experience high risks of chronic morbidity and early mortality. This Review explores current challenges and opportunities in the diagnosis, classification and prognostic assessment of AAV, and outlines a structured framework to support personalized and outcome-focused care.

Sections

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Key points

- Diagnosing ANCA-associated vasculitis (AAV) can be challenging owing to the heterogeneity of the syndromes, the absence of a gold standard and criteria for diagnosis, and the overlapping features with other conditions.
- The development and revision of classification criteria for AAV have been essential for enhancing the accuracy and consistency of research studies.
- As research into the genetic and immunological basis of AAV progresses, classification criteria will continue to evolve, assisting patient stratification and personalized treatment.
- Although the standardized tools — BVAS, VDI and AAV-PRO — have improved our ability to assess disease activity, organ damage and patient quality of life, respectively, comprehensive measures that integrate all these factors remain to be developed.
- Improved disease stratification, combined with patient-centred approaches, will help to refine prognosis, to personalize treatment and ultimately to improve outcomes for patients with AAV.
- An integrated, multifaceted approach to assess AAV is essential for improving patient care, including understanding diagnostic tools, classifying disease severity and predicting outcomes based on a combination of factors.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of three related, rare, challenging and complex conditions with overlapping clinical presentations: granulomatosis with polyangiitis (GPA); microscopic polyangiitis (MPA); and eosinophilic granulomatosis with polyangiitis (EGPA). The outcome of systemic vasculitis has improved from an invariably fatal course to a chronic relapsing–remitting disorder, with survival rates close to 90% after remission-induction treatment[1–3]. Following the introduction of cyclophosphamide in the 1960s, the management of AAV progressed from optimizing glucocorticoid-based and other immune-suppressive regimens to targeted therapies, including rituximab, the complement C5a receptor inhibitor avacopan, for GPA and MPA[4–8], and interleukin-5 (IL-5) inhibition for EGPA[9,10]. Achieving remission, resolving acute life-threatening disease manifestations and markedly reducing the risk of organ damage is now possible for most people with AAV. The frequency of adverse outcomes, including death and end-stage kidney disease, is declining owing to earlier diagnosis and advances in therapy[11,12]. However, substantial mortality and morbidity associated with both the disease and treatment, and reduced life expectancy, remain a reality for many people with AAV[11].

Classification criteria for GPA and EGPA were initially developed by the American College of Rheumatology (ACR) in 1990, were updated in 2022 to include MPA, and improved standardization of patient recruitment for clinical trials[13–15]. Additionally, definitions of AAV were established through the Chapel Hill Consensus Conferences process in 1993 and updated in 2012 (ref. 15). However, these classification criteria and definitions are not designed for diagnosing AAV, and formal diagnostic criteria have not yet been established for AAV. Disease activity and extent in AAV has been quantified for clinical trials using various iterations of the Birmingham vasculitis activity score (BVAS). Organ damage resulting from initial vasculitic activity, disease relapse, adverse effects of treatment or other co-morbidities are captured using damage assessment instruments, including the vasculitis damage index (VDI) and the combined damage assessment (CDA). Finally, so-called generic patient-reported outcomes (PROs) have been studied and validated for use to assess the impact of AAV on physical, mental, and social well-being. A disease-specific PRO for AAV has been developed[16–18]. Consequently, a cohesive and integrated approach that combines the evaluation of the diagnosis, classification, severity, damage and PROs is strongly recommended when studying AAV[6,19].

Despite advances in the treatment of AAV and progresses made in disease classification and assessment, challenges remain in ensuring timely diagnosis, consistent disease assessment, and appropriate treatment stratification[20]. Existing classification criteria and disease activity scores have facilitated research and clinical decision-making, but their limitations — particularly in real-world settings — have become apparent. As precision medicine gains traction and clinical trials become increasingly tailored to patient subgroups, there is a pressing need to reassess how we define, measure and monitor AAV. Recent updates to classification criteria, emerging targeted therapies and a growing emphasis on precision medicine all call for accurate and adaptable tools for diagnosis, assessment and outcome measurement in AAV. Therefore, the field needs to critically examine the current tools used for classification and disease assessment, explore their clinical and research implications, and highlight opportunities for refinement to improve outcomes for patients with AAV.

This Review outlines an integrated approach to evaluation of AAV that considers diagnosis, classification, assessment of severity and prognosis. Discussions include ongoing challenges of diagnosing AAV in the absence of validated diagnostic criteria, followed by development and application of classification criteria and disease definitions. Furthermore, we review current tools for assessing disease activity, organ damage, and patient-reported outcomes, and their utility in both clinical practice and research. Finally, we highlight emerging opportunities to refine these instruments in the context of precision medicine, with the goal of improving disease stratification, treatment individualization and long-term outcomes for individuals living with AAV.

Approach to AAV diagnosis

The frequent occurrence of nonspecific presenting signs and symptoms of AAV and the absence of established diagnostic criteria often result in delays in diagnosis and postponement of the start of treatment, both potentially leading to development of irreversible organ damage[21,22]. AAV symptoms might range from nonspecific constitutional features (such as malaise, fatigue, weight loss, fever, arthralgia and myalgia) to organ-related manifestations (such as pulmonary disease or neuropathy). Incidentally discovered findings such as impaired kidney function, urinary findings suggestive of glomerulonephritis, or radiographic abnormalities suggesting pulmonary disease also prompt evaluation for AAV in otherwise asymptomatic individuals. The diagnosis of AAV is based on a synthesis of data based on clinical presentation, radiographic testing, pathology, and laboratory tests[1,23] (Fig. 1 and Supplementary Fig. 1). Differences in organ manifestations, ANCA specificity, and the presence or absence of peripheral and tissue eosinophilia help to distinguish among the three subtypes of AAV.

The development of diagnostic criteria for AAV has been challenged by protean nature and heterogeneity of the disease combined with the absence of a gold standard. Ideally, such diagnostic criteria should be adaptable to the various clinical contexts, yet sufficiently broad to encompass many potential features and variations in disease severity, while achieving high levels of sensitivity and specificity[24]. This is complicated by the fact that individuals with AAV are often ANCA-negative, whereas common clinical features of AAV, such as constitutional symptoms, are not specific to vasculitis[24,25]. Potentially, deeper understanding of the pathogenesis of AAV, including genetic factors, cytokine profiles, mechanisms leading to loss of immune tolerance, and immune cell signatures associated with GPA, MPA or EGPA, might help to develop biomarkers with the potential to guide diagnostic criteria and improve diagnostic accuracy.

Typical clinical manifestations of AAV subtypes

Disease manifestations, ANCA specificity and histopathology largely overlap among the three subtypes of AAV. However, a large amount of medical literature in the AAV spectrum support clinical use of the three disease subtypes.

Granulomatosis with polyangiitis. Granulomatosis with polyangiitis (GPA) is a small-vessel vasculitis that typically involves the upper and lower respiratory tract and presents with granulomatous inflammation. Common clinical manifestations include nasal crusting, epistaxis, sinusitis, otitis, conductive hearing loss and capillaritis with vasculitis, alveolar haemorrhage, and kidney involvement with glomerulonephritis[26] (Fig. 1a). In patients with severe ear, nose and throat (ENT) involvement, GPA leads to nasal septum perforation and saddle nose deformity. Orbital pseudotumors and subglottic stenosis are also highly suggestive of GPA[27,28]. Although GPA typically presents with upper respiratory tract involvement that is likely to progress to affect the lungs and kidneys, isolated involvement of the lungs is a common presentation[29–31]. The presence of proteinase 3 (PR3)-specific ANCA, is strongly associated with GPA. However, some individuals with GPA are ANCA-negative (10–50%), and the absence of ANCA might delay the diagnosis and is associated with chronic damage at the time of presentation[21,32–34].

Microscopic polyangiitis. Microscopic polyangiitis (MPA) is a small-vessel vasculitis often associated with myeloperoxidase (MPO)-specific ANCA and involves the kidney in 75–100% of cases, whereas clinical manifestations related to granulomatous inflammation such as lung nodules or retroorbital masses are absent as per the 2012 Chapel Hill Consensus Conference (CHCC) disease definition[35–37] (Table 1 and Fig. 1b). Lung involvement in MPA is likely to present in various ways, including pulmonary capillaritis with alveolar haemorrhage or as fibrotic parenchymal disease manifesting as interstitial lung disease[38,39].

Eosinophilic granulomatosis with polyangiitis. Eosinophilic granulomatosis with polyangiitis (EGPA) is a small-vessel vasculitis often accompanied by eosinophilic infiltration and granuloma formation (Fig. 1c). Clinically, EGPA typically presents with a prodromal phase marked by asthma and nasal polyposis, which often precede systemic manifestations by months or years[40]. Blood eosinophilia is consistently present[41] (Table 1). Although the disease is named for eosinophilic granulomatous inflammation, histological identification of eosinophilic granuloma is exceedingly rare.

Manifestations of EGPA can be broadly categorized into two groups: eosinophilic and vasculitic[40]. The eosinophilic manifestations include asthma, nasal polyposis, lung infiltrates and cardiac involvement, particularly myocarditis, which is common and potentially severe[42]. Pleuritis and pericarditis are also more common in EGPA than in GPA or MPA, although they are probably underdiagnosed[43]. The vasculitic features include peripheral nervous system involvement most often presenting with mononeuritis multiplex in 50–70% of patients. Mononeuritis multiplex typically causes sensory deficits, but motor symptoms might also occur. Nerve conduction studies show an axonal damage pattern in EGPA with mononeuritis multiplex, and the frequency of neuropathy is higher in EGPA than in GPA or MPA[44–46]. Kidney involvement is relatively uncommon in EGPA, but possible[47–49].

Stratification by ANCA status reveals distinct phenotypic patterns in EGPA. Positive MPO-ANCA, found in approximately 40% of patients with EGPA, is frequently associated with vasculitic features, such as neuropathy and glomerulonephritis, whereas ANCA-negative EGPA is usually associated with eosinophilic manifestations, including cardiomyopathy and lung infiltrates[47–51]. These clinical differences are supported by genetic studies, which have linked ANCA-positive and ANCA-negative EGPA with partially distinct susceptibility loci: gene variants associated with barrier dysfunction have been implicated in ANCA-negative disease and HLA polymorphisms have been identified in individuals with ANCA-positive EGPA[50,51]. However, both EGPA subsets share a genetic predisposition to eosinophilia and, rather than representing two distinct diseases, EGPA subsets are best understood as a spectrum of overlapping features[50,51].

Laboratory, serological, histopathology and imaging profiles

The inflammatory marker C-reactive protein and erythrocyte sedimentation rate are commonly increased in patients with active disease but are not specific for AAV. Assessment of ANCA titers aids in the diagnosis of AAV, particularly when clinical features are supportive, but their correlation with disease activity or severity remains inconsistent. Perinuclear ANCA and cytoplasmatic ANCA patterns in indirect immunofluorescence of blood samples are still used for ANCA detection and AAV diagnosis despite their low predictive value. ANCA-specificity testing, particularly for MPO and PR3, is crucial for diagnosing AAV and occasionally has a supportive role in predicting risk of relapse (Fig. 1). Current guidelines recommend using third-generation antigen-specificity tests to detect MPO-ANCA and PR3-ANCA, such as enzyme-linked immunosorbent assay (ELISA) or bead assays, which provide more reliable information and have higher specificity (91.4–95.6% and 96.8–98.3%, respectively) than previous generation assays or indirect immunofluorescence, decreasing the false-positive rates[52–54]. Furthermore, ANCA-specificity tests have improved correlation with disease phenotype, standardization, and reproducibility[52–54]. Positive MPO-ANCA has been frequently associated with interstitial lung disease and increased risk of progression from acute or chronic kidney injury to end-stage kidney disease, whereas positive PR3-ANCA has been associated with the presence of lung nodules, ENT involvement and acute kidney injury[55–58]. In terms of treatment response, patients with positive PR3-ANCA and patients with GPA tend to have a higher relapse risk than patients with positive MPO-ANCA or individuals with MPA[59–61].

In the absence of vasculitis, ANCA tests can be positive in patients with inflammatory bowel disease, malignancies, or infections; in infective endocarditis 8% of the patients test positive for ANCA[62] (Box 1). Moreover, manifestations of vasculitis and ANCA seropositivity might

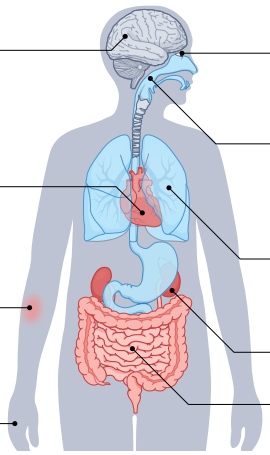
a Granulomatosis with polyangiitis

Central nervous system
Headache, stroke, intracranial haemorrhage
(0%–18%)

Heart
Pericarditis, pericardial effusion, cardiomyopathy, coronary artery disease, heart failure
(2%–15%)

Skin
Palpable purpura, livedo reticularis
(10%–50%)

Peripheral nervous system
Vasculitic neuropathy, mononeuritis multiplex
(14%–40%)



Eyes
Episcleritis, uveitis, optic neuropathy, nerve palsy, retinal vasculitis
(1%–9%)

Ear, nose, throat
Rhinosinusitis, chronic otitis media, sensorineural hearing loss, subglottic stenosis, saddle nose deformity after rhinosinuitis
(75%–99%)

Lungs
Nodules, cavities and pulmonary infilrates: alveolar haemorrhage and pleurisy
(62%–94%)

Kidneys
Acute kidney injury with pauci-immune necrotizing glomerulonephritis (38%–85%)

Gastrointestinal tract:
Abdominal pain, bleeding, diarrhoea, pancreatitis
(0%–7%)

Limited disease (often ANCA-negative)

- Necrotizing granulomatous inflammation usually involves the upper and lower respiratory tract
- Necrotizing vasculitis predominantly affects small to medium vessels
- Necrotizing glomerulonephritis is common

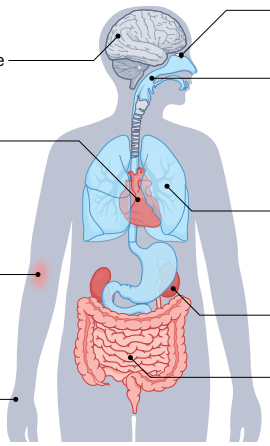
b Microscopic polyangiitis

Central nervous system
Headache, stroke, intracranial haemorrhage
(0%–18%)

Heart
Pericarditis, pericardial effusion, cardiomyopathy, coronary artery disease, heart failure
(2%–15%)

Skin
Palpable purpura, livedo reticularis, nodules, urticarial lesions
(30%–60%)

Peripheral nervous system
Vasculitic neuropathy, mononeuritis multiplex
(14%–40%)



Eyes
Episcleritis, uveitis, optic neuropathy, nerve palsy, retinal vasculitis
(1%–9%)

Ear, nose, throat
Non-granulomatous and non-erosive sinus inflammation, sensorineural hearing loss
(9%–30%)

Lungs
Diffuse alveolar haemorrhage, interstitial pneumonitis or pulmonary fibrosis
(25%–66%)

Kidneys
Acute kidney injury with pauci-immune necrotizing glomerulonephritis (75%–100%)

Gastrointestinal tract
Abdominal pain, bleeding, diarrhoea, abnormal liver tests, cholecystitis, appendicitis
(2%–56%)

- Necrotizing vasculitis predominantly affects small vessels (capillaries, venules or arterioles)
- Necrotizing glomerulonephritis is very common
- Pulmonary capillaritis is common

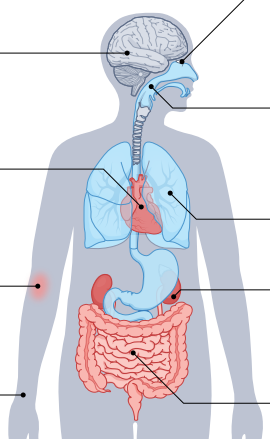
c Eosinophilic granulomatosis with polyangiitis

Central nervous system
Eosinophilia in cerebrospinal fluid, vasculitis, stroke, cranial nerve palsy, cognitive impairment (5%–15%)

Heart
Pericarditis, pericardial effusion, cardiomyopathy, coronary artery disease, heart failure, arrhythmia
(14%–58%)

Skin
Aseptic nodules, palpable purpura, livedo reticularis, urticarial lesions
(30%–69%)

Peripheral nervous system
Vasculitic neuropathy, mononeuritis multiplex
(50%–92%)



Eyes
Orbital granuloma, episcleritis, uveitis, optic neuropathy, nerve palsy, retinal vasculitis
(3%–11%)

Ear nose and throat
Allergic rhinitis, sinusitis, polyposis, otitis media, sensorineural hearing loss
(48%–98%)

Lungs
Asthma
(91%–100%)
Pulmonary infiltrates, pleural effusion, nodules/cavities
(61%–91%)

Kidneys
Interstitial nephritis, less severe pauci-immune necrotizing glomerulonephritis
(10%–27%)

Gastrointestinal tract
Organ perforation, mesenteric ischaemia, colitis
(6%–44%)

EGPA triad: asthma, nasal polyposis, eosinophilia

- Eosinophil-rich and necrotizing granulomatous inflammation involving the respiratory tract
- Necrotizing vasculitis predominantly affects small to medium vessels
- Associated with asthma and eosinophilia

Fig. 1 | Systematic approach to the diagnosis in ANCA-associated vasculitis. The initial assessment of a patient with suspected anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) requires a systematic approach to establish the degree of organ involvement, of which there are several common organ manifestations that present with differing frequencies. The most common manifestations are shaded blue for granulomatosis with polyangiitis (GPA) (**a**), shaded pink for microscopic polyangiitis (MPA) (**b**) and shaded purple for eosinophilic granulomatosis with polyangiitis (EGPA) (**c**). According to the signs and symptoms at AAV presentation, tests will be performed to ascertain the involvement of each probable organ affected. For instance, patients with respiratory tract involvement, particularly ear, nose and throat manifestations such as nasal crusting, epistaxis, sinusitis, otitis and hearing loss, are most likely to be diagnosed with GPA and are frequently evaluated by ear, nose and throat specialists who therefore perform specific ear, nose and throat-related investigations (**a**). By contrast, patients presenting with acute kidney injury are likely to be diagnosed with MPA, and a kidney biopsy will be performed early in the evaluation (**b**). Patients with EGPA frequently present with asthma and therefore pulmonary function tests are usually performed first (**c**). Life-threatening manifestations (yellow shading) involve capillaritis in GPA and MPA. Limited disease can be ANCA-negative in 10–50% of patients with GPA (**a**). As depicted, the heterogeneous clinical presentation of AAV and clinical syndromes hampers the establishment of a standardized first diagnostic evaluation of these patients.

occur in patients with other primary autoimmune diseases, including systemic sclerosis, Sjögren syndrome and rheumatoid arthritis[1,63–66].

A range of laboratory tests are essential to support diagnosis, assess organ involvement, and identify comorbid conditions prior to initiating treatment in AAV. Urinary findings, such as proteinuria, dysmorphic erythrocytes, or red blood cell casts, are indicative of glomerulonephritis. Anti-glomerular basement membrane antibodies are detected in about 6% of patients with AAV and glomerulonephritis[67], and support dual diagnoses of AAV and anti-glomerular basement membrane disease. Troponins and B-type natriuretic peptide can be useful biomarkers when there is suspected cardiac involvement, particularly in EGPA, although not specific to vasculitis-associated disease[68]. Screening for hepatitis B, hepatitis C and human immunodeficiency virus (HIV), as well as other infectious diseases (as, for example, tuberculosis, schistosomiasis and strongyloidiasis in endemic areas) is recommended prior to starting treatment[1,69,70].

Histological findings of vasculitis have been useful in AAV diagnosis and in developing disease definitions and classification. In suspected kidney involvement, biopsy can confirm the hallmark finding of AAV-associated glomerulonephritis (AAV-GN) — that is necrotizing and crescentic glomerulonephritis with absence or minimal presence of immune deposits affecting small vessels, including glomeruli[15,58] — but also permits exclusion of other causes of kidney diseases, such as drug toxicity, IgA vasculitis, or cryoglobulinaemia. Kidney biopsy, as performed in experienced centres, has a high diagnostic yield (sensitivity ≥99%) and is particularly important when patients test negative for PR3-ANCA or MPO-ANCA or when there are doubts about the diagnosis[1]. Furthermore, kidney histology is an important predictor of long-term kidney function in AAV[71]. By contrast, nasal and sinus biopsies have a low diagnostic yield (sensitivity 28–37%) for vasculitis or granuloma[72]. Transbronchial biopsies in GPA also have limited diagnostic value (sensitivity <50%), and are typically used to exclude infection or malignancy[73]. Electromyography might be helpful in mapping any affected nerves and muscles. Nerve and muscle biopsies (as, for example, biopsies of the superficial peroneal nerve) show 60–75% sensitivity for vasculitic neuropathy, which most frequently occurs in patients with EGPA. However, nerve biopsies might lead to sensory impairment, usually mild[74,75]. Skin biopsies, though nonspecific for the type of vasculitis, can support the presence of vasculitis in a patient with suspected AAV.

Imaging is used to assess organ involvement in AAV and is performed based on clinical symptoms or as part of a systematic disease evaluation protocol. Non-contrast high-resolution computed tomography should be considered a routine test to evaluate suspected lung involvement[76,77]. In some cases, chest imaging is also useful in distinguishing between AAV subtypes, as certain lung lesions, such as honeycombing and peripheral reticulation, are often associated with MPO-ANCA positivity, whereas nodular opacities are seen frequently when PR3-ANCA is detectable[55,78]. Furthermore, pulmonary function tests with bronchodilation are mandatory in patients with EGPA who present with asthma. For potential cardiac involvement, a step-up approach starting with an electrocardiogram, followed by echocardiography, and cardiac magnetic resonance imaging, is used to increase the detection rate of cardiac involvement, particularly in EGPA[79].

Differential diagnosis and mimickers of ANCA-associated vasculitis

Other diseases associated with ANCA positivity, such as non-AAV vasculitides, autoimmune diseases[80,81], secondary vasculitis, or mimics of vasculitis[1,62,82] (Box 1), need to be excluded before classifying a patient with GPA, MPA or EGPA. In essence, a broad differential diagnosis exists for most organ manifestations of AAV.

For instance, acute kidney injury with haematuria and proteinuria might be present in several glomerular diseases such as anti-glomerular basement membrane disease, lupus nephritis, IgA nephropathy, cryoglobulinaemic glomerulonephritis, and drug-induced interstitial nephritis[83,84]. In the differential diagnosis of AAV with lung nodules, pulmonary infiltrates or alveolar haemorrhage, conditions such as infections (such as bacterial pneumonia, tuberculosis and fungal infections), malignancy (including primary lung cancer and metastatic disease), other vasculitides (such as anti-glomerular-basement-membrane disease or Behçet's disease), sarcoidosis, pulmonary embolism and drug-induced pneumonitis must be considered. Diagnosing EGPA remains challenging as many conditions share the features of asthma, eosinophilia and pulmonary infiltrates: hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis, parasitic infections, drug reactions, and idiopathic eosinophilic pneumonia. In the absence of ANCA, distinction between these differential diagnoses and EGPA can be difficult[40]. In such cases, the presence of both eosinophilic and vasculitic features — such as peripheral neuropathy, purpura or biopsy-proven vasculitis — is required for establishing the diagnosis of EGPA.

Classification criteria

Classification criteria are essential for defining homogeneous patient groups for enrolment into clinical studies, ensuring that cohorts are uniform and comparable across studies and geographical regions[24]. The 2022 revision of the classification criteria for AAV was prompted by several key factors, including the recognition of the problems with the performance of the 1990 ACR criteria, the increasing contribution of ANCA testing to diagnosis, and advancement in imaging techniques[85–90].

Table 1 | Domains of ANCA-associated vasculitis and associated assessment tool scores

Index	Description	Domains
Disease activity		
BVAS/GPA (2001)[106]	List of items that typically occur in patients with active GPA, providing an overall measure of disease activity using a score from 0 to 68	Organ involvement (general; cutaneous; mucous membranes and eyes; ENT; cardiovascular; gastrointestinal; pulmonary; renal; nervous system) major versus minor disease manifestationsa; new or deteriorated disease within the previous 28 days versus persistent disease; disease status (severe disease or flare[b]; limited disease or flare[c]; persistent disease or flare[d]; remission[e]); physician's global assessment[f] (only in BVAS/GPA)
BVAS V3.0 (2009)[107]	List of items that typically occur in patients with active systemic vasculitis, providing an overall measure of disease activity using a score from 0 to 63	
Damage		
VDI (1997)[113]	The VDI is used to score damage that has been accrued since the onset of vasculitis using a score from 0 to 64 (each item scores 1). Comorbidities present before developing vasculitis should not be scored. The score can either increase or remain the same over time	Organ damage (musculoskeletal; skin or mucous membranes; ocular; ENT; pulmonary; cardiovascular; peripheral vascular disease; gastrointestinal; renal; neuropsychiatric; other)
CDA (2007)[114]	The CDA has 135 individual items in 17 categories and includes some bilaterality for items involving the eyes and ears; 8 items assign gradation. The CDA tool has been developed to improve the description of damage to provide more detail and to consider the possibility of reversibility of some damaged items	Organ damage (musculoskeletal; skin or mucous membranes; ocular; ear; nose; sinuses; subglottic stenosis; pulmonary; cardiac; vascular disease; gastrointestinal; renal; neurologic; psychiatric; endocrine; haematology or oncology; other)
Patient-reported outcomes		
ANCA-associated vasculitis PROs (2017)[16]	Questionnaire composed of 29 items. Each item has 5 answers scored from 0 to 4 (the higher the score, the higher the severity) distributed in 6 domains using a score from 0 to 600	Organ-specific symptoms; systemic symptoms; treatment side effects; physical function; social and emotional impact; concerns about the future
PROs Measurement Information System (PROMIS)[126]	A set of person-centred measures that evaluates and monitors physical, mental and social health in adults and children; it can be used with the general population and with individuals living with chronic conditions	Standardized measures of health status, including pain (intensity, interference), fatigue, emotional distress (depression, anxiety), physical function, sleep disturbance, social roles, cognitive function, and global health
Short Form 36 (SF-36)[127]	A 36-item, patient-reported survey of patient health. The SF-36 is usually used in health economics as a variable in the quality-adjusted life year calculation to determine the cost-effectiveness of a health treatment. The SF-36 is also often utilized in health psychology research to examine the burden of disease The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score the more disability	Assesses health-related quality of life across eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health

AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; BVAS, Birmingham vasculitis activity score; CDA, combined damage assessment; ENT, ear, nose and throat; GPA, granulomatosis with polyangiitis; PRO, patient-reported outcomes; VDI, vasculitis damage index. Disease activity denotes the spectrum of clinical manifestations, which may range from acute and severe episodes to persistent, insidious symptoms; Damage denotes the resultant tissue damage that can induce chronic signs and symptoms reminiscent of active disease, although not necessarily attributable to ongoing inflammatory activity. Patient-reported outcome encompass the overall effect of the disease on physical, social, and psychological domains, including quality of life and employment. [a]Major disease manifestations were those that constitute an immediate threat to the patient's life or to the function of a vital organ (urinary red blood cell casts, pulmonary haemorrhage, and mononeuritis multiplex); minor items do not constitute immediate threats to vital organs or patients' lives and would normally be managed as limited GPA. [b]Severe disease/flare: occurrence of any new/worse item that is major. [c]Limited disease/flare: any new/worse item that is minor. [d]Persistent disease: presence of 1 item representing active disease that has continued since the patient's previous evaluation. [e]Remission: no active disease; that is, no new/worse and no persistent items present. [f]The degree of GPA disease activity within the 28 days prior to the evaluation by marking a vertical line on the 10-cm visual analogue scale.

Classification by clinical subtypes versus ANCA specificity

A debate exists regarding whether to categorize patients with AAV based on clinical disease (GPA, MPA, and EGPA) or based on ANCA specificity (PR3-ANCA versus MPO-ANCA)[91] (Fig. 2). Studies show that patients with positive PR3-ANCA might have different responses to treatment, relapse rates, and long-term outcomes compared with patients that test positive for MPO-ANCA[61,92–98]. Research also highlights that the genetic distinctions among patients with AAV are more closely aligned with ANCA serotype than with clinical or histopathological features[99]. In EGPA, clinical and genetic studies found differences between MPO-ANCA-positive and ANCA-negative individuals, in both clinical features and gene variants that are associated with ANCA status, and this further enhances differences in pathogenesis with implications for patient classification[50,100,101]. Classifying AAV using both clinical disease name and ANCA specificity might better reflect the phenotypic spectrum of AAV[36,97,102]. Observational studies and post hoc analyses have shown that such an approach enhances prognostic accuracy, enables tailored treatment strategies, and helps to improve disease monitoring. However, large-scale prospective studies are lacking, constituting a barrier to adoption of this type of classification. These challenges underline the limitations of relying solely on ANCA positivity, especially given the lack of assay standardization and the presence of ANCA-negative patients with AAV.

Current classification criteria

The 2022 ACR–European Alliance of Associations for Rheumatology (EULAR) criteria have improved sensitivity and specificity for distinguishing AAV from other similar forms of vasculitis when a diagnosis of small- or medium-vessel vasculitis has been made. These criteria also incorporate ANCA specificity (PR3-ANCA and MPO-ANCA) and provide a reliable framework for classifying patients based on both clinical presentation and laboratory results[103] (Box 2). Consequently, patients

can be classified as having GPA in the absence of any granulomatous inflammation (for instance a patient with isolated pauci-immune glomerulonephritis and PR3-ANCA), or as having MPA despite the presence of granulomatous inflammation (for instance a patient with lung nodules and MPO-ANCA)[104]. This is natural because classification criteria are based on a probabilistic scoring that integrates various scenarios and combinations in the context of overlapping clinical and pathological features, a context that is frequent in AAV. The applicability of these criteria might differ across the various ethnic backgrounds. Therefore, the 2022 ACR–EULAR criteria might require additional validation, particularly in populations under-represented in the derivation process research, such as those originating from Africa, Latin America and Asia[103]. Importantly, neither the 2022 ACR–EULAR classification criteria, nor the 2012 CHCC definitions are appropriate for use as diagnostic criteria.

Assessment of disease activity, damage and health-related quality of life

Outcome Measures in Rheumatology (OMERACT) developed a core set of outcome domains and matching instruments for use in clinical trials in AAV[19]. This set includes the domains of disease activity, disease damage, PROs and mortality[19]. The clinical evaluation of disease activity in AAV is complex, given the variable clinical manifestations and involvement of multiple organ systems[105]. There is no consensus on how to grade severity of presentations of AAV, with several proposed systems that have not gained universal approval. The 2022 EULAR recommendations for the management of AAV avoided use of the word 'severe' and referred to disease activity that was, or was not, directly threatening organ function[5]. However, the outcome of a presumably non-life-threatening manifestation is hard to predict and might still contribute to accumulation of organ damage in an individual. The term 'severe' was adopted by the US Food and Drug Administration agency for the approval of avacopan for GPA and MPA. Thus, a comprehensive definition of disease extent and severity in AAV, incorporating BVAS, damage assessment and PROs, would improve patient stratification, risk assessment and the evaluation of treatment responses and outcomes (remission and relapse).

Disease activity in ANCA-associated vasculitis

The BVAS has been widely used to assess disease activity and severity in clinical research in AAV. Several versions of BVAS have been developed for clinical trials. Items are scored only if judged to stem from active disease, with new or worsening symptoms over the preceding

Box 1 | Main differential diagnoses of ANCA-associated vasculitis and diseases associated with ANCA seropositivity

Other small/medium vessel vasculitides: monogenic autoinflammatory diseases; inborn errors associated with anti-neutrophil cytoplasmic antibody (ANCA) positivity; polyarteritis nodosa; and Behçet's disease.

Non-vasculitic systemic rheumatic diseases: systemic lupus erythematosus; sarcoidosis; rheumatoid arthritis; Sjögren's disease; inflammatory myopathies; juvenile chronic arthritis; reactive arthritis; relapsing polychondritis; systemic sclerosis; and antiphospholipid syndrome.

Anti-glomerular-basement-membrane disease: dual positivity of AAV and anti-glomerular basement membrane disease is common; present in 6% of patients with AAV and 30–40% of patients with anti-glomerular basement membrane disease.

Other concurrent glomerular diseases: membranous nephropathy; lupus nephritis; IgA nephropathy; cryoglobulinaemia; and bacterial infection-related glomerulonephritis.

Interstitial nephritis: may be seen when the vasculitis involves the renal medulla.

Drug-induced ANCA-associated vasculitis (AAV): usually occurring within the first year of exposure to the causal agent(s), more likely to affect women than men and individuals who test positive for multiple autoantibodies, including ANCA; mostly specific to myeloperoxidase (MPO), anti-nuclear antibodies and anti-histone antibodies. The most common agents associated with drug-induced AAV are hydralazine, propylthiouracil, thiamazole and carbimazole. Vasculitis occurs in only a minority of the patients.

- **Cocaine-induced AAV:** can lead to midline destructive lesions of the face with a high incidence of nasal septal perforation or oronasal fistulae; systemic involvement is rare in cocaine-induced GPA, but when it occurs, patients may test positive for proteinase-3 (PR3)-specific ANCA
- **Cocaine+levamisole-induced AAV:** skin lesions predominate and both PR3- and MPO-ANCA can be present

Autoimmune gastrointestinal disorders: inflammatory bowel diseases are often associated with positive cytoplasmic ANCA (up to 40%).

Infection: differentiating infective endocarditis from AAV can be particularly challenging, because 8% of these patients test positive for PR3-ANCA, sometimes with high ANCA titres. Other infections (such as bacterial pneumonia, tuberculosis, allergic bronchopulmonary aspergillosis and parasitic infections) might be considered in the appropriate context (for example, in the presence of lung nodules or suspected eosinophilic granulomatosis with polyangiitis, EGPA).

Malignancy: primary lung cancer; metastatic disease; lymphoma; leukaemia; myeloproliferative and myelodysplastic disorders; and hypereosinophilic syndromes.

Cystic fibrosis: non-MPO perinuclear ANCA are common in patients with cystic fibrosis, particularly among those with bacterial airway infections. The ANCA is directed against bactericidal/permeability-increasing protein (BPI), with a strong association with *Pseudomonas aeruginosa* infection and colonization.

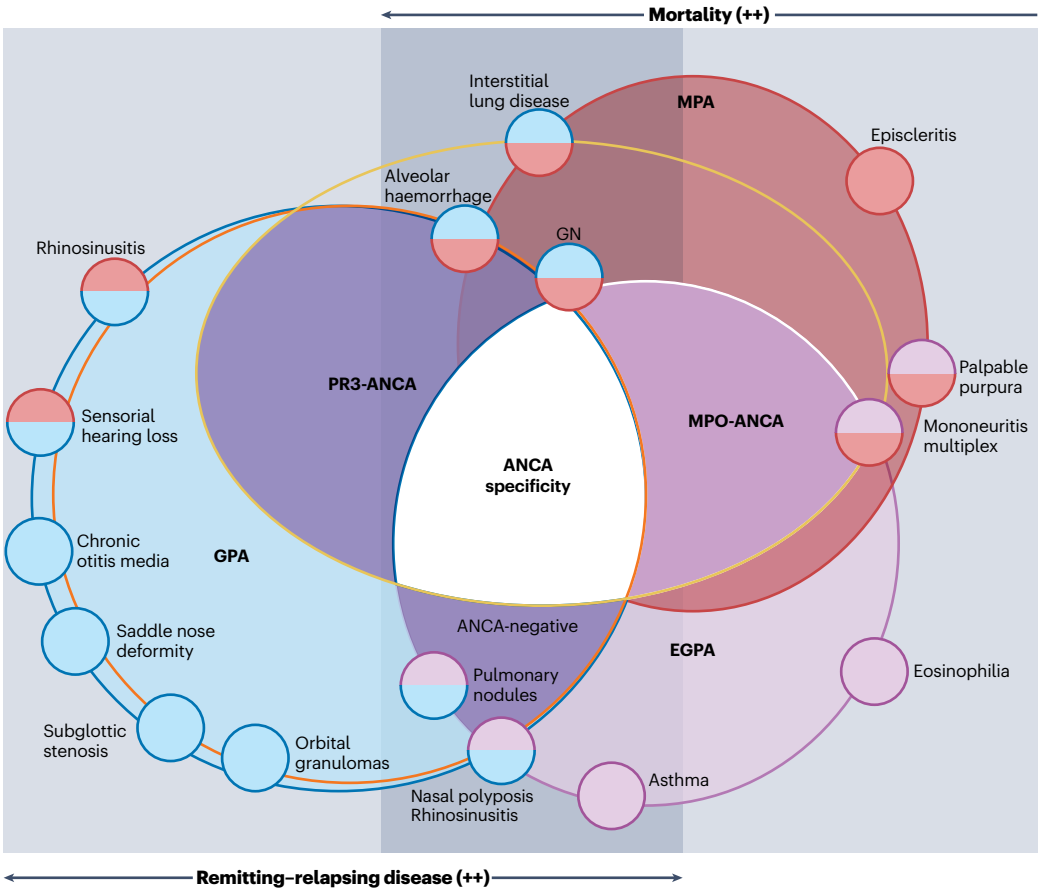


Fig. 2 | Classification by clinical presentation versus autoantibody specificity in ANCA-associated vasculitis. Classification criteria were developed to recruit individuals with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) into clinical trials and other clinical research studies based on specific disease phenotypes so that homogeneous study cohorts can be ensured. There is an ongoing debate on whether patients with AAV should be classified according to their clinical presentation, as in previous practice, or according to antigen specificity of anti-neutrophil cytoplasmic antibody (ANCA). ANCAs are usually specific against proteinase 3 (PR3) or myeloperoxidase (MPO). The initial concept of eosinophilic granulomatosis with polyangiitis (EGPA; shown in purple), granulomatosis with polyangiitis (GPA; shown in blue) and microscopic polyangiitis (MPA; shown in red) under AAV recognized their overlapping clinical and histopathological characteristics, as well as their strong association with positive ANCA serology. The central challenge in developing classification criteria lies in the clinical and biological heterogeneity of AAV. Patients often present with overlapping AAV syndromes and variable ANCA status (PR3-ANCA, MPO-ANCA or ANCA-negative). For example, clinical manifestations typical of GPA almost always overlap with PR3-ANCA or ANCA-negative (outlined by orange circle). By contrast, clinical manifestations of MPA overlap less perfectly with MPO-ANCA and are more heterogeneous (outlined by yellow oval). These overlaps complicate clear distinctions between syndromes and contribute to difficulties in classification. Mortality increases when capillaritis develops, occurring as a relapse of the disease in some patients (darker grey area). Over the years, the importance of ANCA specificity has been highlighted, and now they are included in the classification criteria. ANCA-specificity provides additional prognostic and pathogenic insights. AAV is a relapsing–remitting disease and patients with GPA and PR3-ANCA positivity are at a particularly high risk of relapse, whereas severity of the presentation and mortality are higher in patients with MPA and MPO-ANCA. This highlights the importance of patient phenotype for prediction of prognosis. Integrating both clinical features and ANCA specificity allows for objective and reproducible classification of AAV, advancing research consistency and enabling more accurate patient stratification in clinical trials. GN, glomerulonephritis.

4 weeks contributing to the score[106]. Symptoms that occurred in the past 1–3 months are mentioned but not scored, unless they are still active[106]. BVAS version 3 (BVAS V3.0), provides a score from 0 to 63 based on common manifestations of active vasculitis. The BVAS-GPA, a revised version of BVAS V2 used in several trials of GPA and MPA, distinguishes between major manifestations, which threaten vital organ function, and minor manifestations, which are less severe[107] (Table 1). Major manifestations are assigned 3 points, whereas minor ones are given 1 point, reflecting clinical severity. Across the BVAS versions, weighting of items is based on expert opinion and total scores are not generalizable. High BVAS scores at presentation correlate with poor prognosis, and during follow-up, worsening or new symptoms often lead to escalation of treatment[19,106–109]. However, the BVAS system is almost always used in trials in a dichotomous manner to distinguish

active disease (score ≥1) from remission (score 0), with no reliable manner of scoring intermediate disease states or responses. Nevertheless, BVAS has been a useful tool in the conduct of clinical trials that led to changes in practice.

The BVAS system has several drawbacks, including its subjectivity and variability in clinical assessments, and its limited sensitivity to chronic damage or mild disease. BVAS also lacks any PRO measures. Therefore, combining BVAS with other tools, such as novel biomarkers, damage indexes and PROs, might mitigate some of these limitations and better characterize disease activity and severity (Fig. 3). The limitations of BVAS in accurately estimating disease severity are particularly evident in EGPA (Fig. 3). This is largely due to challenges in scoring asthma and asthma-associated exacerbations, the underrepresentation of ENT symptoms in the BVAS scoring system, and the underestimation of the clinical need to escalate immunosuppression even when BVAS scores remain low. In EGPA, a more accurate assessment of disease

Box 2 | Classification criteria for ANCA-associated vasculitis

The first attempt to develop any structured classification system was made in 1952 by Pearl Zeek[194], who proposed that vasculitis should be classified according to the size of the vessels affected: small, medium or large. Then, Donato Alárcon-Segovia in 1977[195] and Anthony Fauci in 1978[196] proposed classifications based on vessel size and pathophysiology. A set of classification criteria for several types of systemic vasculitis was developed by the American College of Rheumatology (ACR) in 1990 following previous proposals for sub-categorization of vasculitis disease. The Chapel Hill Consensus Conference (CHCC) in 1993 achieved international agreement on a set of definitions of the various vasculitides. In 2007, a four-step algorithm, integrating ACR 1990 and CHCC 1993 criteria in a hierarchic way, categorized patients into a single classification[197]. A revision of the CHCC definitions in 2012 adopted the term 'ANCA-associated vasculitis'. These disease definitions are also used to define patient cohorts for clinical research studies. The classification criteria were revisited by a subsequent classification initiative to produce diagnostic and classification criteria for vasculitis (DCVAS), a large, multinational prospective observational study that included data from over 6,900 patients with vasculitis across 136 sites and 32 countries[88–90,198]. The updated criteria were developed using regression modelling and expert consensus, incorporating both clinical and laboratory data, with weighted criteria that reflect the importance of specific features)[88–90].

Granulomatosis with polyangiitis (GPA)

- Upper and lower respiratory tract symptoms with granulomatous inflammation and typically seropositivity for proteinase-3-specific anti-neutrophil cytoplasmic antibodies (PR3-ANCA). Individuals who present with only one organ manifestation such as ear, nose and throat or lung involvement test negative for ANCA.

2012 CHCC

- Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (such as capillaries, venules, arterioles, arteries and veins); necrotizing glomerulonephritis is common[15].

2022 American College of Rheumatology (ACR)–European Alliance of Associations for Rheumatology (EULAR) classification criteria (presence of at least 5 points)

- **Clinical criteria**: Bloody nasal discharge, ulcers, crusting, congestion or blockage, or septal defect/perforation (3 points); cartilaginous involvement (2 points); conductive or sensorineural hearing loss (1 point)[88].
- **Laboratory, imaging and biopsy criteria:** Cytoplasmic ANCA or PR3-ANCA (5 points); pulmonary nodules, mass or cavitation on chest imaging (2 points); granuloma, extravascular granulomatous inflammation or giant cells on biopsy (2 points); inflammation, consolidation or effusion of the nasal or paranasal sinuses on imaging (1 point); pauci-immune glomerulonephritis on biopsy (1 point); perinuclear ANCA or myeloperoxidase-specific ANCA (MPO-ANCA) (–1 point); blood eosinophil count ≥1×10^9 per litre (–4 points)[88].

Microscopic polyangiitis (MPA)

- Acute kidney injury with glomerulonephritis, typically, generally testing positive for MPO-ANCA, with or without pulmonary capillaritis and absence of granulomatous inflammation.

2022 ACR–EULAR classification criteria (presence of at least 5 points)[89]

- **Clinical criteria**: Bloody nasal discharge, ulcers, crusting, congestion or blockage, or septal defect or perforation (–3 points).
- **Laboratory, imaging and biopsy criteria:** perinuclear ANCA or MPO-ANCA (6 points); fibrosis or interstitial lung disease on chest imaging (3 points); pauci-immune glomerulonephritis on biopsy (3 points); cytoplasmatic ANCA or PR3-ANCA (–1 point); blood eosinophil count ≥1×10^9 per litre (–4 points).

Eosinophilic granulomatosis with polyangiitis (EGPA)

- Upper respiratory tract involvement with nasal polyposis associated with asthma and eosinophilia, usually testing positive for MPO-ANCA, although ANCA-negative disease is frequent.

2012 CHCC

- Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present[15].

2022 ACR–EULAR classification criteria (presence of at least 6 points)

- **Clinical criteria**: Obstructive airways diseases (3 points); nasal polyps (3 points); mononeuritis multiplex (1 point)[90].
- **Laboratory, imaging and biopsy criteria:** Blood eosinophil count ≥1×10^9 per litre (5 points); Extravascular eosinophilic-predominant inflammation on biopsy (2 points); cytoplasmatic ANCA or PR3-ANCA (–3 points); haematuria (–1 point)[90].

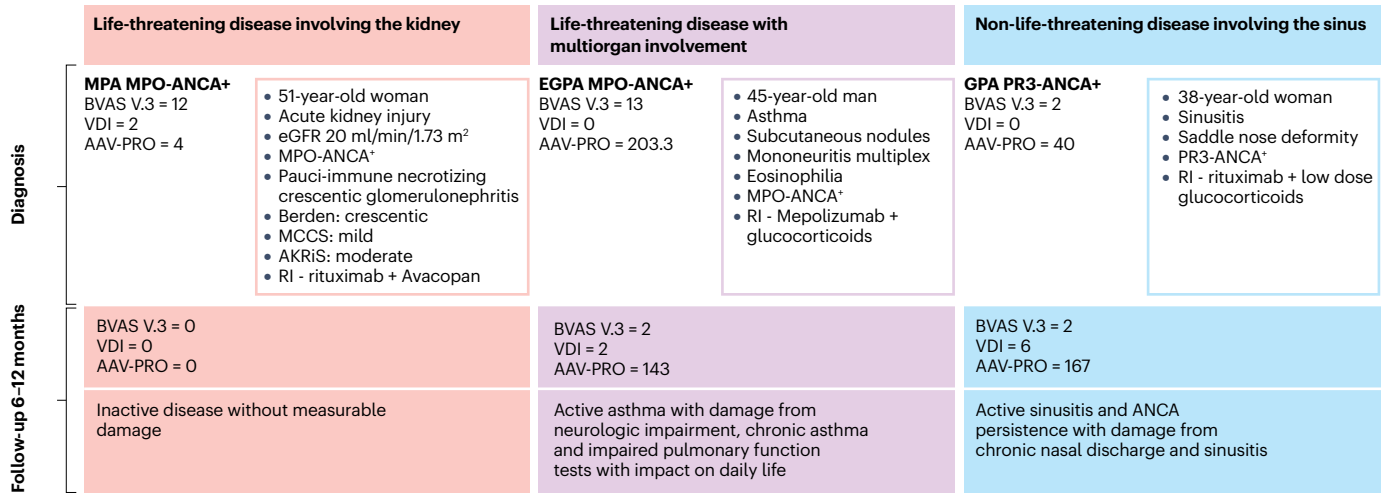


Fig. 3 | Combined assessment of disease activity, organ damage and patient-reported outcomes can help to characterize severity in three stereotypical cases of ANCA-associated vasculitis. Shown are three examples of stereotypical cases of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and how life-threatening versus non-life-threatening and 'limited' versus systemic presentation can affect outcomes differently, particularly in the context of damage (as assessed by the vasculitis damage index (VDI) and patient-reported outcomes (as assessed by AAV-patient-reported outcomes (AAV-PRO). Three representative cases illustrate the spectrum of disease presentation, follow-up and long-term outlook. In a case of microscopic polyangiitis (MPA, MPO-ANCA+), a 38-year-old woman presented with acute kidney injury, haematuria and pauci-immune crescentic glomerulonephritis. At baseline, disease was assessed with a Birmingham vasculitis activity score (BVAS) V3.0 of 12, a VDI of 0, and an AAV-PRO of 4. Treatment with rituximab and avacopan achieved remission, with stable kidney function and no relapse over 24 months. Despite life-threatening kidney involvement at onset, the patient achieved inactive disease without measurable damage. In a case of eosinophilic granulomatosis with polyangiitis (EGPA, MPO-ANCA+), a 45-year-old man presented with asthma, subcutaneous nodules, mononeuritis multiplex and eosinophilia. At baseline, disease was assessed with BVAS V3.0 = 13, VDI = 0 and AAV-PRO = 203.3. He was treated with mepolizumab and glucocorticoids. Over 24 months, asthma relapses required treatment with glucocorticoids, and long-term follow-up showed BVAS v.3 = 2, VDI = 2 and AAV-PRO = 143, reflecting damage related to chronic asthma and motor impairment, with substantial impact on quality of life. In a case of granulomatosis with polyangiitis (GPA, PR3-ANCA+), a 56-year-old woman presented with sinusitis and PR3-ANCA+ tests. At baseline, disease was assessed with BVAS V3.0 = 2, VDI = 0 and AAV-PRO = 40. Despite treatment with rituximab and low-dose glucocorticoids, she persistently tested positive for ANCA and had sinus disease with chronic nasal discharge. At 24 months, relapse required intravenous glucocorticoids, and her follow-up scores were BVAS v.3 = 2, VDI = 6 and AAV-PRO = 167, reflecting damage related to sinus disease and glucocorticoid toxicity. The figure emphasizes that prognosis in AAV depends not only on disease activity, extent and severity at presentation, but also on the accrual of damage and the influence of patient-related factors and comorbidities throughout the disease course. AKRiS, ANCA kidney risk score; eGFR, estimated glomerular filtration rate; MCCS, Mayo Clinic chronicity score; MPO, myeloperoxidase; PR3, proteinase 3; RI, remission induction.

severity requires the use of targeted tools such as the SNOT-22 (ref. 110) and the Asthma Control Questionnaire[111], both of which capture the disease's respiratory and sinonasal burden better than BVAS.

Organ damage

Persistent organ damage in AAV results from disease activity, cumulative relapses, treatment side effects and comorbidities. Damage is quantified using standardized and validated assessment tools. The VDI assesses features persisting for at least three months post-diagnosis after appropriate treatment on a scale from 0 to 64[112,113] (Table 1). A cumulative VDI ≥ 5 correlates with increased mortality risk after two years[112]. An alternative instrument, the CDA score was developed specifically for AAV and has been used in clinical trials such as PEXIVAS, RITAZAREM and ABROGATE[114].

Differentiating between organ damage and disease activity is crucial to avoid unnecessary immunosuppressive treatment[112]. Organ damage mostly occurs within the first 6–12 months, with slower progression thereafter, driven by relapses and therapy[115]. Long-term damage is associated with disease severity, age at presentation, relapse frequency and glucocorticoid use[115]. There is interest in differentiating disease-related from treatment-related damage, given that the latter is predictable and preventable[116].

Glucocorticoid-related toxicity. Despite important advances in treatment, glucocorticoids remain a cornerstone of treating AAV. In practice, glucocorticoids tend to be maintained at higher doses and for longer time than in clinical trials. Patients in practice are often left on a maintenance dose of glucocorticoids. For these reasons, patients are likely to receive substantially more glucocorticoids than the data from clinical trials might suggest is indicated. In the long term, treatment-related damage, especially from glucocorticoids, rivals the damage imposed by the disease itself[115,117].

There is now great interest in reducing glucocorticoid-related toxicity in AAV. In the PEXIVAS trial comparing standard versus reduced-dose glucocorticoid regimens for severe AAV, the efficacy of the two treatments were equivalent but the reduced-dose glucocorticoid arm had significantly (hazard ratio 0.69, 95% confidence interval 0.52–0.93) fewer serious infections in the first year of treatment[7]. The ADVOCATE trial demonstrated that a strategy using avacopan allows for reduced dosing of glucocorticoids and subsequent reduced glucocorticoid-related toxicity as measured by the glucocorticoid toxicity index (GTI)[118] compared to standard prednisone tapering[119,120]. In EGPA, glucocorticoid needs were the highest, mainly due to persistent and severe asthma symptoms, but treatment with anti-IL5 has shown an effective sparing effect[10,121].

Patient-reported outcomes

People with AAV often rate the importance of various manifestations of vasculitis differently from physicians[122,123]. As with all diseases, the perspectives of people with AAV should be respected and incorporated into assessment of any treatment plan and judgement of efficacy of interventions (see Supplementary Box 1). AAV impairs daily functioning across physical, social and psychological domains, affecting health-related quality of life (HRQoL) and employment[112]. Patients with AAV experience reductions in HRQoL that are comparable with HRQoL decreases experienced by patients with other chronic diseases. So-called generic measures of HRQoL, especially the SF-36, have been validated and used regularly to study AAV[18,124,125]. In addition, the disease-specific tool AAV-PRO was developed to more comprehensively capture patients' experiences with AAV[16,126] (Table 1). AAV-PRO domain scores do not correlate with disease activity and damage assessment (including the BVAS and the VDI), and, so AAV-PRO represents an outcome measure that complements clinician-reported endpoints in clinical trials, and aims to be reflective of the specific needs of patients[17] (Fig. 3). Other generic tools such as EQ-5D and PROMIS are also used to estimate PROs in AAV research[127,128]. In the ADVOCATE trial, patients with AAV receiving avacopan showed improvements in HRQoL, as measured by SF-36, EQ-5D-5L and SF-6D, compared with those receiving oral glucocorticoids[8,129]. In patients with EGPA, mepolizumab was associated with a quick and remarkable improvement of HRQoL as measured by the AAV-PRO[129]. These and other findings suggest that treatment, particularly if accompanied by reduced glucocorticoid exposure, can enhance HRQoL in people with AAV. People experience AAV in ways that are poorly measured by BVAS and other clinician-reported outcomes, and their concerns are often ignored[130,131].

Prognosis

Advances in treatment regimens have improved survival in AAV, and the emphasis in clinical management has shifted towards long-term health, preventing disease flares, minimizing treatment toxicity and enhancing HRQoL. Severe comorbidities, such as thromboembolic events and cardiovascular diseases, suggest a complex interaction between the pathogenesis of vasculitis, persistent inflammatory activity and clinical manifestations that do not appear to be direct consequences of vasculitis[132,133]. Comorbidities have thus become central concerns for clinicians.

AAV is characterized by considerable heterogeneity in age at onset, organ involvement, disease severity, treatment response and risk of comorbidity, all of which affect individual prognoses[134]. Long-term outcomes of great interest include remission, relapse, mortality, survival and accrual of damage, particularly progression to end-stage kidney disease or respiratory failure[134]. Additionally, comorbidities such as severe infections, thromboembolic events, cardiovascular risk, malignancy, fertility issues, secondary immunodeficiency and mental health issues must be considered[134].

Remission

Remission of AAV is achieved in 70–90% of cases (Supplementary Table 1). Achieving a BVAS of zero at 3 months correlates with improved survival, reduced risk of end-stage kidney disease, and less damage[135]. Sustained remission for at least 3–6 months predicts favourable outcomes, and is a key end point in interventional trials[134]. Such sustained remission is more difficult to obtain in people with EGPA than in people with other subtypes of AAV, because recurrent respiratory symptoms occur in the former once treatment is reduced[136,137]. PR3-ANCA positivity and increased baseline disease activity are inversely correlated with likelihood of remission in newly diagnosed patients. Refractory disease substantially heightens the risk of early mortality, primarily owing to alveolar haemorrhage and end-stage kidney disease[138].

Relapse

Relapse occurs in 42–57% of people with AAV within 5 years of diagnosis[12,139,140] (Supplementary Table 1). Depending on the AAV severity score used, relapses are classified as major or minor, although untreated minor relapses often progress to major ones[141]. Disease activity at relapse is typically less severe than disease activity at initial diagnosis, as a result of early detection and ongoing immunosuppression[142]. The optimal duration of maintenance therapy and the role of ANCA titres in the prediction of relapse remain key research areas[143–145]. Current guidelines do not recommend treatment adjustments based solely on ANCA levels[4]. However, a rise in ANCA levels, the persistence of a positive test for ANCA, and the reappearance of a positive test for ANCA all correlate with relapse in AAV-GN[145,146]. These findings pertain to people with AAV and kidney involvement, and it remains unclear whether similar findings are observed in other well defined disease clusters (such as AAV with ENT involvement). Emerging biomarkers, such as urinary soluble CD163 (which is already available in clinical practice), urinary levels of $CD4^+$ T cells, and serum complement markers show promise for prediction of relapse but require further validation[147–149].

Kidney outcomes

Kidney involvement in AAV is associated with high morbidity and mortality. Despite therapeutic advances, 25% of people with AAV progress to end-stage kidney disease at 5 years after diagnosis[26,36,94,150–155]. Outcomes are influenced by the timing of obtaining a diagnosis and baseline kidney function. People with GPA are generally diagnosed earlier than patients with MPA owing to extrarenal manifestations. Therefore people with MPA, especially in cases where disease is present only in the kidneys, often present later and with advanced chronic kidney disease[36,153].

Several tools, including the Berden histological classification, the Mayo Clinic chronicity score (MCCS), the ANCA renal risk score (ARRS) and its revised version the ANCA kidney risk score (AKRiS), as well as the percentage of ANCA crescentic score (PACS) help to predict end-stage kidney disease in AAV[71,156–159] (Fig. 4 and Supplementary Table 1). Of these, AKRiS, which includes baseline kidney function as well as histopathological features, is the most reliable predictor of end-stage kidney disease[71,160]. However, these tools do not address the chance of recovery of kidney function, an important outcome given that patients frequently present with severe kidney disease and an eGFR <15 ml min^{-1} per 1.73 m^2 and require acute dialysis. The percentage of normal glomeruli on kidney biopsy was found to help to predict kidney recovery in people with AAV-GN, but this observation needs validation in prospective studies[161]. Recovery of kidney function is not yet an established end point in clinical trials, although it is being explored in current studies. The ADVOCATE trial demonstrated that avacopan improved eGFR in people with baseline eGFR <20 ml min^{-1} per 1.73 m^2, with a significant between-group (active drug versus placebo) difference of 8.4 ml min^{-1} per 1.73 m^2 at 52 weeks[131]. Definitions of kidney function recovery, such as eGFR ≥ 15 ml min^{-1} per 1.73 m^2 or a change in the category of chronic kidney disease, require further validation[162]. Notably, recovery of eGFR continues beyond 52 weeks, as reported in observational studies, underscoring the importance of long-term follow-up in clinical trials[162,163]. Severe chronic kidney disease and the requirement for kidney replacement therapy have profound effects on cardiovascular events, thromboembolism, infection risk, HRQoL and mortality[164–166].

Screening for comorbidities

Patients with AAV are at increased risk of developing comorbidities. Some comorbidities, such as infection[167] and thromboembolic events[168,169], occur early in the disease course (23% in the first year),

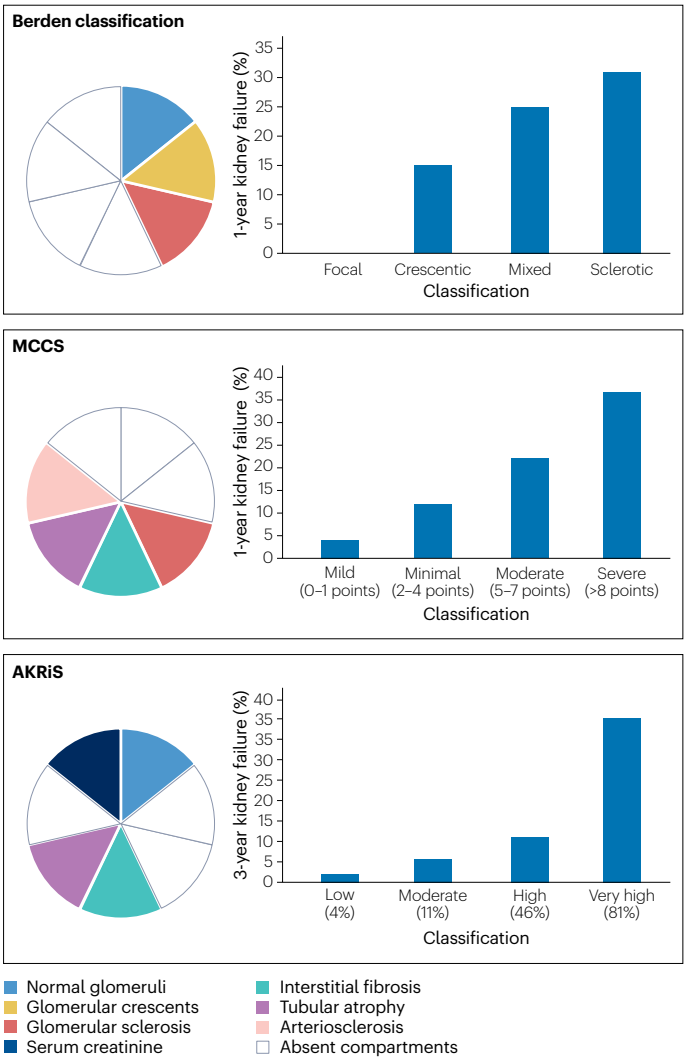


Fig. 4 | Histopathological assessment of kidney for end-stage kidney disease prediction in AAV-associated glomerulonephritis. Various histopathological scores assess kidney histopathological patterns. Berden classification and ANCA kidney risk score (AKRiS) have been developed specifically for the assessment of glomerulonephritis in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV-GN). The Mayo Clinic chronicity score (MCCS) is used in a broad spectrum of diseases with kidney involvement. Berden classification evaluates only glomerular compartment; the MCCS evaluates glomerular and interstitial compartment with additional grading of interstitial fibrosis and tubular atrophy and arteriosclerosis; and the AKRiS combines the evaluation of the glomerular and interstitial compartments with estimated glomerular filtration rate (eGFR). The risk of progression to end-stage kidney disease (eGFR <15 ml min^{-1} per 1.73 m^2 or dialysis) at 12 months and 3 years is shown for each classification (left). In the MCCS and AKRiS, biopsy findings are graded, and patients are assigned to a category according to the total score obtained. The implementation of at least one of the scores in a routine histopathological report is warranted, and the Berden score has been used here in the past by most pathology services.

and others, including cardiovascular disease[1,170,171], osteoporosis[172] and malignancy[134,173,174], occur during long-term follow-up (37% at 10 years). Fertility issues[175] and reduced HRQoL[134] might persist throughout the duration of the disease (Supplementary Table 1). It is unclear whether comorbidities are attributable to immunosuppression, underlying disease or both. Anticipating comorbidities can help to mitigate the metabolic effects of treatments (by using lower-dose glucocorticoid regimens, or alternatives such as avacopan) or the impact on fertility and pregnancy (through counselling and treatment with fertility- and pregnancy-compatible immunosuppression)[176]. Routine prophylaxis against *Pneumocystis jirovecii* pneumonia is recommended and might also reduce the frequency of other bacterial infections[2]. People with AAV that are on rituximab maintenance therapy are at risk for secondary immunodeficiency and should have serum immunoglobulins checked prior to infusion. Cardiovascular disease is the leading cause of mortality in AAV, and screening for cardiovascular risk factors can support prevention of cardiovascular disease and early AAV treatment[2]. Also, age- and sex-adjusted malignancy screening is recommended. People with AAV treated with cyclophosphamide are at increased risk of non-melanoma skin cancer and urothelial malignancy, and screening for haematuria and skin malignancy in these individuals should be lifelong[173,177,178].

Early mortality

Early mortality in AAV is driven primarily by infections and other treatment-related adverse effects. A 'therapy burden' tool can be used to effectively predict risk of early mortality (Supplementary Table 1). Other prognostic factors include markedly reduced kidney function — specifically a baseline eGFR below 30 ml min^{-1} per 1.73 m^2 — which portends poorer kidney survival, and cumulative cyclophosphamide exposure (exceeding ~36 g of cyclophosmamide), which might lead to long-term complications, including malignancy. Advanced age, chronic kidney disease and MPO-ANCA positivity consistently predict poorer survival. Despite improved survival, based on data from cohorts from 2002 to 2017 the overall mortality rate in people with AAV remains 2.7-fold higher than the rate in the general population[179,180].

Long-term outcomes

The five-year survival rate for AAV has risen to 70–80%, a marked improvement from previous decades, owing to earlier diagnosis, effectiveness of immunosuppressive therapies, new treatments, wide availability of ANCA testing and improved supportive care[12]. Similarly, there has been a reduction in the rate of end-stage kidney disease over the past several decades[12,181]. Although mortality rates have decreased, there is still a higher-than-expected mortality compared to the general population, largely caused by complications arising from the disease or its treatment[182]. The five-factor score (FFS) is a prediction system based on the presence of four positive items such as age >65 years, creatinine ≥2.7 mg dl^{-1}, and central nervous system and cardiac involvement, and one negative item, ENT involvement, at the time of diagnosis of vasculitis. The FFS predicts mortality across several types of vasculitis, including AAV[183,184] with a score of above 2 associated with worse outcomes at five years[183,184].

Outlook

An integrated, multifaceted approach to assess AAV is essential for improving patient care (Box 3). This includes understanding diagnostic tools, classifying disease, estimating severity, and predicting outcomes. By better addressing comorbidities, side effects of treatment, and disease progression, clinicians can optimize care and enhance the prognosis for patients living with AAV.

Multidisciplinary management in specialized centres and international collaboration

Multidisciplinary management in specialized centres with vasculitis expertise is considered an overarching principle in treatment guidelines for AAV[4]. Rapid access to multidisciplinary diagnostic evaluation and treatment for an early and accurate diagnosis is often necessary. In addition, patients with relapsing or refractory AAV might need improved access to clinical trials testing new drugs. Dedicated vasculitis centres with appropriately trained healthcare providers experienced in AAV can support patients and provide patient education. Some retrospective studies showed improved outcomes for patients with centre-based management, but prospective studies are needed[185–187].

In addition, collaborative efforts across international research centres, clinical registries and patient populations have the potential to expand knowledge about AAV pathogenesis and management. Global exchange of clinical experience and patient data will clarify differences in presentation and prognosis of AAV on a global scale, enabling the identification of novel biomarkers, treatment strategies and clinical guidelines. Incorporating mechanistic endpoints into clinical trials, such as evaluating the role of specific immune pathways, genetic markers, and immune cell populations, might provide deeper insights into the mechanisms driving disease activity and relapse.

Refinement of classification criteria

The development and revision of classification criteria for AAV have been important for enhancing the accuracy and consistency of research studies. The 2022 ACR–EULAR criteria offer substantial improvements over previous versions, addressing the challenges posed by the diverse clinical and serological features of AAV. ANCA-specificity testing has been shown to predict risk of relapse and has the potential to guide decisions about treatment duration. This underlines the need to analyse clinical trial outcomes based on ANCA specificity[59,145]. Understanding the relative contributions of clinical phenotypes and ANCA specificity is necessary for personalizing treatment and improving outcomes of patients with AAV[36] (Fig. 2).

Integrated view of disease activity, organ damage and PROs

The development of the standardized tools BVAS, VDI and AAV-PRO has advanced the ability to assess disease activity, damage and HRQoL. However, integration of these tools into daily care and assessment of disease activity and damage in AAV has proved difficult. This is particularly evident in patients with EGPA, because estimation of disease activity and damage in EGPA needs to incorporate the assessment of ENT manifestations and asthma more precisely. Current measures of disease activity and damage, especially kidney involvement, might lack sufficient granularity to correctly estimate severity and, thus, to stratify patients in prognostic categories. For instance, the BVAS V3.0 assigns the same score of 12 in the presence of haematuria and proteinuria regardless of whether a patient presents with a creatinine level of 1.54 or 7.50 mg dl^{-1}. The VDI records damage based on eGFR ≤ 50 ml min^{-1} per 1.73 m^2 or significant proteinuria but this does not account for improvements in kidney function[188,189]. The comprehensive end organ and integrated

Box 3 | Future steps towards an integrative approach to the assessment of ANCA-associated vasculitis

An integrated assessment in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) should take into consideration diagnostic approaches, classification criteria and assessment of disease severity and prognosis. The aim is to achieve discriminative assessment with improved identification of patients at a high risk of specific outcomes. This would help to tailor treatments and would bring the field a step closer to personalized medicine in AAV.

Diagnosis

- Developing diagnostic criteria would be beneficial for improved accuracy in stratification and personalization of treatment of AAV

Classification

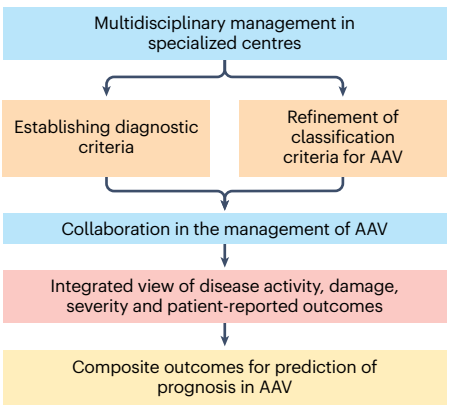
- Validation of the American College of Rheumatology (ACR)–European Alliance of Associations for Rheumatology (EULAR) classification criteria in populations under-represented in initial studies
- Continued international collaborations to perform investigator-initiated clinical trials, but also observational studies

Disease assessment

- Developing a definition of disease extent and severity that combines the activity and damage assessment, and patient-reported outcomes to improve patient stratification, risk assessment, and evaluate response to treatment and outcomes (remission, relapse) in AAV
- Improved granularity when assessing the severity and damage of certain organ manifestations

Outcomes and prognosis

- Inclusion of biomarkers and genetic data in the evaluation of individuals with AAV, especially for prediction of future relapse risk
- Development of composite assessment tools to evaluate response to treatment in AAV



Glossary

Alveolar haemorrhage
The presence of blood within the alveoli (air sacs) of the lungs, often caused by injury or disease; it can lead to difficulties in breathing, coughing up blood and impaired gas exchange.

Capillaritis
An inflammatory process that primarily affects capillaries (the smallest blood vessels in the body) and is characterized histologically by neutrophilic infiltration of the capillary walls, leukocytoclastic vasculitis, fibrinoid necrosis of the vessel and erythrocyte extravasation.

Conductive hearing loss
A type of hearing loss that occurs when sound waves cannot efficiently travel through the outer ear, eardrum or middle ear.

Eosinophilia
Eosinophilia is characterized by an increased number of eosinophils in the blood, defined by an absolute eosinophil count greater than 500 cells per microlitre or an eosinophil percentage that exceeds 10% of the total white blood cell count.

Gold standard
The most reliable and accurate method for diagnosing a condition, testing a procedure or assessing treatment effectiveness; it serves as the benchmark against which other methods or treatments are compared.

Granulomatous inflammation
A chronic inflammatory response characterized by the formation of granulomas, which are aggregates of macrophages, often surrounded by lymphocytes and other immune cells; this type of inflammation typically occurs in response to persistent infections, foreign bodies or certain diseases, such as tuberculosis, sarcoidosis and leprosy.

Interstitial lung disease
A group of pulmonary disorders characterized by inflammation and fibrosis of the lung interstitium, leading to impaired gas exchange and respiratory dysfunction; it can result from various causes, including autoimmune diseases, environmental exposures and medications.

Mononeuritis multiplex
Mononeuritis multiplex is characterized by the simultaneous or sequential inflammation and damage of two or more peripheral nerves, typically affecting different anatomical areas; it often results from systemic diseases such as autoimmune disorders, vasculitis or infections; symptoms include pain, weakness and sensory disturbances like numbness or tingling.

Necrotizing and crescentic glomerulonephritis
A severe kidney disorder characterized by rapid glomerular damage and crescent formation, often leading to acute kidney failure; it is often associated with autoimmune diseases and vasculitis.

Orbital pseudotumours
A benign, non-infectious inflammatory condition of the orbit that causes swelling, pain and potential vision changes, often resembling a tumour.

Saddle nose deformity
A condition characterized by a collapse or depression of the nasal bridge, creating a saddle-like appearance. It can result from trauma, congenital conditions, or diseases like syphilis or granulomatosis with polyangiitis (GPA).

Subglottic stenosis
A narrowing of the airway in the subglottic region, located between the vocal cords and the first tracheal ring; symptoms may include inspiratory stridor, dyspnea and voice abnormalities.

Vasculitis
Inflammation of the blood vessels; it can affect the arteries, veins or capillaries, leading to a variety of symptoms, depending on which vessels and organs are involved.

assessment of disease activity and damage could be used as a measure of AAV severity, because different treatment regimes are needed for a person who has overcome acute kidney failure and a person who progressed to end-stage kidney disease shortly after diagnosis (Fig. 3). Similarly, risk of relapse differs between individuals with AAV, and relapse contributes to cumulative damage (Fig. 3). PROs are not part of the standard assessments, but they are important to understand patients' perceptions of the disease, adherence to the management plan and would help with patient inclusion in an integrated approach towards personalized care (Fig. 3; Supplementary Box 1). In addition, the lack of reliable biomarkers for disease assessment in AAV disconnects evaluation of disease state and pathophysiology, but their integration on combined assessment might help to tailor treatment in the appropriate setting. For example, MPO-ANCA testing could be integrated with clinic and laboratory data to guide maintenance or treatment strategies in people with AAV-GN. Future research should focus on combining disease assessment tools with PROs and biomarkers to better characterize disease and assess outcomes in AAV (Fig. 3).

Composite outcomes for prediction of prognosis

Composite assessment tools have been proposed to improve assessment of response to treatment and outcomes in AAV. These tools integrate various disease measures, including disease activity, damage and treatment toxicity[190,191]. The OMERACT Vasculitis Working Group is developing a composite tool that captures the full disease burden across multiple domains[190,191]. This approach might provide a more holistic assessment of AAV, including assessment of the potential increase in frailty and the long-term consequences of persistent organ damage, and might help to guide clinical trials and patient management in the future[190,191]. Such composite assessment tools could incorporate PROs, biomarkers and genetic data. Genetic data are emerging as a potential biomarker for refining patient management. For instance, polymorphisms in the *PRTN3* gene might increase the amount of PR3 in patients with AAV or increase the risk of relapse in patients with PR3-ANCA[192,193]. Although this approach holds promise, more research is needed to validate the utility of genetic markers in clinical practice, and their integration into personalized treatment strategies will require further refinement. An increased understanding of the pathogenesis of AAV might also help individual risks to be evaluated by integrating genetic and immunological information.

Conclusions

An integrated approach to assessing and managing AAV is essential for improving outcomes. This includes the use of diagnostic tools, accurate disease classification, biomarkers and PROs to personalize treatment. Ongoing international collaborations and clinical registries will help to refine treatment strategies, biomarkers and classification systems. Future clinical trials focused on mechanistic endpoints will further enhance our understanding of the pathophysiology of this complex

disease. By incorporating these strategies, clinicians will be able to personalize and optimize care, reduce complications and improve prognosis for patients with AAV.

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Author contributions

M.C.M. and A.K. had the idea for this review paper, conceptualized the proposal and the manuscript that generated this work, and coordinated the project. P.A.M. and D.J. provided initial review of, and input into, the proposal and the manuscript. All authors contributed to writing and revising the paper.

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