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Review

ANCA-associated vasculitis: From immunopathogenesis to diagnosis and toward precision therapy

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ABSTRACT

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises a group of rare, potentially life-threatening autoimmune disorders characterized by necrotizing inflammation of small vessels. Over recent decades, remarkable advances have been made in unraveling its immunopathogenesis, emphasizing the interplay between genetic predisposition, environmental triggers, loss of immune tolerance, neutrophil extracellular trap formation, and complement-mediated neutrophil activation. This review provides an integrative synthesis of recent mechanistic and clinical insights into AAV, bridging fundamental immunology with translational and therapeutic advances. Based on an extensive literature search of PubMed and Scopus, studies were selected according to methodological quality and clinical relevance. Distinct ANCA specificities, proteinase 3 (PR3) and myeloperoxidase (MPO), define overlapping yet prognostically divergent subsets, with PR3-ANCA linked to relapsing multisystem disease and MPO-ANCA to renal involvement and progression to kidney failure. Therapeutic paradigms have evolved from cyclophosphamide-based induction toward rituximab-centered and glucocorticoid-sparing regimens, with mepolizumab further improving efficacy and safety profiles. Despite five-year survival rates exceeding 85%, long-term morbidity persists, driven by relapse and treatment-related toxicity. However, precision therapy in AAV remains incomplete, as current treatment selection is still guided mainly by disease severity, organ involvement, relapse risk, comorbidities, renal histology, and risk of glucocorticoid-toxicity rather than by validated molecular biomarkers. Emerging data on complement activation, urinary inflammatory biomarkers, B-cell kinetics, and tissue-based transcriptomic profiling may refine disease endotyping and individualized monitoring. Collectively, these advances herald a transition from empirical immunosuppression toward biologically informed, precision-oriented care in vasculitis.

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of rare systemic autoimmune diseases characterized by necrotizing inflammation that primarily targets small-caliber vessels and, to a lesser extent, medium-caliber vessels [1]. These disorders are strongly associated with the presence of ANCA, commonly directed against proteinase 3 (PR3) and myeloperoxidase (MPO) [2].

Clinically, there are three main forms of AAV: granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis; microscopic polyangiitis (MPA); and eosinophilic granulomatosis with polyangiitis (EGPA), previously termed Churg–Strauss syndrome [1].

Despite its low incidence [3], AAV has a disproportionate clinical impact due to its potential to affect vital organs, particularly the kidneys and lungs [4]. Diagnostic assessment remains challenging, given the heterogeneity of clinical manifestations and the frequent overlap with other systemic disorders [5].

A better understanding of the immunopathogenesis of AAV is essential to refine diagnosis and guide targeted therapy. The necessity for an integrated and early clinical approach is further reinforced by

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these considerations [6].

In this context, the present review synthesizes current advances in the immunopathogenesis, diagnosis, and treatment of AAV. It also identifies persisting clinical and translational challenges, with particular attention to precision medicine and the integration of genetic, immunologic, and clinical data to improve patient outcomes, including how emerging biomarkers might guide treatment selection beyond ANCA specificity. Furthermore, the expanding therapeutic landscape, spanning B-cell depletion, complement blockade, and eosinophil-targeted therapies, demands a synthesis of mechanistic and clinical evidence to guide precision use.

2. Methods

This review was based on a structured bibliographic search conducted across PubMed and Scopus, complemented by standard reference textbooks in Immunology, Nephrology, Rheumatology, and Internal Medicine, as well as cross-referencing from selected articles. The search was initially conducted between April and September 2025 and was last updated in June 2026, with a focused post-acceptance update on avacopan in July 2026.

The search prioritized publications in English, available in full text, and published from 2005 onward. Earlier seminal works were also included when they provided key mechanistic, diagnostic, therapeutic, or historical insights.

Eligible studies comprised original research articles, meta-analyses, clinical trials, authoritative reviews, international guidelines, and selected trial registry records on AAV pathophysiology, diagnosis, prognosis, digital tools, or management. Non–peer-reviewed materials and isolated case reports were excluded.

Articles were selected based on their scientific rigor, relevance to the immunopathogenesis or clinical management of ANCA-associated vasculitis, and citation impact within the field. Preference was given to multicenter trials, large cohort studies, international consensus guidelines, translational studies, and clinically relevant digital or data-driven studies that contributed to mechanistic understanding or clinical practice. When multiple studies addressed similar questions, the most recent or comprehensive reports were prioritized.

After source screening, a total of 144 references were included. Data were comparatively analyzed and organized by topic to ensure scientific coherence and accuracy.

This article is a narrative review bridging fundamental immunopathogenic mechanisms with current clinical, therapeutic, prognostic, and digital advances in ANCA-associated vasculitis.

No new data were generated for this review.

3. Anti-neutrophil cytoplasmic antibody-associated vasculitis

3.1. Epidemiology

3.1.1. Incidence and prevalence

Globally, the annual incidence of AAV ranges from 13.3 to 21.6 cases per million person-years, whereas the prevalence ranges from 187 to 210 per million persons [3]. These data were derived from a meta-analysis encompassing 25 studies conducted prior to June 2020, predominantly comprising population-based and hospital-based studies in Europe, North America, Asia, and Oceania [3]. These figures have increased over time, most likely reflecting enhanced case ascertainment, revised classification criteria, and increased patient survival rather than a true rise in disease occurrence [7–10]. Recent Norwegian data from 2000 to 2016 show this trend, with rising MPA incidence and higher overall prevalence [11]. The application of the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) criteria resulted in the reclassification of some cases previously diagnosed as GPA to MPA [12], underscoring the impact of classification systems on epidemiological estimates [13,14] **(**Fig. 1**)**.

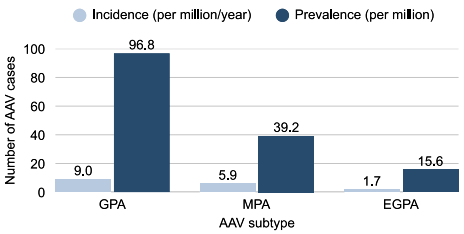

Fig. 1. Global incidence and prevalence of ANCA-associated vasculitis subtypes. The graph shows the mean incidence (per million person-years) and prevalence (per million people) of the main subtypes of ANCA-associated vasculitis (AAV): granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). GPA is the most common subtype, with the highest incidence (9.0) and prevalence (96.8) rates, followed by MPA and EGPA. Information taken from Redondo-Rodriguez et al. [3].

The incidence and prevalence of AAV vary by clinical subtype. Based on a worldwide meta-analysis, incidence rates per million person-years are estimated at 9.0 for GPA, 5.9 for MPA, and 1.7 for EGPA, whereas prevalence per million people is estimated at 96.8 for GPA, 39.2 for MPA, and 15.6 for EGPA [3]. These values should be interpreted as broad comparative estimates, as epidemiological figures vary across studies, populations, and classification criteria.

3.1.2. Geographic distribution

Distinct geographic patterns have been observed for the different AAV subtypes **(**Fig. 2**)**. Epidemiological data reveal a higher incidence of GPA across Europe, whereas MPA predominates in Asian populations [15]. Additionally, both GPA and EGPA show increasing incidence with latitude, with higher rates observed in the Northern Hemisphere, a pattern that may reflect differences in ultraviolet exposure, vitamin D status, or infectious triggers [3]. Such geographic and latitudinal patterns suggest the contribution of environmental and possibly epigenetic factors to disease expression.

Taken together, these patterns underscore the need for standardized classification and consistent epidemiologic methodologies.

3.1.3. Demographic factors

AAV displays characteristic demographic patterns across its subtypes, spanning sex, age at diagnosis, and ethnicity. With respect to sex, a male predominance is evident in MPA (≈ 64% male), whereas GPA and EGPA show an approximately balanced distribution (≈ 52% and ≈ 45% male, respectively) [3]. Pediatric-onset GPA and MPA are more common in females, and GPA is reported more frequently than MPA [16]. The mean age at diagnosis is typically in the sixth to seventh decades of life. In GPA, the mean age at diagnosis is approximately 57 years, whereas in MPA it is older, at about 65 years. Patients diagnosed with EGPA tend to be younger, with a mean age at diagnosis of approximately 52 years [3]. Ethnic disparities have also been documented, with GPA and MPA being more prevalent among Caucasian populations [17].

3.1.4. Serological profile

ANCA positivity varies markedly across AAV subtypes **(**Table 1**)**. In large French and European cohorts, PR3-ANCA predominates in GPA, whereas MPA is usually ANCA-positive and predominantly associated with MPO-ANCA [18,19]. By contrast, most patients with EGPA are ANCA-negative; when ANCA are present, they are mainly directed against MPO, while PR3-ANCA positivity is rare [20]. These patterns should be interpreted in the context of disease phenotype, assay methodology, and cohort composition, particularly because ANCA may be absent in localized GPA and because antigen-specific results are not always reported using identical denominators across cohorts [18].

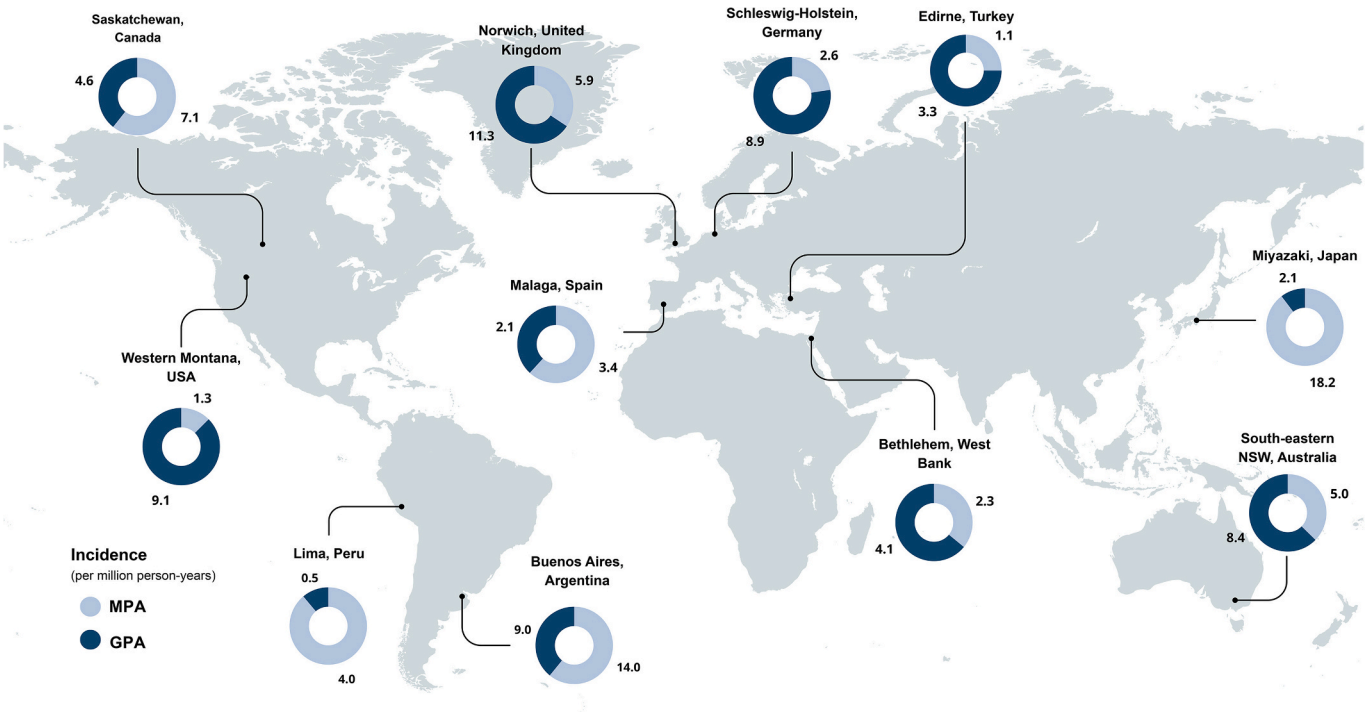

Fig. 2. Geographical distribution of the incidence of ANCA-associated vasculitis. Comparative representation of the incidence between subtypes of ANCA-associated vasculitis (AAV): granulomatosis with polyangiitis (GPA) (dark blue sector) and microscopic polyangiitis (MPA) (light blue sector) in various countries. A higher incidence of GPA is observed in regions of Western Europe and North America, while MPA predominates in Asian countries, such as Japan, and in some Mediterranean regions. The distribution shows geographical and latitudinal variations, suggesting possible environmental influences. Information taken from Redondo-Rodriguez et al. [3]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
ANCA status and antigen specificity across AAV subtypes in large French and European cohorts.

Subtype of AAV	Source cohort	PR3-ANCA (%)	MPO-ANCA (%)	ANCA negative (%)
GPA [18]	FVSG ($n = 795$)	75.0	16.5	8.5
MPA[a] [19]	FVSG ($n = 378$)	3.7	78.4	14.1
EGPA[b] [20]	FVSG & EGPA European Study Group registry ($n = 734$)	2.2	28.6	69.2

Percentages represent cohort-specific estimates rather than universal values; ANCA status and antigen specificity vary across series according to geography, classification criteria, disease phenotype, ascertainment method, and assay methodology [3].
Data sourced from primary cohorts: GPA [18], MPA [19], and EGPA [20]. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibodies; EGPA: eosinophilic granulomatosis with polyangiitis; ELISA: enzyme-linked immunosorbent assay; FVSG: French Vasculitis Study Group; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3.
[a] For MPA, percentages are expressed relative to the 347 patients with available overall ANCA status. PR3-ANCA and MPO-ANCA counts were derived from patients with available ELISA specificity; 17 ANCA-positive patients lacked antigen-specific ELISA results and 4 had dual MPO/PR3 positivity. Accordingly, the displayed MPA percentages should not be summed as mutually exclusive categories.
[b] For EGPA, ANCA status was available for 734 of the 845 patients in the cohort; percentages are expressed relative to these 734 ANCA-evaluable patients.

3.2. Etiology

3.2.1. Genetic factors

Genome-wide association studies (GWASs) have identified several genes associated with AAV susceptibility [21–23]. A strong association has been demonstrated between the major histocompatibility complex (MHC) class II and AAV, as well as a genetic dissociation between the clinical subtypes MPA and GPA [22].

PR3-ANCA has been linked to the human leukocyte antigen (*HLA*)-*DP* gene, whereas MPO-ANCA is associated with the *HLA-DQ* gene but not with *HLA-DP* [22]. This association has been consistently observed in patients with MPA and in some patients with GPA harboring MPO-ANCA [22]. These data suggest a relationship between specific HLA genomic factors, namely the *HLA-DPB1*04:01* allele for PR3-ANCA/GPA and *HLA-DRB1*09:01* for MPO-ANCA/MPA, and the ANCA antigenic target, rather than with the clinical subtype itself [24].

Beyond HLA, several non-MHC loci contribute to AAV susceptibility, particularly in PR3-ANCA/GPA [25]. Variants in the *PRTN3* gene, which encodes proteinase 3, are associated with increased neutrophil PR3 expression and a higher risk of GPA. The *PTPN22* 620 W allele has also been linked to GPA by altering T-cell receptor signaling [26]. Loss-of-function *SERPINA1* alleles (Z and S) reduce alpha-1 antitrypsin activity. This deficiency is one of the most consistently replicated genetic risk factors for GPA and has been associated with worse outcomes [27].

Beyond genetic and environmental determinants, regulatory mechanisms such as post-transcriptional modulation and chromatin remodeling may further influence immune tolerance in AAV, although these aspects remain insufficiently characterized [22,23].

Together, these findings support the biological distinction between PR3-ANCA and MPO-ANCA disease and reinforce the value of ANCA specificity in disease stratification.

3.2.2. Environmental factors and chemical substances

Several environmental exposures, particularly silica dust and infectious agents, have been identified as risk factors for AAV [28], with multiple epidemiological studies demonstrating a strong link between silica exposure and the MPO-ANCA variant of the disease [29]. As an

example, large-scale seismic events have been observed to coincide with a higher incidence of AAV, likely due to elevated ambient silica concentrations [30], a common soil constituent [31]. An increased prevalence of AAV has also been reported among agricultural workers, attributed to both silica exposure and contact with pesticides and solvents that may act as pathogenic triggers.

It is suggested that silica may contribute to AAV pathogenesis by triggering an inflammatory response involving alveolar macrophage activation [32], neutrophil recruitment, and lymphocyte stimulation. In this process, neutrophil-derived MPO is processed by macrophages and presented to immune cells, facilitating MPO-ANCA development [32,33].

A correlation between bacterial infections and AAV has been documented, particularly in relation to *Staphylococcus aureus* (*S. aureus*) colonization and GPA [34]. *S. aureus*–derived superantigens can nonspecifically activate T and B lymphocytes, thereby promoting cell proliferation and cytokine release [35]. Moreover, the presence of toxic shock syndrome toxin-1, produced by *S. aureus*, has been identified as a risk factor for disease relapse [35].

Exposure to certain medications, including propylthiouracil, hydralazine, D-penicillamine, minocycline, and levamisole-adulterated cocaine, has been demonstrated to induce AAV [36–38]. The pathogenesis of drug-induced AAV is heterogeneous. In some cases, such as with propylthiouracil, hydralazine, and D-penicillamine, the proposed mechanism includes the stimulation of polyclonal B lymphocytes, which leads to ANCA production [39]. In the case of levamisole-adulterated cocaine, however, proposed mechanisms include vascular toxicity, neutrophil extracellular trap formation, and broader autoimmune activation, rather than direct B-cell stimulation [38]. Furthermore, drug-induced AAV frequently targets multiple antigens, and ANCA production generally ceases upon drug withdrawal [39].

Finally, tobacco smoking has been associated with an increased risk of AAV, particularly for MPO-ANCA disease, with both former and current smokers demonstrating elevated susceptibility [40].

Taken together, these findings emphasize a multifactorial model in which genetic susceptibility interacts with environmental and epigenetic factors to drive loss of tolerance and ANCA formation.

3.3. Pathogenesis

3.3.1. ANCA production and role

ANCA are autoantibodies directed against enzymes located in neutrophil granules, namely PR3 and MPO. These autoantibodies play a central role in the pathophysiology of AAV, although their presence alone does not always predict disease [41].

Following the loss of tolerance, driven by the genetic and environmental factors previously described [42], PR3 and MPO are processed and presented by antigen-presenting cells (and other innate cells), which produce a cytokine milieu (for example, IL-1β, IL-6, TGF-β, and IL-23) that can favor differentiation of $CD4^+$ T cells with Th17 characteristics and support B-cell help [6]. This process results in the production of interleukin 17 (IL-17), which stimulates macrophages to produce inflammatory mediators such as tumor necrosis factor (TNF-α) and interleukin 1 beta (IL-1β) [6]. These cytokines, in turn, induce neutrophil priming, leading to the translocation of MPO and PR3 from intracellular granules to the cell surface [43].

In parallel, expanded T-cell subsets that deliver B-cell help, especially T follicular helper (Tfh) and peripheral helper (Tph) cells that secrete IL-21, are increased in active AAV. These cells support B-cell differentiation and high-affinity ANCA production [44]. In addition, they prime neutrophils and can induce the translocation of ANCA antigens, which are normally located in intracellular granules, to the cell surface [39]. Upon receiving signals from T lymphocytes, B lymphocytes proliferate and differentiate into plasma cells that produce ANCA [43]. The pathogenicity of antibodies depends on multiple features, such as titer, isotype/subclass, epitope specificity, and affinity, as well as Fc glycosylation patterns. Several studies have associated alterations, such as reduced galactosylation and changes in fucosylation, with disease activity and relapse risk [45].

It is important to note that, although ANCA types share common immunopathological pathways, they have distinct production mechanisms that reflect different immunological stimuli, genetic influences, and inflammatory contexts [46].

The production of MPO-ANCA is associated with impaired clearance of neutrophil extracellular traps (NETs), due to reduced activity of serum deoxyribonuclease I (DNase I), which is the enzyme responsible for cleaving the deoxyribonucleic acid (DNA) of NETs. The presence of anti-NET antibodies has also been reported in some patients and may contribute to NETs persistence [47]. These mechanisms extend MPO exposure to the immune system and potentially promote loss of tolerance [48].

In addition to these NET-related mechanisms, B-cell activating factor (BAFF), a cytokine essential for B-cell survival and maturation, is also frequently elevated in active AAV, where it correlates with disease activity and supports the expansion and activation of ANCA-producing B cells [6,49].

In the specific case of PR3-ANCA, a mechanism of molecular mimicry has been proposed in which *S. aureus* expresses genetic sequences complementary to the human *PRTN3* gene, which encodes PR3. This genetic homology could explain a mechanism of molecular mimicry, through which chronic exposure to *S. aureus* could contribute to the loss of immune tolerance and the development of PR3-ANCA, but this remains an area of active investigation rather than a definitive explanation [46,50].

The sequence of immune events described is summarized in Fig. 3, which illustrates ANCA production, cell activation, and the inflammatory consequences at the vascular level.

3.3.2. Contribution of neutrophils and NETs

When primed, neutrophils can display MPO or PR3 antigens on their cell surface that are recognized by ANCA. These antibodies bind to the antigens, and their Fc regions simultaneously interact with the Fcγ receptors present on neutrophils [43]. This interaction triggers uncontrolled activation, resulting in the excessive release of cytokines, reactive oxygen species (ROS), and proteolytic enzymes [51]. The result is the formation of NETs [43,52]. A variety of signaling pathways have been implicated in the regulation of NETosis in AAV, including Receptor-Interacting Protein Kinase 3 (RIPK3) and cyclophilin D–dependent mechanisms. Ongoing research is exploring therapeutic strategies that enhance NETs clearance, such as DNase I administration or the restoration of efferocytosis, the process by which phagocytes engulf and remove apoptotic or damaged cells [53].

Platelets also participate by forming platelet–leukocyte aggregates that enhance NETs formation (e.g., via thrombin–protease-activated receptor (PAR) signaling) and by contributing to activation of the alternative complement pathway [54].

NET-associated proteases, including neutrophil-derived matrix metalloproteinases (MMPs) such as MMP-9, can further contribute to endothelial injury by promoting endothelial MMP-2 activation, apoptosis, extracellular matrix degradation, and vascular dysfunction. At the same time, ANCA antigens contained within NETs can activate the alternative complement pathway and intensify the autoimmune response [52,55–57].

Thus, ANCA can trigger a vicious cycle of NETs production, leading to continuous exposure of ANCA antigens to the immune system. Individuals with AAV may have an increased propensity to form NETs due to bacterial infections with *S. aureus*, which strongly induce NETs [58] and appear to be associated with relapses [52,59]. Consistent with this, GPA is characterized by nasal mucosal dysbiosis, with enrichment of *S. aureus* and loss of commensal species, which has been implicated as a local trigger of inflammation and relapse [60].

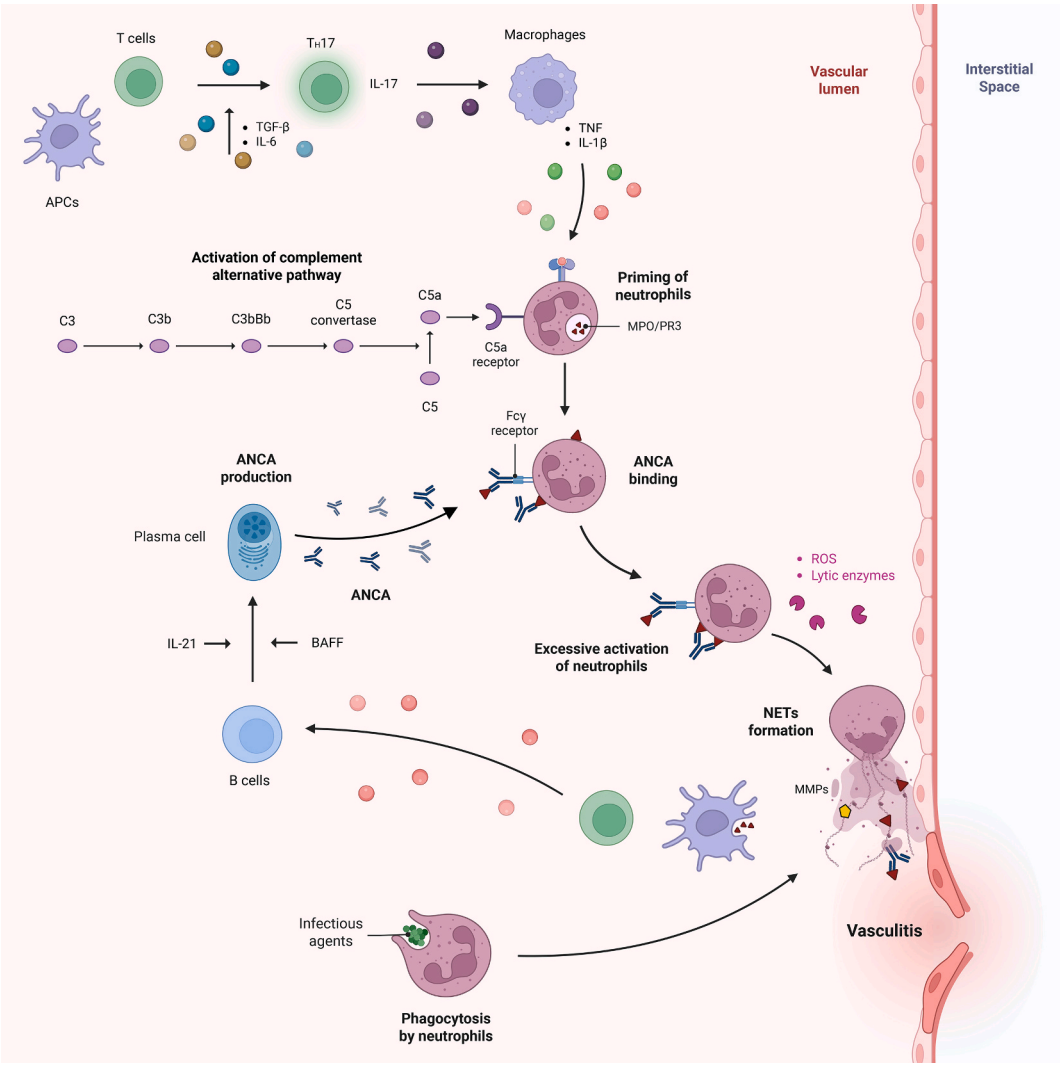

Fig. 3. Integrated immunopathogenic mechanisms in ANCA-associated vasculitis. The loss of tolerance to myeloperoxidase (MPO) and proteinase 3 (PR3) triggers an autoimmune response involving both innate and adaptive immune systems. Antigen-presenting cells (APCs) activate $CD4^+$ T cells, promoting the differentiation of Th17 cells and the release of IL-17A, which enhances the production of cytokines by macrophages. Complement activation through C5a–C5aR signaling primes neutrophils, enabling ANCA binding and Fcγ receptor engagement. This leads to respiratory burst and degranulation. Impaired degradation of neutrophil extracellular traps (NETs) exposes autoantigens, histones, and matrix metalloproteinases (MMPs), thereby sustaining vascular injury. B-cell activating factor (BAFF) and T-cell-derived IL-21 further drive chronic ANCA production, thus reinforcing the inflammatory loop. Based on Nakazawa et al. [41]. Created in BioRender. Domingos, T.G. (2026) https://BioRender.com/v7trxn1

3.3.3. *Complement system activation*

The complement system plays a central role in the pathophysiology of AAV, particularly in disease associated with MPO-ANCA [61].

Studies in mouse models have shown that the alternative complement pathway is essential for the development of the disease. Mice deficient in complement component 4 (C4) develop vasculitis when administered MPO-ANCA, like normal mice. However, mice lacking complement component 5 (C5) or factor B do not develop the disease, which suggests the importance of this pathway [61]. One key mechanism involves the activation of neutrophils by the anaphylatoxin C5a. Upon binding to C5a receptor 1 (C5aR1), C5a amplifies neutrophil activation and drives necrotizing small-vessel injury across multiple organs, with glomerulonephritis (GN) serving as a representative example of this pathogenic process [62,63]. Consistent with these experimental findings, clinical studies have shown elevated factor B and properdin, together with glomerular deposition of alternative-pathway components, supporting a self-amplifying C5a–neutrophil feedback loop in active disease [64].

C5a also induces neutrophil tissue factor release, contributing to a hypercoagulable state in patients with vasculitis [44,65]. Furthermore, elevated serum levels of C3a and C5a are observed in patients with active vasculitis, which supports the activation of the alternative pathway and the stimulation of neutrophils through C5aR1 [43,66].

These insights into the C5a–C5aR1 axis are not only mechanistic but have also motivated clinical trials of targeted inhibitors, underscoring the translational relevance of complement activation in AAV.

Altogether, neutrophil activation, NETs formation, and complement amplification establish a self-perpetuating cycle that promotes endothelial injury and necrotizing vasculitis.

3.4. *Clinical manifestations*

According to the 2012 Revised Chapel Hill Consensus Conference definitions, AAV is a group of necrotizing small-vessel vasculitides characterized by few or no immune deposits, most associated with MPO-ANCA or PR3-ANCA [1].

Despite these predominant patterns, AAV displays marked clinical heterogeneity, with manifestations varying widely according to the

specific subtype, the organs involved, and the extent of vascular injury [67]. GPA typically involves the upper and lower respiratory tracts, where granulomatous inflammation may precede systemic disease and occasionally extend to ocular or orbital structures [67–69]. MPA predominantly affects the kidneys, usually manifesting as pauci-immune necrotizing glomerulonephritis with microscopic hematuria and non-nephrotic proteinuria, and may present with rapidly progressive renal dysfunction, often accompanied by pulmonary capillaritis or interstitial lung disease [4,67–70]. EGPA combines asthma, eosinophilia, and nasal polyps, and typically progresses through overlapping allergic, eosinophilic, and vasculitic phases. ANCA-positive forms exhibit vasculitic features such as neuropathy, whereas ANCA-negative forms are characterized by eosinophil-driven cardiac and pulmonary injury [67,68,71]. Disease presentation and severity are determined by the level of vascular involvement and disease activity [72].

Early recognition of these organ-specific features and timely initiation of therapy are critical to prevent irreversible damage and improve long-term outcomes. Table 2 summarizes the spectrum of organ involvement across the three principal AAV subtypes.

Across all subtypes, patients may exhibit nonspecific constitutional symptoms, such as malaise, fever, fatigue, and weight loss, that can precede organ-specific involvement by several weeks or months [68,73].

Respiratory involvement also contributes to subtype differentiation. GPA is mainly characterized by granulomatous upper and lower airway disease, whereas EGPA is dominated by asthma and eosinophilic pulmonary inflammation [67–69]. In MPA, pulmonary involvement includes diffuse alveolar hemorrhage (DAH) and interstitial lung disease, the latter is particularly associated with MPO-ANCA positivity, often shows a usual interstitial pneumonia (UIP) pattern, and is reported more frequently in Japanese and other Asian cohorts than in predominantly Caucasian populations [79–81].

Cardiac and neurological manifestations are most prognostically relevant in EGPA, reflecting eosinophil-driven myocardial and peripheral nerve damage [67,68,71,74]. Although GPA is most often associated with central nervous system involvement due to its granulomatous pattern, central nervous system (CNS) manifestations may also occur in MPA and EGPA, albeit infrequently [74,78].

Renal involvement is the key prognostic determinant in AAV, most prominent in MPO-ANCA MPA, where pauci-immune necrotizing glomerulonephritis is the dominant renal lesion and may lead to rapidly progressive loss of kidney function [4,67–70]. PR3-ANCA GPA can also develop glomerulonephritis, but typically within a broader multisystemic pattern and with a higher relapse tendency [75,76]. In contrast, renal disease is less frequent and usually milder in EGPA, occurring mainly in ANCA-positive vasculitic forms [67,68,71]. These patterns reflect the subtype-specific immunopathogenic pathways driving renal involvement.

Taken together, these phenotypic patterns reflect the underlying immunopathogenic mechanisms, namely granulomatous inflammation in PR3-ANCA GPA, pauci-immune necrotizing vasculitis (without granulomas) in MPO-ANCA MPA, and eosinophilic inflammation in EGPA. Integrating these mechanisms facilitates accurate subtype differentiation and prognostic assessment, while providing a foundation for continued progress toward precision-based therapy.

3.5. Diagnosis

A comprehensive understanding of the immunopathogenic mechanisms underlying AAV is critical for accurate diagnosis. The diagnostic process should therefore integrate clinical presentation, laboratory and imaging findings, and, whenever possible, histological confirmation, to capture both the systemic and organ-specific dimensions of the disease.

The diagnosis can be particularly challenging, as these are rare diseases with highly heterogeneous and often non-specific clinical presentations. They may be encountered in virtually any medical specialty; ANCA testing can be negative or non-specific; and histological

Table 2
Clinical spectrum of organ involvement in ANCA-associated vasculitis.

Organ/System	GPA	MPA	EGPA
Cutaneous System	Purpura, nodules, and ulcerations are frequent due to granulomatous inflammation of dermal arterioles [68,73].	Purpura, skin ulcers, and livedo may be observed [68,73].	Purpura and subcutaneous nodules are common, often associated with eosinophilic infiltration [68].
Cardiovascular System	Cardiac involvement may manifest as conduction abnormalities or, less commonly, as pericarditis, myocarditis, or ischemic events [68].	Cardiac manifestations include transient conduction disturbances and reduced ventricular contractility [68].	Cardiac disease is frequent and is a leading cause of mortality due to eosinophilic myocarditis or endomyocardial fibrosis [67,71,74].
ENT System	ENT disease is highly prevalent and may precede systemic involvement. Manifestations include chronic sinusitis, nasal crusting, septal perforation, subglottic stenosis, and may extend to the orbit, causing scleritis, uveitis, or orbital pseudotumor [67–69].	ENT involvement is less frequent than in GPA; when present, it may include mild sinusitis or otitis [67].	Nasal polyps and chronic eosinophilic sinusitis dominate the presentation [68,72].
Gastrointestinal System	GI involvement includes abdominal pain and bleeding. Severe hemorrhage or perforation are rare but associated with poor outcomes [4,68].	Abdominal pain and intestinal bleeding may occur due to mesenteric vasculitis [67].	Gastrointestinal involvement in EGPA is characterized by eosinophilic inflammation, with manifestations including abdominal pain [12].
Renal/Urinary System	Renal involvement occurs in a substantial proportion of patients, usually as pauci-immune necrotizing crescentic GN with microscopic hematuria and non-nephrotic proteinuria [4,67–70]. It generally occurs within a broader multisystemic phenotype, and PR3-ANCA positivity is associated with a higher relapse risk [75,76].	Renal involvement is the hallmark of MPA and is often severe, frequently associated with MPO-ANCA. It may present as renal-limited vasculitis in older patients and may progress rapidly as RPGN, with a high risk of irreversible kidney damage at onset [4,67–70].	Renal disease is uncommon and usually mild; when present, mainly in ANCA-positive cases, it may show pauci-immune GN or eosinophilic interstitial nephritis, with progression to kidney failure being rare [3,67–69].
Common features	Across renal AAV, common features include pauci-immune necrotizing crescentic GN, microscopic hematuria, often with dysmorphic erythrocytes or red-cell casts, and usually non-nephrotic proteinuria [4,67–70,77].		

(continued on next page)

Table 2 (*continued*)

Organ/System	GPA	MPA	EGPA
Neurological System	Neurological involvement is less commonly peripheral; however, GPA is the subtype most associated with CNS disease, including pachymeningitis and cranial neuropathies [74,78].	Neurological involvement is predominantly peripheral, most commonly presenting as mononeuritis multiplex due to ischemic nerve injury [74].	Neurological manifestations are frequent and primarily peripheral, driven by eosinophilic inflammation or vasculitis, and may lead to persistent deficits [74].
Respiratory System	Disease of the upper and lower respiratory tract disease are defining features. Nodules, cavitary lesions, and DAH are typical, often causing dyspnea, cough, and hemoptysis [67–69].	Pulmonary involvement occurs in nearly half of MPA patients, with manifestations such as DAH and interstitial lung disease, often with a UIP pattern. UIP may precede MPA in MPO-ANCA patients and is less responsive to immunosuppressants, while non-UIP patterns often respond better [79,80].	Asthma is nearly universal and often precedes vasculitis by years. Pulmonary infiltrates and DAH may occur, particularly in ANCA-positive cases [12,67].

ANCA: antineutrophil cytoplasmic antibodies; CNS: central nervous system; DAH: diffuse alveolar hemorrhage; EGPA: eosinophilic granulomatosis with polyangiitis; ENT: ear, nose, and throat; GI: gastrointestinal; GN: glomerulonephritis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; RPGN: rapidly progressive glomerulonephritis; UIP: usual interstitial pneumonia.

confirmation is not always feasible, with the sensitivity and specificity of biopsy varying according to the organ involved.

At present, no universally accepted diagnostic criteria exist for AAV. Notably, updated classification criteria were proposed in 2022 by the ACR/EULAR, aiming to differentiate AAV subtypes [12].

3.5.1. *Clinical, laboratory, and imaging assessment*

In cases of pulmonary involvement, respiratory symptoms such as persistent cough or dyspnea warrant a complete blood count to detect possible hemoglobin decline, which may indicate pulmonary hemorrhage [82]. Definitive diagnosis of DAH requires bronchoscopy with bronchoalveolar lavage (BAL). BAL also enables microbiological sampling to assess for infection [83]; however, in life-threatening DAH, immunosuppressive therapy should not be delayed when AAV is strongly suspected, and empirical antimicrobial coverage may be required while microbiological results are pending. Treatment decisions should therefore be individualized according to clinical severity, infectious risk, and the likelihood of active vasculitis [12,82,83]. In all patients presenting with DAH, testing for anti–glomerular basement membrane (anti-GBM) antibodies is mandatory, as recommended by the EULAR guidelines. This evaluation is crucial because a subset of AAV cases, particularly those positive for MPO-ANCA, may overlap with anti-GBM disease, which carries a poorer renal prognosis and may require prompt plasma exchange in addition to standard immunosuppressive therapy [12].

All patients should undergo initial chest imaging to assess for thoracic involvement, even in the absence of respiratory symptoms, as pulmonary manifestations are common and may influence diagnosis and management. Chest X-ray is a rapid, accessible screening tool and is typically recommended as the first-line modality [84]. However, chest X-ray may miss subtle or early findings, while chest computed tomography (CT) offers higher sensitivity for detecting nodules, masses, cavitation, and interstitial changes, which are key discriminators in GPA and MPA [85].

For suspected upper airway involvement, CT of the paranasal sinuses is indicated to assess structural and inflammatory changes [86–88]. Additionally, otorhinolaryngologic examination is a key component of the diagnostic process [82].

In all patients, it is essential to perform a urinalysis to identify microhematuria and/or proteinuria, even in the absence of renal dysfunction, edema, or new-onset hypertension [82]. If proteinuria is detected, quantification should be performed, using the protein-to-creatinine ratio or a 24-h urine collection [82]. Microscopic examination of urine sediment is also recommended to detect dysmorphic erythrocytes, particularly acanthocytes, which are highly specific markers of glomerular origin and strongly suggest active glomerular injury [77].

Cardiac assessment is essential, particularly in EGPA, where cardiac involvement strongly influences prognosis [67]. A baseline electrocardiogram (ECG) and measurement of cardiac biomarkers (high-sensitivity troponin and N-terminal pro–B-type natriuretic peptide) are recommended for all patients, followed by transthoracic echocardiography to screen for ventricular dysfunction and pericardial disease. When symptoms, abnormal biomarkers, or unexplained ECG or echocardiographic findings raise concern, cardiac magnetic resonance imaging (MRI) should be performed to detect myocarditis or endomyocardial fibrosis [67,82].

For patients presenting with symptoms of peripheral neuropathy, such as paresthesia, numbness, or muscle weakness, electroneuromyography is indicated [89]. In suspected CNS disease, manifested by seizures, cognitive impairment, or focal neurological deficits, brain or spine MRI is recommended to detect structural lesions [78].

These investigations not only establish the extent of organ involvement but also provide the clinical framework within which serological and histopathological results must be interpreted.

3.5.2. *Serologic assessment of ANCA*

Because ANCA are directly implicated in the pathophysiology of AAV, their detection represents a pivotal step in diagnostic confirmation and disease stratification.

As summarized in Table 1, ANCA positivity and antigen specificity vary across AAV subtypes. Accordingly, serological evaluation is strongly recommended as part of the diagnostic work-up [90].

Currently, the main methods for ANCA detection are indirect immunofluorescence (IIF) and antigen-specific immunoassays, including enzyme-linked immunosorbent assay (ELISA)-based methods [90,91]. IIF distinguishes cytoplasmic (C-ANCA) and perinuclear (P-ANCA) patterns, generally associated with PR3-ANCA and MPO-ANCA, respectively [91]. However, atypical fluorescence patterns may occur and can reflect antibodies against other neutrophil antigens, such as lactoferrin, elastase, or bactericidal permeability-increasing protein; these specificities are not routinely used for AAV diagnosis because their diagnostic and prognostic significance is less well established than that of PR3-ANCA and MPO-ANCA [90–92]. Accordingly, antigen-specific immunoassays for PR3-ANCA and MPO-ANCA are preferred in suspected GPA and MPA because they directly detect the clinically validated ANCA specificities most strongly associated with AAV diagnosis and classification [90–92].

The choice of fixative strongly influences ANCA pattern recognition. Ethanol fixation promotes artifactual MPO redistribution to the nuclear periphery, producing the characteristic P-ANCA pattern. In contrast, formalin preserves the native intracellular localization of granule proteins, preventing MPO perinuclear redistribution; as a result, anti-MPO antibodies no longer yield a P-ANCA pattern, while the cytoplasmic staining typical of PR3-ANCA (C-ANCA) is maintained [91].

ELISA provides antigen-specific identification of PR3-ANCA and MPO-ANCA [90,91]. In this assay, antigens are immobilized on a solid phase, and autoantibodies in the patient's serum bind specifically to

them. This interaction is subsequently detected by an enzyme-labeled antibody, enabling a quantitative and specific measurement [90].

Current consensus recommends high-quality antigen-specific immunoassays (PR3- and MPO-ANCA) as the preferred initial screening method for GPA and MPA, without the categorical need for IIF. Indirect immunofluorescence may be reserved for cases with negative or low-positive immunoassay results when clinical suspicion remains high [92]. This recommendation follows the 2017 revised international consensus on ANCA testing [92] and its 2020 update [90].

Nonetheless, ANCA negativity does not exclude AAV. A considerable subset of patients with GPA or MPA may test negative by both IIF and antigen-specific immunoassays. In these cases, if clinical suspicion remains high, repeat testing with complementary methodologies and histopathological evaluation of affected tissue is warranted [92]. Conversely, ANCA positivity alone is insufficient for diagnosis, as false-positive results may occur. These are particularly associated with low-titer immunoassay results and with several non-vasculitic conditions, including inflammatory bowel disease, autoimmune liver disease, systemic autoimmune disorders, chronic infections such as infective endocarditis, and exposure to drugs like hydralazine, propylthiouracil, minocycline, or levamisole-adulterated cocaine [92]. In that regard, serologic testing should always be interpreted within the clinical context and supported by histopathological confirmation whenever feasible to ensure diagnostic accuracy and prognostic relevance.

3.5.3. Histopathological assessment

Histopathology provides the most definitive confirmation of vasculitic injury and remains indispensable for correlating serologic findings with underlying tissue pathology, thereby guiding therapeutic decision-making in AAV [93]. The diagnostic yield of biopsy varies by site, with tissue samples obtained from the kidney, lung, muscle, skin, nerve, or nasal mucosa depending on the clinical context [94]. Among these, renal biopsy provides the highest diagnostic value [93].

Renal histology typically reveals pauci-immune necrotizing crescentic GN (Fig. 4) [4]. Increasing emphasis is placed on assessing not only acute lesions (cellular crescents, fibrinoid necrosis) but also chronic features such as glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis [93].

Beyond descriptive morphology, renal biopsy findings can also be categorized using prognostic classification systems, such as the Berden histopathologic classification and the ANCA Renal Risk Score (ARRS) [95,96]. These tools are widely used and are further detailed in the Prognosis section.

Despite their specificity, histopathological findings may occasionally be inconclusive or nonspecific [74]. While biopsy continues to play an important role in diagnosis, it may be unnecessary when clinical presentation and serological results are highly suggestive of AAV or when the risks outweigh the expected diagnostic benefit [4,12].

Accurate diagnosis requires integration of clinical, serologic, and histopathologic findings, as ANCA testing alone is insufficient and biopsy remains the gold standard when feasible.

3.6. Therapeutic approaches

Accurate diagnosis and early identification of organ-threatening involvement are decisive for optimizing therapeutic outcomes. Recent advances in classification and diagnostic precision have directly informed treatment algorithms, paving the way for more targeted, steroid-sparing regimens.

Over recent decades, treatment of AAV has advanced considerably, with the incorporation of more targeted and safer therapies aimed at achieving sustained remissions with fewer adverse effects [97]. Historically, prior to the introduction of glucocorticoids (GC) in combination with cyclophosphamide (CYC), AAV carried a dismal prognosis, with one-year mortality exceeding 80% [97]. The advent of GC plus CYC dramatically improved outcomes, with two-year survival rates approaching 75% [97].

Treatment of AAV is typically divided into two phases: induction of remission and maintenance of remission (Fig. 5). Each phase should be tailored according to disease severity and comorbidities [4,46]. Induction, generally lasting three to six months, aims to rapidly suppress active inflammation and halt organ damage. This is followed by maintenance therapy, typically extending over two to four years, to prevent relapse [4]. Current recommendations largely align the management of GPA and MPA, given their immunopathological and therapeutic similarities, whereas EGPA requires a distinct approach due to its specific clinical and pathophysiological features.

3.6.1. Induction of remission in GPA and MPA

In patients with life-threatening organ involvement, such as GN, pulmonary hemorrhage, or cardiac disease, high-dose GC combined with potent immunosuppressants is recommended [12].

Historically, CYC has been the standard of care and remains an important option in severe cases, particularly in patients with severe disease involving vital organs [12]. However, several clinical trials, including the landmark RAVE trial, demonstrated that rituximab (RTX), an anti-CD20 monoclonal antibody, is non-inferior to CYC and superior in preventing relapse in relapsing disease, though patients with severe renal impairment (serum creatinine >4 mg/dL) were excluded from this trial [98]. As such, CYC is sometimes preferred in these situations. In selected cases, combination therapy with RTX and CYC may be considered to reduce cumulative CYC exposure [70].

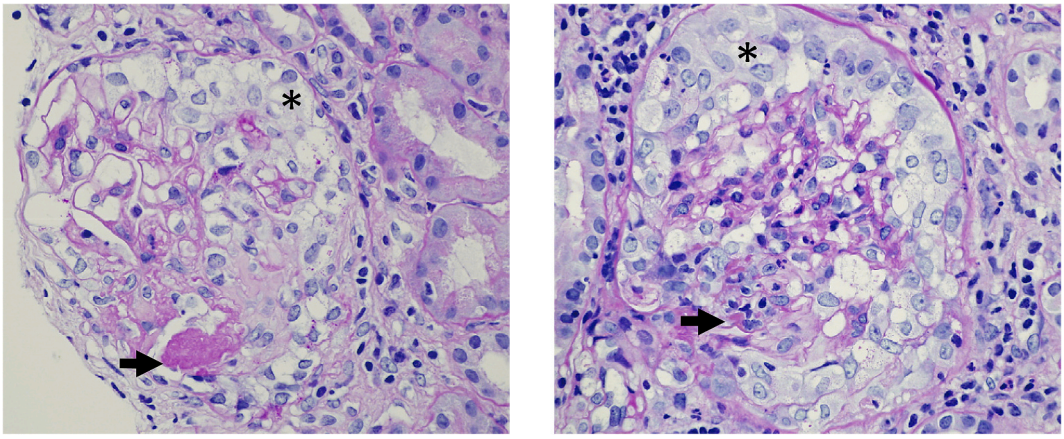

Fig. 4. Renal histopathological findings. Renal biopsy from a patient with ANCA-associated vasculitis showing pauci-immune necrotizing glomerulonephritis, with fibrin deposition (arrow) and cellular crescents (*). Adapted from Molnár et al. [5], CC BY 4.0.

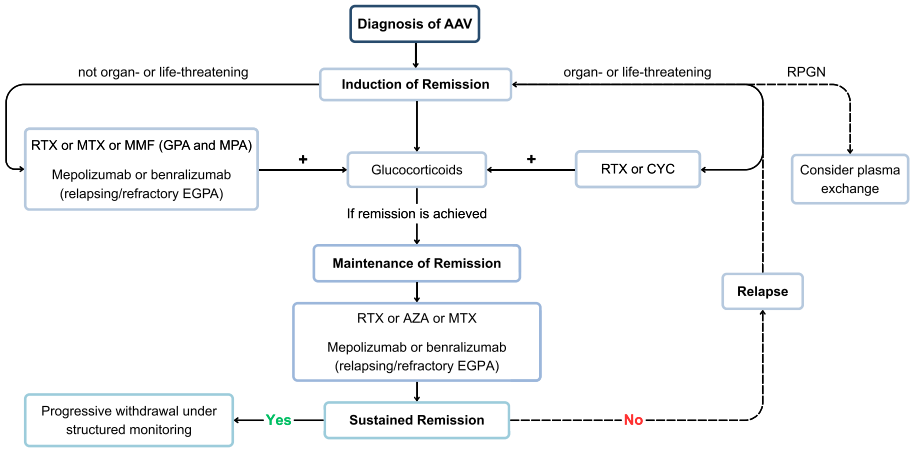

Fig. 5. Therapeutic management algorithm for ANCA-associated vasculitis (AAV). In granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), remission is induced with glucocorticoids plus rituximab (RTX) or cyclophosphamide (CYC), while methotrexate (MTX) or mycophenolate mofetil (MMF) may be considered in non–organ-threatening disease. In eosinophilic granulomatosis with polyangiitis (EGPA), mepolizumab or benralizumab may be considered for relapsing or refractory disease. Maintenance relies on RTX, azathioprine (AZA), MTX, or MMF, and plasma exchange remains an option for rapidly progressive glomerulonephritis (RPGN) or severe alveolar hemorrhage. Relapse generally requires re-initiation of induction therapy. Adapted from Hellmich et al. [12].

GC remains a cornerstone of induction therapy. However, concerns about cumulative toxicity, especially in elderly patients [99], have prompted evaluation of reduced-dose regimens. The PEXIVAS trial [100], which enrolled patients with severe disease defined by reduced estimated glomerular filtration rate (eGFR <50 mL/min/1.73 m^2) or pulmonary hemorrhage, demonstrated that a reduced-dose GC regimen was as effective as the standard approach, with lower risk of adverse effects [100]. Current consensus favors initiating high-dose therapy with tapering to 5 mg/day by four to five months in severe disease, while lower-dose regimens may be considered in patients without organ-threatening manifestations [12].

In patients with non–organ-threatening disease, RTX is recommended as the preferred induction agent in current guidelines, while methotrexate (MTX) and mycophenolate mofetil (MMF) remain alternatives in selected cases [12]. Although both MTX and MMF have been associated with higher relapse rates, their use may be guided by disease phenotype and renal function [101,102]. MTX remains a useful option for localized or ENT-predominant GPA without renal impairment or other organ-threatening manifestations, but should be used with caution and at reduced doses when eGFR falls below 60 mL/min/1.73 m^2 and is contraindicated below 30 mL/min/1.73 m^2 [70,101,103]. Particular caution is also warranted when MTX is combined with other antifolate agents, including co-trimoxazole, as additive toxicity may increase the risk of cytopenia or myelosuppression [104]. In contrast, MMF may be more appropriate in selected patients with non-severe ANCA-associated GN, particularly when renal function limits MTX use [12,70,102,105].

Within this evolving therapeutic landscape, avacopan, an oral C5aR1 antagonist that disrupts the C5a–neutrophil amplification loop, exemplified the translation of complement biology into targeted therapy for GPA and MPA [106,107]. Following the ADVOCATE trial, it was approved as an adjunct to standard induction therapy and incorporated into treatment recommendations as a potential strategy to reduce GC exposure [12,106]. However, the ADVOCATE publication was retracted in 2026 following concerns regarding trial conduct, endpoint assessment, and the reliability of the reported efficacy findings [108]. These concerns prompted the United States Food and Drug Administration to propose the withdrawal of TAVNEOS approval and the European Medicines Agency's Committee for Medicinal Products for Human Use to recommend revocation of the European marketing authorisation for Tavneos; postmarketing reports of serious drug-induced liver injury have further contributed to the reassessment of its benefit–risk profile [109,110]. At the time of writing, both regulatory procedures remained ongoing, and no final decisions had been issued [109,110], while the AAV management recommendations cited in this review continued to include avacopan [12]. Accordingly, these developments have introduced substantial uncertainty regarding the evidence supporting the efficacy and GC-sparing role of avacopan. Its future place in AAV treatment remains uncertain and should be reassessed in light of final regulatory decisions, the response of the marketing authorisation holder, future guideline updates, and the availability of additional reliable evidence.

Plasma exchange may be considered as an adjunctive therapy in patients with severe GN (serum creatinine >3.4 mg/dL or dialysis requirement) or alveolar hemorrhage with hypoxemia [12,70]. The earlier MEPEX trial demonstrated a short-term reduction in risk of progression to end-stage kidney disease (ESKD) with plasma exchange in severe renal vasculitis, although without sustained long-term benefit [111]. More recently, PEXIVAS found no overall survival or renal survival advantage [100], suggesting that plasma exchange should be reserved for carefully selected cases [12].

3.6.2. *Induction of remission in EGPA*

Therapeutic strategies in EGPA differ from those used in GPA and MPA, reflecting its distinct pathophysiology and clinical phenotype. Because EGPA-specific trials are scarce, many recommendations are extrapolated from those diseases, and the intensity of induction therapy is guided primarily by the presence and severity of organ- or life-threatening manifestations.

In patients with organ- or life-threatening manifestations, high-dose GC should be combined with either CYC or RTX, with RTX increasingly recognized as an alternative to CYC rather than being reserved for cases of intolerance or contraindication [12,103]. In the absence of such manifestations, GC alone can induce remission in most patients, but relapses are frequent during tapering, so an additional agent is often considered to limit cumulative GC exposure [12,103]. Mepolizumab (MEPO), an interleukin-5 inhibitor, is the best-established GC-sparing option in this setting: the ACR conditionally favors adding it to GC at induction, whereas EULAR positions it primarily for relapsing or refractory disease [12,103]. MEPO can therefore be used as part of remission induction in non-severe EGPA and not only for relapse prevention [103,112]. Benralizumab, an interleukin-5 receptor antagonist, has since shown non-inferiority to MEPO in relapsing or refractory EGPA and represents a further eosinophil-targeted option [113].

As remission is achieved, the therapeutic focus must shift from inflammation control to long-term relapse prevention, balancing efficacy with minimization of cumulative immunosuppression.

3.6.3. Maintenance of remission in GPA and MPA

Following induction, maintenance therapy aims to reduce relapse risk, which remains high in AAV [4]. The MAINRITSAN [114] and RITAZAREM [115] trials demonstrated that fixed-interval RTX was superior to azathioprine (AZA) for maintaining remission, with significantly lower relapse rates [70,114,115]. Alternatives include AZA, MTX, or MMF, though these are associated with higher relapse risk [70] and are generally reserved for situations where RTX is contraindicated or unavailable [12].

In less severe cases without life-threatening involvement, maintenance therapy may be continued with the same agent used during induction, commonly RTX, MTX, or AZA [12].

3.6.4. Maintenance of remission in EGPA

MEPO has demonstrated efficacy in relapsing, non–life-threatening EGPA. The MIRRA trial confirmed that MEPO significantly reduced relapse rates, improved disease control, and lowered GC requirements, with a favorable safety profile [112]. More recently, benralizumab demonstrated non-inferiority to MEPO in the MANDARA trial and is now also approved for relapsing or refractory EGPA [113]. In cases of organ-threatening EGPA, maintenance follows strategies similar to GPA and MPA, with AZA, MTX, RTX, MEPO, or other approved biologic options selected according to disease phenotype, prior response, and treatment availability [12].

The management of AAV is evolving from broad immunosuppression to mechanism-based precision therapy, integrating B-cell depletion and eosinophil-targeted biologics to achieve sustained remission with minimal GC exposure and toxicity.

3.6.5. Toward biomarker-guided treatment selection

Despite these advances, treatment selection in AAV is still guided mainly by clinical phenotype and risk considerations, including disease severity, organ involvement, relapse risk, and risk of GC-related toxicity, rather than by validated molecular biomarkers [12,107]. Refining therapy beyond ANCA antigen specificity will require biomarkers that reflect individual disease biology and predict treatment response, an area in which immunological, transcriptomic, and urinary candidates are beginning to emerge.

Serial $CD19^+$ B-cell and ANCA monitoring has been tested prospectively in the MAINRITSAN2 trial, in which an individually tailored RTX re-infusion strategy based on $CD19^+$ B-cell reappearance and/or ANCA reappearance or an increase in titer was associated with relapse rates that were not statistically different from fixed-schedule RTX, while using fewer infusions [116].

Pharmacogenomic approaches may also contribute to future treatment individualization, although evidence in AAV remains limited. In a pharmacogenomic analysis of the RAVE trial, variants in Fcγ receptor and cytochrome P450 genes were examined in relation to response to RTX or CYC, but no pharmacogenomic marker has yet been validated to guide routine induction treatment selection [117].

Tissue-based profiling has shown more direct therapeutic potential: spatial and single-cell transcriptomic analysis of kidney biopsies from patients with ANCA-associated glomerulonephritis (ANCA-GN) identified cytokine-producing $CD4^+$ and $CD8^+$ T cells as a pathogenic renal inflammatory signature and, through computational drug prediction, nominated ustekinumab, an anti–IL-12/IL-23 p40 monoclonal antibody, which was associated with clinical and renal responses when used as add-on therapy in a small proof-of-concept series [118].

Non-invasively, urinary soluble CD163 has shown the ability to distinguish active renal vasculitis from remission and extrarenal disease activity, and, particularly when combined with urinary monocyte chemoattractant protein-1 (MCP-1) or new/worsening proteinuria, may help identify renal inflammatory activity and inform decisions about repeat biopsy in selected clinical contexts [119,120].

However, these approaches remain insufficiently validated for routine treatment selection and should currently be interpreted as promising tools rather than established decision-making instruments [107].

3.6.6. Emerging therapies

As biomarker-informed stratification evolves, emerging therapies targeting complement, B cells, plasma cells, and eosinophil-associated pathways may further expand individualized treatment options.

Upstream complement inhibition is under study with the factor B inhibitor iptacopan [121] and the anti–factor Bb antibody ruxoprubart [122], both in phase 2 studies combined with RTX. Obinutuzumab, a type II anti-CD20 antibody, is being investigated for its ability to achieve deeper B-cell depletion and reduce the risk of relapse [123]. In highly refractory AAV, plasma cell–directed therapy with daratumumab, an anti-CD38 monoclonal antibody, has also been reported in small case-based studies, but remains experimental and requires prospective validation [124]. Early-phase cellular therapies, including anti-CD19 chimeric antigen receptor T-cell (CAR-T) products, are entering clinical evaluation for autoimmune diseases [125–127].

In EGPA, investigational strategies are also expanding beyond currently approved biologics. Depemokimab, a long-acting anti–IL-5 antibody, is currently being evaluated in the phase 3 OCEAN trial in adults with relapsing or refractory EGPA, aiming to assess whether sustained IL-5 blockade can provide prolonged remission and further GC tapering [128]. Janus kinase (JAK) inhibition is another early investigational strategy in EGPA, supported by preliminary clinical experience with tofacitinib and nonclinical data with selective JAK1 inhibition, although controlled clinical evidence is still lacking [129]. In parallel, tezepelumab, an anti-thymic stromal lymphopoietin (TSLP) inhibitor monoclonal antibody, is being investigated in the phase 2b RACEMATE trial as a strategy to target epithelial alarmin-driven inflammation in non-severe active EGPA [130].

Together, these emerging therapies reflect a shift toward more targeted and durable approaches in AAV and EGPA, aiming to achieve sustained remission while minimizing treatment-related toxicity.

3.7. Prognosis

The marked improvement in survival observed over recent decades largely reflects advances in immunosuppressive therapy and earlier disease recognition. Nevertheless, residual morbidity remains substantial, emphasizing the need for continuous refinement of treatment and monitoring strategies.

3.7.1. Overall survival

The introduction of modern combined immunosuppressive regimens, as well as the use of RTX, has substantially improved survival in AAV [131].

In a recent large retrospective observational study from Istanbul (1997–2021), the 5-year survival rate was 88.1%, and overall survival over the full follow-up period was 80.3%. A stratification of patients according to clinical subtypes revealed that GPA patients demonstrated 5-year and overall survival rates of 91% and 84.5%, respectively. In contrast, MPA patients exhibited significantly lower rates of 81% and 67.2%, respectively [132]. Despite these advances, infection remains the leading cause of mortality during both induction and maintenance phases, followed by active vasculitis, cardiovascular disease, and malignancy related to cumulative immunosuppression [12,133].

3.7.2. Prognostic factors and scores

Advanced age has been identified as a major independent predictor of mortality in AAV, and male sex has also been associated with a less favorable outcome [133]. Current evidence suggests that ANCA specificity provides more prognostic information than clinical subtype alone. Specifically, patients with MPO-ANCA have a higher likelihood of developing kidney failure, whereas those with PR3-ANCA are more prone to relapse [75].

These variables are incorporated into several prognostic and damage-assessment tools. In EGPA, the Five-Factor Score (FFS) remains useful for mortality risk assessment, but it does not capture all clinically relevant manifestations, particularly peripheral nervous system involvement; therefore, severe neurologic disease such as mononeuritis multiplex may still justify more intensive immunosuppression even in the absence of FFS-defined poor-prognosis factors [134,135]. The Birmingham Vasculitis Activity Score (BVAS) quantifies disease activity and correlates with relapse risk [136], while the Vasculitis Damage Index (VDI) measures accumulated, often treatment-related, organ damage [137]. In research settings, the Combined Damage Assessment Index (CDA) has been used to capture a broader spectrum of damage, although its greater complexity and lower feasibility make it less suitable for routine clinical practice, in contrast to the VDI [138].

In addition, kidney-specific instruments provide robust prognostic information: the Berden histopathologic classification stratifies biopsy findings, with clear predictive value for renal survival [95], and the ARRS integrates eGFR at presentation with the proportion of normal glomeruli and crescents, allowing accurate risk stratification for ESKD at diagnosis [96]. Collectively, these tools encompass both general and organ-specific predictors: FFS for mortality in EGPA, BVAS for activity, VDI for cumulative damage, and ARRS/Berden for kidney outcomes, supporting individualized clinical decision-making and standardized reporting in research.

3.7.3. Renal prognosis

Renal involvement remains the single most important predictor of outcome [4]. Patients presenting with severely impaired kidney function, particularly those with an estimated glomerular filtration rate below 15 mL/min/1.73 m^2, face a significantly higher risk of mortality and progression to end-stage kidney disease [70]. Long-term follow-up studies report cumulative incidences of kidney failure rising steadily with disease duration.

Renal histopathology provides further prognostic insight: a higher percentage of normal glomeruli on biopsy is strongly associated with renal survival. For patients progressing to kidney failure, transplantation offers excellent outcomes, with a 10-year patient survival rate of approximately 86% reported in contemporary European cohorts, clearly outperforming dialysis [139].

3.7.4. Relapse

Relapse is common in AAV, affecting 15–45% of patients within the first two to three years of follow-up. This variability reflects differences in follow-up duration, patient characteristics, and the choice of maintenance therapy [140]. PR3-ANCA positivity has been shown to consistently predict a substantially higher relapse risk compared with MPO-ANCA [76]. In this context, RTX has demonstrated greater efficacy than AZA for relapse prevention [114].

The presence of additional clinical features, including pulmonary, cardiovascular, and upper respiratory tract involvement, has been associated with an increased risk of relapse. This underscores the importance of a meticulous systemic assessment at the time of diagnosis and during long-term follow-up [75].

Prognosis is now largely determined by ANCA specificity and renal involvement, highlighting the role of individualized risk stratification tools for long-term outcomes.

3.8. Artificial intelligence and digital tools in AAV

Artificial intelligence and digital tools are increasingly being explored in AAV, although their role remains preliminary. Current applications include automated histopathological assessment, disease phenotyping, relapse identification, and the analysis of large real-world datasets. In renal disease, a deep-learning pipeline has been developed to classify glomerular lesions in ANCA-GN according to the Berden histopathological classification [141].

Other data-driven approaches have used registry and electronic health record data to improve disease subclassification, relapse ascertainment, and case identification. For example, model-based clustering of large European registry datasets has identified clinically meaningful GPA/MPA subgroups with prognostic value beyond conventional clinical diagnosis or ANCA specificity [142]. A computable phenotype using ANCA changes, blood and urine tests, imaging findings, immunosuppression status, and treatment modifications has also been developed to identify relapse retrospectively when BVAS data are missing or unreliable [143]. Natural language processing has further improved the identification of AAV cases in electronic health records, reducing dependence on International Classification of Diseases, Tenth Revision (ICD-10) codes alone [144].

Although these approaches have shown promising results in specific applications, their performance and generalizability across different clinical settings remain uncertain. Accordingly, they may support case finding, registry-based research, biopsy assessment, and relapse ascertainment, but they do not replace expert clinical, serological, and histopathological evaluation [141–144].

4. Discussion

The literature describes AAV as an immune-mediated small-vessel vasculitis in which dysregulated immune mechanisms drive vascular injury. The apparent rise in incidence and prevalence likely reflects improved case detection and survival [7,8]. Rates differ by subtype and geography, with GPA more common in Europe and MPA in Asia [15]. As shown in Fig. 2, this geographic variation supports the hypothesis that environmental exposure and latitude may influence disease expression. Beyond improved case ascertainment, rising prevalence may also reflect environmental and epigenetic changes, although their relative contribution remains uncertain.

From genetic predisposition to clinical phenotype, AAV can be understood as a continuum in which genetic background and environmental triggers interact to shape immune dysregulation and disease expression. Susceptibility reflects the combined influence of genomic factors and exposures such as silica, infections, selected medications, and tobacco [21–23]. Together, these factors promote loss of tolerance [42], pathogenic neutrophil activation [39,43], complement activation [57,61], and small-vessel damage [57]. This mechanistic framework supports the biological distinction between PR3-ANCA and MPO-ANCA disease and helps explain differences in clinical presentation, relapse tendency, renal involvement, and treatment response. Nevertheless, the relative contribution of each pathogenic driver varies across patients and remains difficult to define within current clinical classification.

Translating this biology into a diagnosis still relies on the integration of clinical, serological, and histopathological data [12]. However, while PR3/MPO immunoassays are central, the persistence of ANCA-negative cases and the limitations of serology in atypical or limited disease reinforce the need to interpret ANCA testing within a broader clinical and histological framework.

High clinical suspicion should prompt repeat testing and biopsy when feasible [92]. Renal tissue remains the most informative [93], and kidney-specific tools (Berden classes and the ARRS) add prognostic precision beyond descriptive pathology [95,96]. In practice, a positive ANCA test supports but does not confirm the diagnosis. Biopsy provides the highest diagnostic yield and should be prioritized when management would change. ANCA specificity, organ pattern, and biopsy chronicity should drive treatment and follow-up strategy.

Therapeutically, induction has shifted from CYC-based to RTX-centered strategies for many patients, with CYC retained for selected severe presentations [70,98]. In parallel, reduced-dose GC regimens have shown that disease control can increasingly be achieved with lower GC exposure [100]. These developments mark a clear move toward treatment individualization, although routine treatment selection remains largely guided by clinical phenotype, organ involvement, relapse

risk, and comorbidity rather than by validated molecular predictors [12,70,107].

For maintenance, B-cell depletion reduces relapse more effectively than traditional antimetabolites and is the preferred approach when available and appropriate [114,115]. Recent trials have shown that GC exposure can be reduced without compromising short-term disease control, while plasma exchange is no longer supported for routine use after PEXIVAS demonstrated no overall survival or renal benefit in unselected severe AAV populations [100].

These targeted strategies are likely to broaden further, with agents directed at complement activation, B-cell depletion, plasma-cell persistence, and eosinophil-associated pathways now being evaluated across the AAV spectrum [121–130]. However, most of these approaches remain investigational, and it remains unclear whether they will provide more durable remission, better organ protection, or lower cumulative treatment-related toxicity than current regimens.

Prognosis has improved substantially with contemporary drug regimens [131], yet long-term outcomes remain driven by age, comorbidity, and especially renal involvement at presentation [75,133]. Because ANCA specificity is related to outcomes, with MPO-ANCA being more closely associated with kidney failure [75], and PR3-ANCA conferring a higher relapse risk [76], reporting the disease based on clinical subtype and ANCA specificity provides clearer risk stratification. Although survival rates now exceed 85% at five years, morbidity remains significant due to treatment-related toxicity and chronic kidney damage. Several scores can help quantify risk, including the FFS for mortality risk assessment in EGPA, the BVAS for disease activity and relapse risk [134,136], and the Berden/ARRS for renal survival [95,96]. Integrating these tools supports standardized prognostic assessment and may help align treatment intensity with long-term renal and systemic risk.

Complementing established prognostic scores, artificial intelligence and digital methods are beginning to be explored in AAV, mainly to support histopathological assessment, the analysis of large clinical datasets, and electronic health record-based case identification, relapse ascertainment, and data-driven disease subclassification [141–144]. Because their accuracy, interpretability, and generalizability across clinical settings remain insufficiently established, these tools should currently be regarded as adjunctive research and decision-support instruments used alongside expert clinical, serological, and histopathological evaluation.

Taken together, these findings mark a turning point in AAV care, from the empirical suppression of inflammation toward strategies that seek to sustain remission, protect organs, and reduce the long-term burden of treatment.

5. Future perspectives

The progress achieved in AAV has changed the clinical landscape, but it has also made the remaining gaps clearer.

One priority is to clarify how environmental exposures, aging-related factors, and epigenetic regulation influence disease expression and long-term outcomes. In parallel, better molecular, urinary, imaging, and tissue-based markers are needed to improve the recognition of active disease, particularly in atypical, limited, ANCA-negative, or clinically silent forms. Such tools may help distinguish persistent inflammation from irreversible damage and support earlier, more confident clinical decisions.

Improving disease assessment is also essential for a more personalized therapeutic approach. In view of the uncertainty surrounding avacopan, the therapeutic potential of complement inhibition in AAV requires confirmation in independent, rigorously conducted studies. Such studies should first establish whether a favorable benefit–risk profile can be demonstrated and, if so, identify the patients most likely to benefit, the optimal treatment duration, and the biomarkers that could guide patient selection and treatment monitoring.

The same principle applies to maintenance therapy. Although RTX-based regimens have improved relapse prevention, the optimal duration of treatment and the safest timing of withdrawal remain uncertain [114]. This is especially relevant in patients with previous relapse, PR3-ANCA disease, persistent low-level ANCA positivity, or incomplete immunological remission [115]. Future work should clarify whether these findings should lead to closer monitoring, individualized retreatment strategies, or simply continued observation.

Looking ahead, artificial intelligence may help connect clinical, histological, registry, and electronic health record data in AAV. Future work should refine and externally validate AI-assisted biopsy evaluation, while also improving tools for relapse ascertainment, patient stratification, and registry-based research [141–144].

Finally, refractory disease and frequent relapses remain among the clearest unmet needs. New approaches, including complement-directed therapies, deeper B-cell depletion, eosinophil-targeted strategies, and cellular therapies such as CAR-T, should be evaluated according to their durability, safety, organ protection, and place within existing treatment pathways. Ultimately, the next step in AAV care is not simply to add more treatments, but to use each option with greater precision, preserving remission while reducing long-term harm.

6. Conclusion

AAV remains a complex group of autoimmune small-vessel vasculitides, in which clinical heterogeneity reflects substantial underlying biological diversity. Differences between PR3-ANCA, MPO-ANCA, and ANCA-negative disease influence organ involvement, relapse risk, renal prognosis, and therapeutic response, making early recognition and integrated clinical, serological, and histological assessment essential for individualized management.

At the same time, advances in immunopathogenesis have reshaped the understanding and treatment of these diseases. The roles of neutrophil activation, NETs formation, complement amplification, B-cell dysregulation, and eosinophil-driven inflammation have helped explain distinct disease phenotypes and supported the development of more targeted approaches. In this context, RTX, MEPO, and benralizumab have expanded therapeutic options and reinforced the move away from broad, GC-heavy immunosuppression toward more selective and potentially safer strategies.

Despite this progress, AAV care remains only partly precision-based. In daily practice, treatment decisions are still guided mainly by disease severity, organ involvement, relapse risk, comorbidity, and treatment availability rather than by validated molecular predictors. The field has therefore moved closer to biologically informed care, but true precision medicine will depend on translating these mechanistic insights into practical tools that help preserve remission, protect organs, reduce the long-term burden of treatment, and ultimately improve both survival and quality of life for patients with AAV.

CRediT authorship contribution statement

Tomás G. Domingos: Conceptualization, Methodology, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Henrique Borges:** Writing – review & editing. **Vítor Silvestre-Teixeira:** Writing – review & editing, Supervision. **Teresa M. Jerónimo:** Conceptualization, Visualization, Writing – review & editing, Supervision.

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Declaration of competing interest

The authors declare that they have no known competing financial

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Data availability

No data were used for the research described in the article.

References

[1] Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1–11. https://doi.org/10.1002/art.37715.
[2] de Groot K, Csernok E, van der Woude D. History of antineutrophil cytoplasmic autoantibodies: milestones in rheumatology. Z Rheumatol 2024. https://doi.org/10.1007/s00393-024-01599-4.
[3] Redondo-Rodriguez R, Mena-Vázquez N, Cabezas-Lucena AM, Manrique-Arija S, Mucientes A, Fernández-Nebro A. Systematic review and metaanalysis of worldwide incidence and prevalence of antineutrophil cytoplasmic antibody (ANCA) associated vasculitis. J Clin Med 2022;11. https://doi.org/10.3390/jcm11092573.
[4] Geetha D, Jefferson JA. ANCA-associated vasculitis: core curriculum 2020. Am J Kidney Dis 2020;75:124–37. https://doi.org/10.1053/j.ajkd.2019.04.031.
[5] Molnár A, Studinger P, Ledó N. Diagnostic and therapeutic approach in ANCA-associated glomerulonephritis: a review on management strategies. Front Med (Lausanne) 2022;9. https://doi.org/10.3389/fmed.2022.884188.
[6] Kronbichler A, Lee KH, Denicolò S, Choi D, Lee H, Ahn D, et al. Immunopathogenesis of ANCA-associated vasculitis. Int J Mol Sci 2020;21:1–27. https://doi.org/10.3390/ijms21197319.
[7] Watts RA, Hatemi G, Burns JC, Mohammad AJ. Global epidemiology of vasculitis. Nat Rev Rheumatol 2022;18:22–34. https://doi.org/10.1038/s41584-021-00718-8.
[8] Nelveg-Kristensen KE, Szpirt W, Carlson N, McClure M, Jayne D, Dieperink H, et al. Increasing incidence and improved survival in ANCA-associated vasculitis - a Danish nationwide study. Nephrol Dial Transplant 2022;37:63–71. https://doi.org/10.1093/ndt/gfaa303.
[9] Watts RA, Mahr A, Mohammad AJ, Gatenby P, Basu N, Flores-Suárez LF. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Nephrol Dial Transplant 2015;30:i14–22. https://doi.org/10.1093/ndt/gfv022.
[10] Rathmann J, Segelmark M, Englund M, Mohammad AJ. Stable incidence but increase in prevalence of ANCA-associated vasculitis in southern Sweden: a 23-year study. RMD Open 2023;9:e002949. https://doi.org/10.1136/rmdopen-2022-002949.
[11] Kilian KR, Brunborg C, Holme SS, Torhild G, Gunnarsson R, Molberg Ø. Incidence and prevalence of ANCA-associated vasculitis in Oslo, Norway, applying different criteria-based case definitions: a population-based cohort study. RMD Open 2025;11. https://doi.org/10.1136/rmdopen-2025-005526.
[12] Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis 2023;83:30–47. https://doi.org/10.1136/ard-2022-223764.
[13] Ecclestone T, Watts RA. Classification and epidemiology of vasculitis: emerging concepts. Best Pract Res Clin Rheumatol 2023;37:101845. https://doi.org/10.1016/j.berh.2023.101845.
[14] Van Leeuwen JR, Hafemann S, Van Der Boog P, Van Der Woude D, Rabelink T, Teng YKO. The impact of reclassification by the 2022 ACR/EULAR classification criteria on risk factors for relapse in patients with ANCA-associated vasculitis. Clin Kidney J 2023;16:2754. https://doi.org/10.1093/ckj/sfad225.
[15] Fujimoto S, Watts RA, Kobayashi S, Suzuki K, Jayne DRW, Scott DGI, et al. Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the UK. Rheumatology (Oxford) 2011;50:1916–20. https://doi.org/10.1093/rheumatology/ker205.
[16] Iudici M, Quartier P, Terrier B, Mouthon L, Guillevin L, Puéchal X. Childhood-onset granulomatosis with polyangiitis and microscopic polyangiitis: systematic review and meta-analysis. Orphanet J Rare Dis 2016;11. https://doi.org/10.1186/s13023-016-0523-y.
[17] Mahr A, Guillevin L, Poissonnet M, Aymé S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. Arthritis Rheum 2004;51:92–9. https://doi.org/10.1002/art.20077.
[18] Iudici M, Pagnoux C, Courvoisier DS, Cohen P, Hamidou M, Aouba A, et al. Granulomatosis with polyangiitis: study of 795 patients from the French Vasculitis study group registry. Semin Arthritis Rheum 2021;51:339–46. https://doi.org/10.1016/j.semarthrit.2021.02.002.
[19] Nguyen Y, Pagnoux C, Karras A, Quéméneur T, Maurier F, Hamidou M, et al. Microscopic polyangiitis: clinical characteristics and long-term outcomes of 378 patients from the French Vasculitis Study Group Registry. J Autoimmun 2020;112:102467. https://doi.org/10.1016/j.jaut.2020.102467.
[20] Papo M, Sinico RA, Teixeira V, Venhoff N, Urban ML, Iudici M, et al. Significance of PR3-ANCA positivity in eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Rheumatology (Oxford) 2021;60:4355–60. https://doi.org/10.1093/rheumatology/keaa805.
[21] Xie G, Roshandel D, Sherva R, Monach PA, Yue Lu E, Kung T, et al. Association of granulomatosis with polyangiitis (Wegener's) with HLA-DPB1*04 and SEMA6A gene variants evidence from genome-wide analysis. Arthritis Rheum 2013;65:2457–68. https://doi.org/10.1002/art.38036.
[22] Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DR, et al. Genetically distinct subsets within ANCA-associated vasculitis Europe PMC funders group. N Engl J Med 2012;367:214–23. https://doi.org/10.1056/nejmoa1108735.
[23] Rahmattulla C, Mooyaart AL, Van Hooven D, Schoones JW, Bruijn JA, Dekkers OM, et al. Genetic variants in ANCA-associated vasculitis: a meta-analysis. Ann Rheum Dis 2016;75:1687–92. https://doi.org/10.1136/annrheumdis-2015-207601.
[24] Singh H, Maiti K, Saha S, Senapati S. Meta-analysis revealed HLA susceptibility markers in ANCA-associated vasculitis and its clinical subtypes. Rheumatology (Oxford) 2025. https://doi.org/10.1093/rheumatology/keaf265.
[25] Witko-Sarsat V, Lesavre P, Lopez S, Bessou G, Hieblot C, Prum B, et al. A large subset of neutrophils expressing membrane proteinase 3 is a risk factor for vasculitis and rheumatoid arthritis. J Am Soc Nephrol 1999;10:1224–33. https://doi.org/10.1681/asn.v1061224.
[26] Jagiello P, Aries P, Arning L, Wagenleiter SEN, Csernok E, Hellmich B, et al. The PTPN22 620W allele is a risk factor for Wegener's granulomatosis. Arthritis Rheum 2005;52:4039–43. https://doi.org/10.1002/art.21487.
[27] Mahr AD, Edberg JC, Stone JH, Hoffman GS, St.clair EW, Specks U, et al. Alpha1-antitrypsin deficiency-related alleles Z and S and the risk of Wegener's granulomatosis. Arthritis Rheum 2010;62:3760–7. https://doi.org/10.1002/art.27742.
[28] Paroli M, Gioia C, Accapezzato D. New insights into pathogenesis and treatment of ANCA-associated vasculitis: autoantibodies and beyond. Antibodies (Basel) 2023;12:25. https://doi.org/10.3390/antib12010025.
[29] Gómez-Puerta JA, Gedmintas L, Costenbader KH. The association between silica exposure and development of ANCA-associated vasculitis: systematic review and meta-analysis. Autoimmun Rev 2013;12:1129–35. https://doi.org/10.1016/j.autrev.2013.06.016.
[30] Takeuchi Y, Saito A, Ojima Y, Kagaya S, Fukami H, Sato H, et al. The influence of the great East Japan earthquake on microscopic polyangiitis: a retrospective observational study. PLoS One 2017;12. https://doi.org/10.1371/journal.pone.0177482.
[31] Scott J, Hartnett J, Mockler D, Little MA. Environmental risk factors associated with ANCA associated vasculitis: a systematic mapping review. Autoimmun Rev 2020;19:102660. https://doi.org/10.1016/j.autrev.2020.102660.
[32] Lane SE, Watts RA, Bentham G, Innes NJ, Scott DGI. Are environmental factors important in primary systemic vasculitis? A case-control study. Arthritis Rheum 2003;48:814–23. https://doi.org/10.1002/art.10830.
[33] Chen M, Kallenberg CGM. ANCA-associated vasculitides—advances in pathogenesis and treatment. Nat Rev Rheumatol 2010;6:653–64. https://doi.org/10.1038/nrrheum.2010.158.
[34] Stegeman CA, Cohen Tervaert JW, Sluiter WJ, Manson WL, De Jong PE, Kallenberg CGM. Association of chronic nasal carriage of *Staphylococcus aureus* and higher relapse rates in Wegener granulomatosis. Ann Intern Med 1994;120:12–7. https://doi.org/10.7326/0003-4819-120-1-199401010-00003.
[35] Popa ER, Stegeman CA, Abdulahad WH, van der Meer B, Arends J, Manson WM, et al. Staphylococcal toxic-shock-syndrome-toxin-1 as a risk factor for disease relapse in Wegener's granulomatosis. Rheumatology (Oxford) 2007;46:1029–33. https://doi.org/10.1093/rheumatology/kem022.
[36] Chen M, Kallenberg CGM. The environment, geoepidemiology and ANCA-associated vasculitides. Autoimmun Rev 2010;9:A293–8. https://doi.org/10.1016/j.autrev.2009.10.008.
[37] Choi HK, Merkel PA, Walker AM, Niles JL. Drug-associated antineutrophil cytoplasmic antibody-positive vasculitis: prevalence among patients with high titers of antimyeloperoxidase antibodies. Arthritis Rheum 2000;43:405–13. https://doi.org/10.1002/1529-0131(200002)43:2<405::aid-anr22>3.0.co;2-5.
[38] Donkers JWJ, Feijen RA, Rutgers A. (Levamisole adulterated) Cocaine-induced Vasculitis: what is known/current evidence. Curr Treat Opt Rheumatol 2024;10:35–42. https://doi.org/10.1007/s40674-024-00215-5.
[39] Cartin-Ceba R, Peikert T, Specks U. Pathogenesis of ANCA-associated vasculitis. Curr Rheumatol Rep 2012;14:481–93. https://doi.org/10.1007/s11926-012-0286-y.
[40] McDermott G, Fu X, Stone JH, Wallwork R, Zhang Y, Choi HK, et al. Association of cigarette smoking with antineutrophil cytoplasmic antibody–associated vasculitis. JAMA Intern Med 2020;180:870–6. https://doi.org/10.1001/jamainternmed.2020.0675.
[41] Falk RJ, Jennette JC. ANCA disease: where is this field heading? J Am Soc Nephrol 2010;21:745–52. https://doi.org/10.1681/asn.2009121238.
[42] Jarrot PA, Kaplanski G. Pathogenesis of ANCA-associated vasculitis: an update. Autoimmun Rev 2016;15:704–13. https://doi.org/10.1016/j.autrev.2016.03.007.
[43] Nakazawa D, Masuda S, Tomaru U, Ishizu A. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. Nat Rev Rheumatol 2019;15:91–101. https://doi.org/10.1038/s41584-018-0145-y.
[44] Liu Z, Li X, Fan N, Wang H, Xia W, Li W, et al. Increased circulating PD-1hiCXCR5− peripheral T helper cells are associated with disease activity of

ANCA-associated vasculitis. Clin Exp Immunol 2022;207:287–96. https://doi.org/10.1093/cei/uxac002.
[45] Wojcik I, Wuhrer M, Heeringa P, Stegeman CA, Rutgers A, Falck D. Specific IgG glycosylation differences precede relapse in PR3-ANCA associated vasculitis patients with and without ANCA rise. Front Immunol 2023;14:1214945. https://doi.org/10.3389/fimmu.2023.1214945.
[46] Hilhorst M, Van Paassen P, Tervaert JWC. Proteinase 3-ANCA vasculitis versus myeloperoxidase- ANCA vasculitis. J Am Soc Nephrol 2015;26:2314–27. https://doi.org/10.1681/asn.2014090903.
[47] Nakazawa D, Shida H, Tomaru U, Yoshida M, Nishio S, Atsumi T, et al. Enhanced formation and disordered regulation of NETs in myeloperoxidase-ANCA-associated microscopic polyangiitis. J Am Soc Nephrol 2014;25:990–7. https://doi.org/10.1681/asn.2013060606.
[48] Hakkim A, Fürnrohr BG, Amann K, Laube B, Abed UA, Brinkmann V, et al. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. Proc Natl Acad Sci USA 2010;107:9813–8. https://doi.org/10.1073/pnas.0909927107.
[49] Nagai M, Hirayama K, Ebihara I, Shimohata H, Kobayashi M, Koyama A. Serum levels of BAFF and APRIL in myeloperoxidase anti-neutrophil cytoplasmic autoantibody-associated renal vasculitis: association with disease activity. Nephron Clin Pract 2011;118. https://doi.org/10.1159/000323393.
[50] Pendergraft WF, Preston GA, Shah RR, Tropsha A, Carter CW, Jennette JC, et al. Autoimmunity is triggered by cPR-3(105-201), a protein complementary to human autoantigen proteinase-3. Nat Med 2004;10:72–9. https://doi.org/10.1038/nm968.
[51] Falk RJ, Terrell RS, Charles LA, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. Proc Natl Acad Sci USA 1990;87:4115–9. https://doi.org/10.1073/pnas.87.11.4115.
[52] Kessenbrock K, Krumbholz M, Schönermarck U, Back W, Gross WL, Werb Z, et al. Netting neutrophils in autoimmune small-vessel vasculitis. Nat Med 2009;15:623–5. https://doi.org/10.1038/nm.1959.
[53] Shiratori-Aso S, Nakazawa D. The involvement of NETs in ANCA-associated vasculitis. Front Immunol 2023;14:1261151. https://doi.org/10.3389/fimmu.2023.1261151.
[54] Miao D, Li DY, Chen M, Zhao MH. Platelets are activated in ANCA-associated vasculitis via thrombin-PARs pathway and can activate the alternative complement pathway. Arthritis Res Ther 2017;19:1–10. https://doi.org/10.1186/s13075-017-1458-y.
[55] Saffarzadeh M, Juenemann C, Queisser MA, Lochnit G, Barreto G, Galuska SP, et al. Neutrophil extracellular traps directly induce epithelial and endothelial cell death: a predominant role of histones. PLoS One 2012;7. https://doi.org/10.1371/journal.pone.0032366.
[56] Wang H, Wang C, Zhao MH, Chen M. Neutrophil extracellular traps can activate alternative complement pathways. Clin Exp Immunol 2015;181:518–27. https://doi.org/10.1111/cei.12654.
[57] Carmona-Rivera C, Zhao W, Yalavarthi S, Kaplan MJ. Neutrophil extracellular traps induce endothelial dysfunction in systemic lupus erythematosus through the activation of matrix metalloproteinase-2. Ann Rheum Dis 2015;74:1417–24. https://doi.org/10.1136/annrheumdis-2013-204837.
[58] Fuchs TA, Abed U, Goosmann C, Hurwitz R, Schulze I, Wahn V, et al. Novel cell death program leads to neutrophil extracellular traps. J Cell Biol 2007;176:231–41. https://doi.org/10.1083/jcb.200606027.
[59] Kallenberg CGM, Heeringa P, Stegeman CA. Mechanisms of disease: pathogenesis and treatment of ANCA-associated vasculitides. Nat Clin Pract Rheumatol 2006;2:661–70. https://doi.org/10.1038/ncprheum0355.
[60] Wagner J, Harrison EM, Martinez Del Pero M, Blane B, Mayer G, Leierer J, et al. The composition and functional protein subsystems of the human nasal microbiome in granulomatosis with polyangiitis: a pilot study. Microbiome 2019;7:1–17. https://doi.org/10.1186/s40168-019-0753-z.
[61] Xiao H, Schreiber A, Heeringa P, Falk RJ, Jennette JC. Alternative complement pathway in the pathogenesis of disease mediated by anti-neutrophil cytoplasmic autoantibodies. Am J Pathol 2007;170:52–64. https://doi.org/10.2353/ajpath.2007.060573.
[62] Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. Nat Rev Rheumatol 2014;10:463–73. https://doi.org/10.1038/nrrheum.2014.103.
[63] Schreiber A, Xiao H, Jennette JC, Schneider W, Luft FC, Kettritz R. C5a receptor mediates neutrophil activation and ANCA-induced glomerulonephritis. J Am Soc Nephrol 2009;20:289–98. https://doi.org/10.1681/asn.2008050497.
[64] Moiseev S, Lee JM, Zykova A, Bulanov N, Novikov P, Gitel E, et al. The alternative complement pathway in ANCA-associated vasculitis: further evidence and a meta-analysis. Clin Exp Immunol 2020;202:394–402. https://doi.org/10.1111/cei.13498.
[65] Huang YM, Wang H, Wang C, Chen M, Zhao MH. Promotion of hypercoagulability in antineutrophil cytoplasmic antibody–associated vasculitis by C5a-induced tissue factor–expressing microparticles and neutrophil extracellular traps. Arthritis Rheumatol 2015;67:2780–90. https://doi.org/10.1002/art.39239.
[66] Gou SJ, Yuan J, Chen M, Yu F, Zhao MH. Circulating complement activation in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis. Kidney Int 2013;83:129–37. https://doi.org/10.1038/ki.2012.313.
[67] Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, et al. ANCA-associated vasculitis. Nat Rev Dis Primers 2020;6. https://doi.org/10.1038/s41572-020-0204-y.
[68] Johnson Richard, Floege Jurgen, Tonelli Marcello. Comprehensive clinical nephrology. 7th ed. Elsevier; 2023. p. 294–304.
[69] Almaani S, Fussner LA, Brodsky S, Meara AS, Jayne D. ANCA-associated vasculitis: an update. J Clin Med 2021;10. https://doi.org/10.3390/jcm10071446.
[70] Floege J, Jayne DRW, Sanders JSF, Tesar V, Rovin BH. KDIGO 2024 clinical practice guideline for the management of Antineutrophil cytoplasmic antibody (ANCA)–associated Vasculitis. Kidney Int 2024;105:S71–116. https://doi.org/10.1016/j.kint.2023.10.008.
[71] Sayer M, Chapman GB, Thomas M, Dhaun N. Cardiovascular disease in anti-neutrophil cytoplasm antibody-associated vasculitis. Curr Rheumatol Rep 2024;26:12–23. https://doi.org/10.1007/s11926-023-01123-8.
[72] Yates M, Watts R. ANCA-associated vasculitis. Clin Med 2017;17:60–4. https://doi.org/10.7861/clinmedicine.17-1-60.
[73] Falk RJ, Hogan S, Carey TS, Jennette JC. Clinical course of anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and systemic vasculitis. Ann Intern Med 1990;113:656–63. https://doi.org/10.7326/0003-4819-113-9-656.
[74] Koike H, Nishi R, Ohyama K, Morozumi S, Kawagashira Y, Furukawa S, et al. ANCA-associated vasculitic neuropathies: a review. Neurol Ther 2022;11:21–38. https://doi.org/10.1007/s40120-021-00315-7.
[75] He P, Hu JP, Tian XJ, He LJ, Sun SR, Huang C. Prevalence and risk factors of relapse in patients with ANCA-associated vasculitis receiving cyclophosphamide induction: a systematic review and meta-analysis of large observational studies. Rheumatology (Oxford) 2021;60:1067–79. https://doi.org/10.1093/rheumatology/keaa667.
[76] Lionaki S, Blyth ER, Hogan SL, Hu Y, Senior BA, Jennette CE, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis Rheum 2012;64:3452–62. https://doi.org/10.1002/art.34562.
[77] Saha MK, Massicotte-Azarniouch D, Reynolds ML, Mottl AK, Falk RJ, Jennette JC, et al. Glomerular hematuria and the utility of urine microscopy: a review. Am J Kidney Dis 2022;80:383–92. https://doi.org/10.1053/j.ajkd.2022.02.022.
[78] Lubas A, Staszewski J, Maliborski A, Mosakowska M, Spłocharski G, Bilbin-Bukowska A, et al. Vascular and vasogenic manifestations of systemic ANCA-associated vasculitis with renal involvement in non-contrast brain MRI in patients with acute disease onset. J Clin Med 2022;11. https://doi.org/10.3390/jcm11164863.
[79] Borie R, Crestani B. Antineutrophil cytoplasmic antibody-associated lung fibrosis. Semin Respir Crit Care Med 2018;39:465–70. https://doi.org/10.1055/s-0038-1669914.
[80] Specks U, Marty PK. Interstitial lung disease, antineutrophil cystoplasmic antibodies and microscopic polyangiitis. Rheumatology (Oxford) 2025;64:i42–7. https://doi.org/10.1093/rheumatology/keae557.
[81] Kadura S, Raghu G. Antineutrophil cytoplasmic antibody-associated interstitial lung disease: a review. Eur Respir Rev 2021;30. https://doi.org/10.1183/16000617.0123-2021.
[82] Chevet B, Cornec D, Casal Moura M, Cornec-Le Gall E, Fervenza FC, Warrington KJ, et al. Diagnosing and treating ANCA-associated vasculitis: an updated review for clinical practice. Rheumatology (Oxford) 2023;62:1787–803. https://doi.org/10.1093/rheumatology/keac623.
[83] Mudgal M, Balaji S, Gajendiran AP, Subramanya A, Murugan SK, Gondhi V, et al. Connective tissue disorder-induced diffuse alveolar hemorrhage: a comprehensive review with an emphasis on airway and respiratory management. Life (Basel) 2025;15. https://doi.org/10.3390/life15050793.
[84] Koldingsnes W, Jacobsen EA, Sildnes T, Hjalmarsen A, Nossent HC. Pulmonary function and high-resolution CT findings five years after disease onset in patients with Wegener's granulomatosis. Scand J Rheumatol 2005;34:220–8. https://doi.org/10.1080/03009740410011271.
[85] Guggenberger KV, Bley TA. Imaging in vasculitis. Curr Rheumatol Rep 2020;22. https://doi.org/10.1007/s11926-020-00915-6.
[86] Tateyama K, Umemoto S, Iwano S, Hirano T, Suzuki M. Sinonasal manifestations of granulomatosis with polyangiitis: a retrospective analysis. Auris Nasus Larynx 2024;51:625–30. https://doi.org/10.1016/j.anl.2024.04.002.
[87] Gozzi L, Cozzi D, Zantonelli G, Giannessi C, Giovannelli S, Smorchkova O, et al. Lung involvement in pulmonary vasculitis: a radiological review. Diagnostics (Basel) 2024;14:1416. https://doi.org/10.3390/diagnostics14131416.
[88] Tee QX, Wong A, Nambiar M, Lau KK. Granulomatosis with polyangiitis: common and uncommon presentations. J Med Imaging Radiat Oncol 2022;66:1089–96. https://doi.org/10.1111/1754-9485.13471.
[89] Bischof A, Jaeger VK, Hadden RDM, Luqmani RA, Pröbstel AK, Merkel PA, et al. Peripheral neuropathy in antineutrophil cytoplasmic antibody-associated vasculitides: insights from the DCVAS study. Neurol Neuroimmunol Neuroinflamm 2019;6. https://doi.org/10.1212/nxi.0000000000000615.
[90] Moiseev S, Cohen Tervaert JW, Arimura Y, Bogdanos DP, Csernok E, Damoiseaux J, et al. 2020 International consensus on ANCA testing beyond systemic vasculitis. Autoimmun Rev 2020;19. https://doi.org/10.1016/j.autrev.2020.102618.
[91] Vanderlocht J, van Beers JJBC, Limburg PC, Damoiseaux J, Roozendaal C. Antigen-specific detection of autoantibodies against myeloperoxidase (MPO) and proteinase 3 (PR3). In: Methods Mol Biol. 1901. Humana Press Inc.; 2019. p. 153–76. https://doi.org/10.1007/978-1-4939-8949-2_12.
[92] Bossuyt X, Cohen Tervaert JW, Arimura Y, Blockmans D, Flores-Suáez LF, Guillevin L, et al. Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol 2017;13:683–92. https://doi.org/10.1038/nrrheum.2017.140.

[93] Moura MC, Fervenza FC, Specks U, Sethi S. Kidney biopsy chronicity grading in antineutrophil cytoplasmic antibody-associated vasculitis. Nephrol Dial Transplant 2022;37:1710–21. https://doi.org/10.1093/ndt/gfab250.
[94] Suresh E. Diagnostic approach to patients with suspected vasculitis. Postgrad Med J 2006;82:483–8. https://doi.org/10.1136/pgmj.2005.042648.
[95] Berden AE, Ferrario F, Hagen EC, Jayne DR, Jennette JC, Joh K, et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol 2010;21:1628–36. https://doi.org/10.1681/asn.2010050477.
[96] Brix SR, Noriega M, Tennstedt P, Vettorazzi E, Busch M, Nitschke M, et al. Development and validation of a renal risk score in ANCA-associated glomerulonephritis. Kidney Int 2018;94:1177–88. https://doi.org/10.1016/j.kint.2018.07.020.
[97] Rajasekaran A, Rizk DV. Evolution of therapy for ANCA-associated vasculitis with kidney involvement. Kidney360 2023;4:1794–805. https://doi.org/10.34067/kid.0000000000000289.
[98] Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32. https://doi.org/10.1056/nejmoa0909905.
[99] Waki D, Nishimura K, Tokumasu H, Kadoba K, Mukoyama H, Saito R, et al. Initial high-dose corticosteroids and renal impairment are risk factors for early severe infections in elderly patients with antineutrophil cytoplasmic autoantibody-associated vasculitis: a retrospective observational study. Medicine (Baltimore) 2020;99. https://doi.org/10.1097/md.0000000000019173.
[100] Walsh M, Merkel PA, Peh C-A, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med 2020;382:622–31. https://doi.org/10.1056/nejmoa1803537.
[101] De Groot K, Rasmussen N, Bacon PA, Tervaert JWC, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461–9. https://doi.org/10.1002/art.21142.
[102] Jones RB, Hiemstra TF, Ballarin J, Blockmans DE, Brogan P, Bruchfeld A, et al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. Ann Rheum Dis 2019;78:399–405. https://doi.org/10.1136/annrheumdis-2018-214245.
[103] Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol 2021;73:1366–83. https://doi.org/10.1002/art.41773.
[104] Bourré-Tessier J, Haraoui B. Methotrexate drug interactions in the treatment of rheumatoid arthritis: a systematic review. J Rheumatol 2010;37:1416–21. https://doi.org/10.3899/jrheum.090153.
[105] Moura MC, Gauckler P, Anders H-J, Bruchfeld A, Fernandez-Juarez GM, Floege J, et al. Management of antineutrophil cytoplasmic antibody–associated vasculitis with glomerulonephritis as proposed by the ACR 2021, EULAR 2022 and KDIGO 2021 guidelines/recommendations. Nephrol Dial Transplant 2023;38. https://doi.org/10.1093/ndt/gfad090.
[106] Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis [retracted]. N Engl J Med 2021;384:599–609. https://doi.org/10.1056/nejmoa2023386.
[107] Antonelou M, Anwari KJ, Salama AD. Anti-neutrophil cytoplasmic antibody-associated vasculitis: biological insights and biomarker-guided disease management. Nat Rev Nephrol 2026. https://doi.org/10.1038/s41581-026-01081-1.
[108] Rubin EJ, Jayne DRW, et al. Retraction: avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med 2021;384:599–609. https://doi.org/10.1056/NEJMe2608684. N Engl J Med. 2026.
[109] U.S. Food and Drug Administration. CDER proposes to withdraw approval of TAVNEOS. 2026 [accessed 19 July 2026], https://www.fda.gov/drugs/drug-alerts-and-statements/cder-proposes-withdraw-approval-tavneos;.
[110] European Medicines Agency. EMA recommends revoking marketing authorisation for Tavneos. 2026 [accessed 19 July 2026], https://www.ema.europa.eu/en/news/ema-recommends-revoking-marketing-authorisation-tavneos;.
[111] Jayne DRW, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007;18:2180–8. https://doi.org/10.1681/asn.2007010090.
[112] Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med 2017;376:1921–32. https://doi.org/10.1056/nejmoa1702079.
[113] Wechsler ME, Nair P, Terrier B, Walz B, Bourdin A, Jayne DRW, et al. Benralizumab versus mepolizumab for eosinophilic granulomatosis with polyangiitis. N Engl J Med 2024;390:911–21. https://doi.org/10.1056/nejmoa2311155.
[114] Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaître O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771–80. https://doi.org/10.1056/nejmoa1404231.
[115] Smith RM, Jones RB, Specks U, Bond S, Nodale M, Al-Jayyousi R, et al. Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial. Ann Rheum Dis 2023;82:937–44. https://doi.org/10.1136/ard-2022-223559.
[116] Charles P, Terrier B, Perrodeau É, Cohen P, Faguer S, Huart A, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis 2018;77:1144–50. https://doi.org/10.1136/annrheumdis-2017-212878.
[117] Cartin-Ceba R, Indrakanti D, Specks U, Stone JH, Hoffman GS, Kallenberg CGM, et al. The pharmacogenomic association of Fcγ receptors and cytochrome P450 enzymes with response to rituximab or cyclophosphamide treatment in antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol 2017;69:169–75. https://doi.org/10.1002/art.39822.
[118] Engesser J, Khatri R, Schaub DP, Zhao Y, Paust HJ, Sultana Z, et al. Immune profiling-based targeting of pathogenic T cells with ustekinumab in ANCA-associated glomerulonephritis. Nat Commun 2024;15. https://doi.org/10.1038/s41467-024-52525-w.
[119] O'Reilly VP, Wong L, Kennedy C, Elliot LA, O'Meachair S, Coughlan AM, et al. Urinary soluble CD163 in active renal vasculitis. J Am Soc Nephrol 2016;27:2906–16. https://doi.org/10.1681/asn.2015050511.
[120] Moran SM, Monach PA, Zgaga L, Cuthbertson D, Carette S, Khalidi NA, et al. Urinary soluble CD163 and monocyte chemoattractant protein-1 in the identification of subtle renal flare in anti-neutrophil cytoplasmic antibody-associated vasculitis. Nephrol Dial Transplant 2020;35:283–91. https://doi.org/10.1093/ndt/gfy300.
[121] A Randomized, Controlled Study to Evaluate LNP023 (Iptacopan) in Patients With Active ANCA-associated Vasculitis. ClinicalTrials.gov Identifier: NCT06388941 2024. https://clinicaltrials.gov/study/NCT06388941 (accessed August 20, 2025).
[122] A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of NM8074 in Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV). ClinicalTrials.gov Identifier: NCT06226662. n.d. https://clinicaltrials.gov/study/NCT06226662 (accessed August 20, 2025)
[123] van Leeuwen JR, Bredewold OW, Rabelink TJ, Teng YKO. Obinutuzumab in rituximab-intolerant antineutrophil cytoplasmic antibody–associated vasculitis patients. Kidney Int Rep 2025;10:1288–91. https://doi.org/10.1016/j.ekir.2025.01.022.
[124] Ostendorf L, Burns M, Wagner DL, Enghard P, Amann K, Mei H, et al. Daratumumab for the treatment of refractory ANCA-associated vasculitis. RMD Open 2023;9. https://doi.org/10.1136/rmdopen-2022-002742.
[125] Phase 1B. Open-Label Study of KYV-101, an Autologous Fully-Human Anti-CD19 Chimeric Antigen Receptor T-Cell (CD19 CAR T) Therapy, in Adult Patients With Treatment Refractory Dermatomyositis. ClinicalTrials.gov Identifier: NCT06298019 2024. https://clinicaltrials.gov/study/NCT06298019 (accessed August 20, 2025).
[126] CARTIMMUNE: A Single-Center Study of Patients With Autoimmune Diseases Receiving an Autologous Fully-Human Anti-CD19 Chimeric Antigen Receptor T-Cell (KYV 101). ClinicalTrials.gov. Identifier: NCT06152172 2023, https://clinicaltrials.gov/study/NCT06152172 (accessed August 20, 2025).
[127] A Phase 1 Study Evaluating SC291, a Hypoimmune, Allogeneic CD19-directed CAR T Cell Therapy, in Subjects With Severe Relapsed or Refractory Autoimmune Diseases (GLEAM). ClinicalTrials.gov Identifier: NCT06294236 2024. https://clinicaltrials.gov/study/NCT06294236 (accessed August 20, 2025).
[128] Efficacy and Safety of Depemokimab Compared With Mepolizumab in Adults With Relapsing or Refractory Eosinophilic Granulomatosis With Polyangiitis (EGPA). ClinicalTrials.gov Identifier: NCT05263934 n.d. https://clinicaltrials.gov/study/NCT05263934 (accessed May 29, 2026)
[129] Liu Y, Zhan M, Chen R, Sun X, Li M, Chen H, et al. Tofacitinib in combination with glucocorticoids in the treatment of eosinophilic granulomatosis with polyangiitis: a pilot study of 11 cases. Rheumatology (Oxford) 2025;64:6294–301. https://doi.org/10.1093/rheumatology/keaf397.
[130] Explore the Efficacy and Mechanism of Action of Tezepelumab in Eosinophilic Granulomatosis With Polyangiitis. ClinicalTrials.gov Identifier: NCT06230354 n.d, https://clinicaltrials.gov/study/NCT06230354 (accessed June 2, 2026).
[131] Flossmann O, Berden A, De Groot K, Hagen C, Harper L, Heijl C, et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 2011;70:488–94. https://doi.org/10.1136/ard.2010.137778.
[132] Bektaş M, Ince B, Zaralı S, Gülseren ÜA, Ük E, Ağargün BF, et al. Damage accrual and predictors of mortality in ANCA-associated vasculitis: a retrospective observational study. Rheumatol Int 2025;45. https://doi.org/10.1007/s00296-025-05883-7.
[133] Sánchez Álamo B, Moi L, Bajema I, Faurschou M, Flossmann O, Hauser T, et al. Long-term outcomes and prognostic factors for survival of patients with ANCA-associated vasculitis. Nephrol Dial Transplant 2023;38:1655–65. https://doi.org/10.1093/ndt/gfac320.
[134] Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P. The five-factor score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French vasculitis study group (FVSG) cohort. Medicine (Baltimore) 2011;90:19–27. https://doi.org/10.1097/md.0b013e318205a4c6.
[135] Samson M, Puéchal X, Devilliers H, Ribi C, Cohen P, Bienvenu B, et al. Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors. Autoimmun Rev 2014;13:945–53. https://doi.org/10.1016/j.autrev.2014.08.002.
[136] Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham vasculitis activity score (version 3). Ann Rheum Dis 2009;68:1827–32. https://doi.org/10.1136/ard.2008.101279.
[137] Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Höglund P, et al. Damage in the ANCA-associated vasculitides: long-term data from the European Vasculitis Study Group (EUVAS) therapeutic trials. Ann Rheum Dis 2015;74:177–84. https://doi.org/10.1136/annrheumdis-2013-203927.
[138] Suppiah R, Flossmann O, Mukhtyar C, Alberici F, Baslund B, Brown D, et al. Measurement of damage in systemic vasculitis: a comparison of the vasculitis

damage index with the combined damage assessment index. Ann Rheum Dis 2011;70:80–5. https://doi.org/10.1136/ard.2009.122952.
[139] Sánchez Álamo B, Moi L, Bajema I, Berden A, Flossmann O, Hruskova Z, et al. Long-term outcome of kidney function in patients with ANCA-associated vasculitis. Nephrol Dial Transplant 2024;39:1483–93. https://doi.org/10.1093/ndt/gfae018.
[140] Samson M, Devilliers H, Thietart S, Charles P, Pagnoux C, Cohen P, et al. Score to assess the probability of relapse in granulomatosis with polyangiitis and microscopic polyangiitis. RMD Open 2023;9. https://doi.org/10.1136/rmdopen-2022-002953.
[141] Wester Trejo MAC, Sadeghi M, Singh S, Mahmoodian N, Sharifli S, Hruskova Z, et al. Explainability of a deep learning-based classification model for antineutrophil cytoplasmic autoantibody–associated glomerulonephritis. Kidney Int Rep 2025;10:457–65. https://doi.org/10.1016/j.ekir.2024.11.005.
[142] Gisslander K, White A, Aslett L, Hrušková Z, Lamprecht P, Musiał J, et al. Data-driven subclassification of ANCA-associated vasculitis: model-based clustering of a federated international cohort. Lancet Rheumatol 2024;6:e762–70. https://doi.org/10.1016/s2665-9913(24)00187-5.
[143] Scott J, White A, Walsh C, Aslett L, Rutherford MA, Ng J, et al. Computable phenotype for real-world, data-driven retrospective identification of relapse in ANCA-associated vasculitis. RMD Open 2024;10. https://doi.org/10.1136/rmdopen-2023-003962.
[144] van Leeuwen JR, Penne L, Rabelink T, Knevel R, Teng YKO. Using an artificial intelligence tool incorporating natural language processing to identify patients with a diagnosis of ANCA-associated vasculitis in electronic health records. Comput Biol Med 2024;168. https://doi.org/10.1016/j.compbiomed.2023.107757.