ANCA-associated vasculitis

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Abstract

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are a group of disorders involving severe, systemic, small-vessel vasculitis and are characterized by the development of autoantibodies against the neutrophil proteins leukocyte proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). The three AAV subgroups, namely granulomatosis with polyangiitis (GPA), microscopic polyangiitis and eosinophilic GPA (EGPA), are defined on the basis of clinical features. However, genetic and other clinical findings suggest that these clinical syndromes may be better classified as PR3-positive AAV (PR3-AAV), MPO-positive AAV (MPO-AAV) and, for EGPA, by the presence or absence of ANCA ($ANCA^+$ or $ANCA^-$, respectively). Although any tissue can be involved in AAV, the upper and lower respiratory tract and kidneys are most commonly and severely affected. AAVs have a complex and unique pathogenesis, with evidence for a loss of tolerance to neutrophil proteins, which leads to ANCA-mediated neutrophil activation, recruitment and injury, with effector T cells also involved. Without therapy, prognosis is poor, but treatments, typically immunosuppressants, have improved survival, albeit with considerable morbidity from glucocorticoids and other immunosuppressive medications. Current challenges include improving measures of disease activity and risk of relapse, uncertainty about optimal therapy duration and a need for targeted therapies with fewer adverse effects. Meeting these challenges requires a more detailed knowledge of the fundamental biology of AAV, and co-operative international research and clinical trials with meaningful input from patients.

[H1] Introduction

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are diseases characterized by inflammation of blood vessels, endothelial injury and tissue damage. Three types of small-vessel vasculitis, namely granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome), feature a loss of tolerance to neutrophil primary granule proteins, most often leukocyte proteinase 3 (PR3; also known as myeloblastin) or myeloperoxidase (MPO) (Table 1). The vessels involved in AAV are typically capillaries, arterioles and venules, but small arteries and veins may also be affected. Autoimmunity is documented clinically by serum ANCAs against PR3 (PR3-ANCA) or MPO (MPO-ANCA), which are generally associated with the main syndromic AAV presentations (Box 1). AAVs collectively represent one of several types of autoimmune vasculitis (Figure 1).

GPA and MPA can involve small blood vessels in any organ or tissue, but commonly affect the upper and lower respiratory tract and the kidneys (Box 2). Patients with AAV typically present with severe organ-threatening or life-threatening disease, although less severe presentations also occur. GPA is predominantly associated with PR3-ANCA, and its clinical features typically include sinonasal disease, lower respiratory tract involvement with pulmonary haemorrhage and granulomatous inflammation, and glomerulonephritis. MPA is usually associated with MPO-ANCA, and clinical features include more severe renal disease and some of the manifestations of GPA but without granulomatous inflammation. EGPA is characterized by asthma, eosinophilia and, in many (but not all) cases, vasculitis. EGPA is less common than GPA or MPA and, in some cases, is associated with ANCAs, mainly MPO-ANCA (Table 1). Although categorized as a form of AAV, EGPA has less overlap with the other AAVs than that between GPA and MPA in its genetic, pathogenetic and clinical features, and management and is typically considered a separate entity.

Improvements in treatment and prognosis for patients with AAV have resulted from translation of both pre-clinical and clinical research findings. Here, we provide an updated overview of the clinical and molecular features of AAVs, present current pathophysiological concepts, discuss established and upcoming therapeutic options, emphasise the value of patient-oriented outcomes, and provide a perspective on future challenges in AAV research and treatment.

[H1] Epidemiology

[H2] Incidence and prevalence

Although fulfilling most definitions of a 'rare disease', with a historical estimated prevalence of 48–184 cases per million persons[1], rheumatologists, nephrologists, clinical immunologists and other physicians regularly encounter patients with AAV. In fact, more recent studies report rates of prevalence of between 300-421 per million persons[2,3], an inflation likely explained by improving survival and better case definition.

The global impacts of AAVs in terms of premature mortality[4], quality of life (QOL)[5] and societal economic costs[6] are considerable. Since the introduction of commercially available ANCA assays in the mid-1990s and enhanced physician awareness, there has been a noticeable increase in apparent AAV incidence. For example, the incidence rate of GPA between 1975 and 2001 in Sweden increased from 3.3 to 11.9 cases per million persons per year[7]. The plateauing of incidence rates since then indicates that the true incidence has likely remained stable, although the lack of standardized diagnostic criteria may affect case ascertainment.

There is wide geographical variation in AAV incidence (Figure 2), which is partly explained by methodological differences in study design, although specific patterns can be observed. First, GPA (PR3-AAV) mainly affects countries in which the population is predominantly of European ancestry and is seldom observed in East Asian countries. By contrast, MPA (MPO-AAV) predominates in Asian countries, such as China and Japan[8,9]. Second, the incidence of GPA is influenced by latitude, as the incidence is lower towards the equator[10,11]. The disparity in incidence among ethnicities is further supported by studies examining multi-ethnic populations. Surveys in France and USA both indicate at least a two-fold higher incidence of GPA and MPA in white populations than in other ethnicities[12,13]. A more recent UK study identified a similar signal, but this was mostly explained by the older age of the white population[14]. EGPA is strongly linked to asthma and eosinophilia in terms of both its clinical features and genetic make-up, though epidemiological data pertaining to EGPA are limited, as are data from Africa and South Asia for all types of AAV. It is unclear whether lack of access to ANCA testing in low-income and middle-income countries is resulting in not only a lack of data, but also under-diagnosis and under-treatment of AAV in these areas.

AAV in children is rare and less common than some other forms of vasculitis (including Kawasaki disease and IgA vasculitis). GPA seems to be more common than MPA or EGPA, and unlike adults, AAV in children is likely to be more common in females[15].

[H2] Risk factors and disease determinants

There is compelling evidence implicating genetic factors in the pathogenesis of AAV, although genetic predisposition alone does not explain this complex disorder. As the typical age of onset ranges between middle to older age and there is an equal sex distribution in AAV prevalence, it is likely that environmental factors have a key role in AAV aetiology. Some epidemiological studies report a cyclical occurrence of GPA, which is consistent with an infectious trigger. Although the majority of studies describe an increase in the incidence of GPA in winter[16-19], a higher summer incidence and no seasonal change have also been reported [20,21]. Indeed, increased rates of chronic *Staphylococcus aureus* nasal carriage, observed among patients with GPA have been associated with an increased relapse risk[22,23].

More granular epidemiological inspections of putative environmental causes are limited to small exploratory studies. An association between silica exposure and MPO-AAV has been consistently observed[24,25]. The high prevalence of silica in the natural environment (for example, in cement) is one proposed explanation for the apparent upsurge in AAV incidence following major earthquakes in 1995 and 2011 in Japan[26,27]. However, this correlation was not replicated in the aftermath of the 2011 earthquake in Christchurch, New Zealand[28], a discordance that potentially highlights the importance of AAV gene–environment interactions. Anecdotally, clinicians commonly observe a disparity in prevalence between urban and rural areas, although the epidemiological data to support this disparity are mixed[29]. For example, in a rural region of the UK, farming has been identified as a risk factor for both GPA and MPA[24], indirectly implicating pesticide and fertilizer exposure as potential pathogenetic factors. By contrast, pollution, specifically carbon monoxide levels, has been associated with increased AAV risk in population-dense China[30]. Other postulated risk factors include UV light[31], smoking[32], solvents[24] and occupational solvent exposure[24], but no single environmental factor seems to confer a major population-attributable risk. Similarly, specific drugs are responsible for some cases of vasculitis with syndromes similar to AAV (Box 3).

Ultimately, many epidemiological studies have treated AAV as a single disease construct and lack the power to examine the possibility that distinct environmental associations exist across the pathogenetically distinct sub-types.

[H1] Mechanisms/pathophysiology

AAVs are characterized by microvascular endothelial inflammation leading to extravascular inflammation, progressive injury, tissue destruction, fibrosis and loss of function. GPA and MPA develop by the loss of immunological T and B cell tolerance to one of two neutrophil proteins, PR3 or MPO. Mechanisms of acute injury in GPA and MPA are unique to this group of disorders and are overviewed schematically in Figure 3. Specifically, loss of tolerance leads to the development of ANCAs, autoantibodies that activate neutrophils. ANCA-activated neutrophils localize to vulnerable microvascular beds, where they induce injury and release the autoantigen for presentation by antigen-presenting cells (such as dendritic cells (DCs)), allowing antigen recognition by effector T cells that mediate further injury. Key elements of loss of tolerance, the generation of effector responses, and mechanisms of microvascular injury are summarized in Figures 4 and 5.

The pathogenesis of AAVs has been explored in *in vitro* assays and *in vivo* in animal models and in human studies. In animal studies, MPO-AAV is characterized by anti-MPO autoreactivity affecting the kidneys[33]. Although glomerular and pulmonary vessels are particularly vulnerable, there is little evidence to indicate why some vascular beds are preferentially involved. Furthermore, the mechanisms underpinning the frequent occurrence of granulomatous inflammation in PR3-AAV and its near absence in MPO-AAV are undefined. The response to injury, including the extent of tissue destruction and/or fibrosis, is likely to be contingent on the characteristics of the affected tissue, and the intensity and chronicity of local vasculitic inflammation.

[H2] Genetics

[H3] GPA and MPA. Evidence for a genetic contribution to the aetiology of AAVs has come largely from registry studies, which revealed that the familial relative risk (RR 1.56) is similar to that for rheumatoid arthritis (RR 1.5-5.0) but lower than that for other immune-mediated diseases[34]. Identifying robust genetic associations with AAV is challenging due to its fairly low prevalence, although candidate gene studies that utilized cohorts combining patients with GPA and those with MPA, and occasionally those with EGPA, found associations with the major histocompatibility complex (MHC) genes, in particular the *HLA-DP*04:01* locus[35]. The European Vasculitis Genetics Consortium reported the first genome-wide association study (GWAS) in AAV[36], which identified both MHC and non-MHC associations with disease and demonstrated that GPA and MPA are genetically distinct. Moreover, sub-analyses revealed that the strongest associations were not with the clinical

syndromes per se, but with ANCA specificity. The Vasculitis Clinical Research Consortium[37,38] confirmed these associations and provided the first evidence for genetic variants, for example in *PTPN22*, that are common to both PR3-AAV and MPO-AAV, suggesting there was also a shared genetic component to these diseases. How much of the clinical similarity between the two syndromes is driven by this shared genetic architecture, rather than antigenic similarity, awaits the outcome of larger GWAS that are better powered to assess associations with PR3-AAV and MPO-AAV separately.

Although the causal variant or variants at each locus remain unresolved, these genetic studies shed light on the underlying disease pathogenesis. Some variants represent genes, such as *PTPN22* associated with other autoimmune diseases[39], and larger studies are likely to identify further commonalities. Other variants are more specific to AAV. Genetic variants at both *SERPINA1* (encoding α1-antitrypsin) and *PRTN3* (encoding PR3) independently lead to increased plasma levels of PR3, suggesting that altered availability of circulating PR3 is a key driver in loss of tolerance to PR3 and the subsequent development of PR3-AAV. The association of *HLA-DP*04:01* with PR3-AAV may simply reflect the role of HLA (MHC) in presenting PR3 peptides to the immune system. However, this HLA-DP molecule also binds to the natural killer (NK) cell receptor NKp44, leading to NK cell activation[40], which might represent an alternative or additional mechanism that underpins the relationship between *HLA-DP* and PR3-AAV.

[H3] EGPA. One GWAS examining EGPA has identified 11 loci associated with EGPA[41] and demonstrated that EGPA comprises two genetically distinct subtypes, MPO-ANCA$^+$ EGPA and ANCA$^-$ EGPA These subtypes align with the clinical differences existing between these patient subsets[42,43]. Some of the identified loci are associated with eosinophil count in addition to EGPA, and Mendelian randomization revealed that increased risk of eosinophilia underlies susceptibility to EGPA, with additional genetic or environmental factors required for the development of disease.

[H2] Environmental factors and infections

The increasing incidence of AAV in the sixth and older decades of life implies a role for age-related factors and various accumulating environmental factors (discussed above), although these factors remain ill-defined. Whereas some observational studies implicate infectious triggers in AAV pathogenesis, the precise infectious agents remain unclear. Mechanistic *in vitro* and *in vivo* animal model studies suggest several ways in which, infection might promote loss of tolerance or disease relapse in AAV. These include

autoantigen exposure by the formation of neutrophil extracellular traps (NETs) that may be resistant to degradation in AAV[44], by molecular mimicry (that is, microbial antigens sharing sequence similarity with a host protein), and by the priming of neutrophils for ANCA-induced activation[33] (Figure 4). Some attention has focused on *S. aureus*, with reports of increased rates of nasal carriage in relapsing GPA patients [22] and experimental data implicating a plasmid-encoded 6-phosphogluconate dehydrogenase sequence from some *S. aureus* strains in by molecular mimicry in MPO-AAV[45].

[H2] ANCA antigens

As autoreactivity to either MPO or PR3 is central to the majority of cases of AAV, the characteristics of the key autoantigens are important. In most patients with AAV there is a single dominant autoantigen. MPO and PR3 are found primarily in neutrophils and are also produced by monocytes and macrophages. Although PR3 and MPO are mainly synthesized by immature neutrophils, altered DNA methylation and increased expression of *PRTN3* and *MPO* in mature neutrophils is implicated in disease pathogenesis[46]. PR3 and MPO are not only key AAV autoantigens, they also have damaging effects on the endothelium in microvascular inflammation. They are released by multiple mechanisms, including by degranulation and microparticle release, and as constituents of NETs[47].

PR3 is a 29kDa serine protease with pro- and mature forms[48], which are located within azurophilic granules. The variable expression of PR3 on the surface of neutrophils is in part dependent on co-expression with CD177, which binds to and colocalizes with the β2 integrin CD11b as part of the CD11b/CD18 complex[49,50]. Cell surface PR3 expression is increased in apoptotic neutrophils, which limits macrophage phagocytosis and promotes a pro-inflammatory microenvironment[48]. MPO is abundant in human neutrophils as a major component of azurophilic granules. Mature MPO is composed of light and heavy chains as a highly cationic homodimeric glycoprotein, bound to a haem group. The heavy chain is extensively but variably glycosylated[51,52]. Pro-inflammatory stimuli increase cell surface MPO levels, and MPO is released in inflammatory states, where it catalyses the formation of reactive intermediates, including hypohalous acids. The AAVs are typically considered systemic autoimmune diseases, each with dominant autoreactivity to only a single autoantigen. However other autoantigens have been associated with AAV, including lysosome-associated membrane protein 2 (LAMP2)[53], peptides complementary to PR3 (cPR3)[54,55], moesin[56], plasminogen[57,58], peroxidasin[59] and pentraxin 3[60]. Infection has been

implicated in loss of tolerance to some of these antigens. In rats, a LAMP2 epitope, found in myeloid cells and endothelial cells, and homologous to part of the bacterial adhesin FimH, induces AAV[53]. Reactivity to cPR3, derived from the non-coding strand of PR3 cDNA, and potentially initiated after infection[54], may trigger anti-PR3 autoreactivity. While several studies support a role for LAMP2 in MPA or GPA, or cPR3 in the pathogenesis of PR3-AAV, not all reports implicate these alternative antigens in disease[61,62].

[H2] Loss of tolerance to ANCA antigens

[H3] Central and peripheral mechanisms of tolerance. Central and peripheral mechanisms prevent damaging autoreactivity and autoimmune diseases by maintaining tolerance to self-antigens. In most autoimmune diseases, loss of T cell tolerance allows the emergence of T helper (Th) cells, that are central to autoantibody production by cells of the B cell lineage, and also themselves promote tissue injury. Loss of B cell tolerance allows the emergence of autoreactive B cells and plasma cells that produce damaging autoantibodies. Memory T and B cells that develop over time are important in chronicity and relapse. This is the case in AAV (Figure 4). Loss of tolerance to neutrophil proteins occurs prior to the onset of symptoms of AAV[63]. Our understanding of this process is imprecise; whereas dysregulated neutrophil apoptosis might predispose to loss of tolerance, there is no clear evidence that this is essential. Defects in both central and peripheral tolerance are present in AAV. Central tolerance to antigens in AAV is imperfect, as autoantigen-specific T cells and 'natural' autoantibodies are present in healthy individuals[64]. In the thymus, critical for T cell tolerance, MPO expression is under the control of the autoimmune regulator (AIRE) and *Aire*$^{-/-}$ mice exhibit stronger autoimmunity to MPO[65]. However, *AIRE*-deficient individuals do not seem to develop AAV, consistent with the existence of multiple layers of tolerance to MPO. Animal studies support a role for regulatory T (T_{reg}) cells in limiting autoimmune disease[65], and patients with AAV have fewer T_{reg} cells and regulatory B (B_{reg}) cells, with T_{reg} cells having a diminished capacity to suppress effector responses ex vivo[66-69], with T_{reg} cell abnormalities linked to antigen-specific effector IL-17-producing T helper (T_H17)-like cells[67,70]. To better understand loss of tolerance, and to move toward harness tolerogenic therapeutic platforms, and more precise diagnostic tools and biomarkers, immunodominant T and B cell epitopes have been defined for MPO, but not for PR3[70-73]. Conformational and linear B cell epitopes exist for both MPO-ANCA and PR3-ANCA[74-76]. An MHC-promiscuous $CD4^+$ T cell MPO epitope overlaps with a linear B cell epitope and a $CD8^+$ T

cell epitope[70-73], and is nephritogenic in mice. Knowledge of these epitopes enables translational strategies to improve disease monitoring and re-establish tolerance.

[H3] Maintenance of autoreactive B cells. After the loss of tolerance, the survival of autoreactive lymphocytes promotes ongoing and chronic disease (Figure 4). In the case of AAV, B cell survival factor B cell-activating factor (BAFF) is produced by ANCA-stimulated neutrophils and BAFF levels are elevated in AAV[77,78], suggesting that interactions between BAFF and its receptors on autoreactive B cells and plasmablasts promote autoimmunity. After therapeutic B cell depletion, BAFF may promote relapse by promoting the recovery of autoreactive B cells. B cells and B cell aggregates are present in more chronic lesions, implying additional roles for antigen-specific B cells beyond antibody production, as pro-inflammatory cells or as antigen-presenting cells[79,80].

[H2] The role of ANCA and neutrophils

[H3] ANCAs activate neutrophils and monocytes.

A critical consequence of loss of T and B cell tolerance is the production of ANCAs that bind to and activate neutrophils, so that they adhere in vulnerable microvascular beds and induce injury (Figures 3 and 5). ANCAs are usually of the IgG isotype, but IgA and IgM ANCA have also been reported[81,82]. ANCAs bind to their autoantigen, activate neutrophils and initiate injury[83]. *In vitro* studies support a model whereby both $F(ab')_2$–antigen and Fc–FcγR interactions are required, by G-protein-coupled pathways and SYK, respectively[84,85]. The effects of ANCAs on neutrophils include changes in adhesion molecule expression[86,87], alterations in cytoskeletal proteins such as polymerization of F-actin[88], and the generation of reactive oxygen species [89]. Mediator release occurs by several mechanisms: degranulation, NET formation and the release of microparticles[90]. The release of cytokines, proteases and other molecules induces necrotizing crescentic glomerulonephritis in mice[91]. A report of placental MPO-ANCA transfer to a neonate with pulmonary haemorrhage and microscopic haematuria supports a role for ANCAs in AAV pathogenesis[92]. The *in vivo* pathogenicity of ANCA-activated neutrophils has been convincingly demonstrated in experimental MPO-AAV[91,93] and evidence also exists for PR3-AAV[94,95]. ANCA also activate monocytes *ex vivo*, as monocytes express PR3 and MPO, albeit to a lesser degree than neutrophils. Compared with studies in neutrophils, the pathogenic implications of any direct effects of ANCA on monocytes is less certain[96,97]. Whether the 5–10% of patients with GPA or MPA who are

ANCA$^-$ have a relevant autoantibody is unresolved. Patients may be MPO-ANCA$^+$ but their ANCAs may react to an epitope that is masked in conventional assays[72] or to other antigens, including LAMP2[98] or pentraxin 3[60]. There are ANCA epitopes that are derived from pathogenic sequences as well as from endogenous proteins, while other factors, including ANCA sialylation and glycosylation may contribute to the inconsistent relationship between ANCA and disease activity[72,99,100].

[H3] Neutrophil priming and activation state. Although ANCAs may activate neutrophils without additional inflammatory signals, neutrophil priming by exogenous or endogenous proinflammatory signals promotes the damaging effects of these cells after ANCA-induced activation (Figures 3 and 4). In addition to the functional consequences of genetic variation in *PRTN3* and its inhibitor *SERPINA1*[101] and epigenetically mediated increases in PR3 and MPO[46,102], neutrophils from AAV patients, even in remission, produce more intracellular reactive oxygen species, NETs and have a greater capacity to active the alternative pathway of complement (see below)[103,104]. The precise contributions of intrinsic properties of neutrophils and their response to priming events are unclear, but both are likely to be relevant. Neutrophil priming in AAV occurs by several mechanisms, of which the most well defined are the complement system (see below), toll-like receptors (TLRs) and cytokines (including TNF and IL-18)[33]. TLRs are expressed on several relevant cell types, including neutrophils, monocytes and microvascular endothelial cells. Engagement of TLRs by pathogen-associated molecular patterns (PAMPs) or in sterile inflammation by damage-associated molecular patterns (DAMPs) activates neutrophils and the endothelium[105-108].

[H3] Complement activation via the alternative pathway

Complement, specifically the C5a receptor (C5aR), is a validated therapeutic target in acute AAV[109-111]. Evidence implicates neutrophil cell surface C5a–C5aR interactions in neutrophil priming and activation[109,112-115]. Although paracrine and autocrine sources of C5a are possible, circulating C5a may be more important[116], and little evidence exists for a role for the membrane attack complex (which comprises the complement subunits C5b, C6, C7, C8 and C9)[109] in neutrophil priming and activation. In addition to activating neutrophils, C5a enhances neutrophil retention in the microvasculature and promotes T cell antigen recognition by activating dendritic cells[115]. Three different pathways (classical, lectin and alternative) can be responsible for C5 activation, and in AAV evidence points to the alternative pathway being the key to pathological C5a/C5aR interactions. In mice, deficiency of Factor B (important to the alternative pathway), but not C4 (the classical/lectin pathway) was protective in experimental anti-MPO antibody induced glomerulonephritis[112], while

Factor Bb immunostaining in glomeruli correlated with renal injury[117]. Though not prominent, complement deposition is present in some human kidneys in AAV and may also be relevant to tissue pathology[118]. Low serum C3 levels in AAV with renal involvement are associated with unfavourable outcomes[119,120]. Other potential roles for complement in AAV include damaging relationships with pattern recognition receptors and with pro-coagulant molecules[118].

[H3] ANCA-induced neutrophil recruitment to the microvasculature

ANCA-activated neutrophils mediate microvascular injury by adhering to microvascular endothelial cells in vulnerable tissues, via integrin–endothelial adhesion molecule and chemokine–chemokine receptor interactions (Figure 5). ANCA enhances contact between neutrophils and activated endothelial cells via β2 integrins and C–X–C motif chemokine receptor 2 (CXCR2) in flow chamber assays[121]. *In vivo* microscopy studies using inflamed post-capillary venules have shown incremental recruitment of ANCA-activated neutrophils, consistent with *in vitro* mechanisms[122,123]. However, in the glomerulus, the mechanisms of ANCA-induced neutrophil adhesion are dependent on the ANCA concentration, so it is mediated by β2 integrin at low ANCA levels, whereas α4 integrin mediates adhesion at high ANCA levels and without additional stimuli (such as lipopolysaccharide) that themselves induce glomerular leukocyte recruitment[87].

[H2] T cells and cellular immunity

In addition to humoral immunity, cellular immunity is important in AAV pathogenesis, as CD4+ T cells promote ANCA production and CD4+ and CD8+ cells recognise ANCA antigens deposited in peripheral tissues by activated neutrophils (Figures 3 and 5). The class-switched, high-affinity nature of IgG ANCA implies T cell help via T follicular helper (T_{FH}) cells[124], the abundance of which is increased in GPA[125]. $CD4^+$ T effector memory cell abundance is increased in the blood and urine in AAV[126] and $CD4^+$ and $CD8^+$ cells are present in lesions[127-129]. Both T_H1 and T_H17 effector cytokine profiles have been observed in AAV[130,131], including T_H1 profiles in granulomatous lesions[132]. $CD4^+CD28^-$ cytotoxic T cells found in the blood of patients with GPA are linked to cytomegalovirus (CMV) infection, which is itself associated with poor AAV outcomes[133]. Furthermore, subclinical CMV infection and reactivation in immunosuppressed AAV patients may impair immune responses to infection, as the antiviral drug valacyclovir improved vaccine responses in CMV seropositive AAV patients[134].

Analyses of $CD8^+$ T cell transcriptomes of patients with active AAV at diagnosis reveal that patients can be stratified into two groups correlating with differences in long-term outcomes[135]. $CD8^+$ and $CD4^+$ T cell transcriptome data shows that reduced expression of genes linked to T cell exhaustion correlates with relapsing disease[136]. The correlation between exhaustion, with progressive loss of T effector function, and favourable disease outcome extends across a range of autoimmune and autoinflammatory diseases[136] and implies that therapeutics targeting this process may improve the management of AAV.

Effector T cells participate in tissue injury in AAV. When ANCA-activated neutrophils localize to inflamed tissues, they release their autoantigen[129,137]. The widespread deposition of the autoantigens in AAV in inflamed tissues makes these antigens available for recognition by effector T cells. Experimental studies, largely in experimental anti-MPO glomerulonephritis demonstrate a role for MPO-specific cells of both T_H17 (earlier) and T_H1 type (later)[138], while $CD8^+$ T cells also cause experimental injury[73].

[H2] Monocytes and macrophages

Macrophages are prominent in AAV lesions, are the most abundant cell type in glomeruli [128,129], and are important in both acute and chronic injury (Figure 5). ANCAs bind to intermediate monocytes that release pro-inflammatory cytokines and chemokines[96,97], while experimentally, inflammatory monocytes participate in glomerular crescent formation[139]. Macrophages are activated by effector T_H1 and T_H17 cells at sites of injury, participate in granuloma formation, form macrophage extra cellular traps in tissues[129] and in chronic inflammation profibrotic macrophages contribute to disease progression and damage.

[H2] The pathogenesis of EGPA

The pathogenesis of EGPA is not well understood. It is likely to be substantially different to both GPA and MPA, but the extent of the similarities and differences is unclear. Furthermore, the clinical presentations, genetic associations and the response to therapies between $ANCA^+$ and $ANCA^-$ EGPA patients imply distinct elements to the pathogenesis of these forms of EGPA[41-43]. Genetic associations with genes that influence eosinophil numbers and those that underlie asthma are common to both $ANCA^-$ and $ANCA^+$ patients. However, in $ANCA^-$ EGPA patients, the association with genes affecting barrier function (including *GPA33)* implies a role for mucosal dysfunction, whereas in $ANCA^+$ EGPA patients, the HLA associations are consistent with $ANCA^+$ EGPA being an eosinophilic autoimmune disease.

In addition to genetic studies, observational studies implicate eosinophil dysfunction in the pathogenesis of EGPA. Eosinophil mediated injury via the release of granule proteins itself can induce tissue resident cells to release pro-inflammatory mediators. Some of these tissue cell derived molecules, such as IL-25, affect both adaptive (type 2 T helper, T_H2 cell) and innate (group 2 innate lymphoid cells, ILC2) lymphoid cells[140]. Both Th2 and ILC2 cells produce IL-5 and IL-13 key cytokines that promote eosinophil proliferation and function[141,142]. IL-5's role has been validated by trials of mepolizumab, an anti-IL-5 monoclonal antibody in EGPA[143]. T_H2 cell-associated chemokines, such as CC-chemokine ligand 26 (CCL26; also known as eotaxin 3), enhance eosinophil recruitment[142]. Other T cell-associated cytokines are also elevated in patients with EGPA, but thus far there is no clear evidence that a particular pattern of cytokine or chemokine production characterizes $ANCA^+$ or $ANCA^-$ EGPA. A direct relationship between MPO-ANCA and eosinophils has not yet been demonstrated in $ANCA^+$ patients with EGPA.

H2 Chronicity and relapse in AAV

The pathogenesis of AAV is characterized by complex pathways to tissue injury and damage involving both humoral and cellular effector systems. Much of the work on the pathogenesis of AAV has been in systems modelling acute injury. Although largely unexplored, mechanisms operative in disease induction are also likely to be relevant to relapse. Some observational evidence points towards infection, in part related to chronic sinonasal mucosal damage, being important in relapse, and determinants of T cell activity and exhaustion may also be able to identify those at high risk of relapse.

[H1] Diagnosis, screening and prevention

[H2] Diagnostic and classification criteria

Clear definitions of GPA, MPA, EGPA and other systemic vasculitides are provided by the updated 2012 Chapel Hill Consensus Conference (CHCC)[144] which, as the name implies, was consensus driven and not data driven (Figure 1, Table 1). In 2006, an algorithm was developed for applying the 1990 American College of Rheumatology (ACR) classification, 1993 CHCC definitions and ANCA specificity to streamline classification of patients with GPA, MPA and EGPA for epidemiological studies and clinical trial purposes, but cannot be regarded as providing diagnostic criteria for clinical practice[145]. The current Diagnostic and Classification Criteria for Vasculitis (DCVAS) study further develops classification and diagnostic criteria in AAV[146].

[H2] Clinical presentation

The different types of AAV share non-specific clinical features of systemic inflammation, such as weight loss, malaise, fatigue, arthralgia and myalgia relating to the systemic autoimmune pathophysiology (Box 2, Figure 6). These are frequently misinterpreted as infections, malignancies, depression or osteoarthritis, especially in older patients[147]. This is pertinent as some conditions such as infective endocarditis not only share clinical features with AAV but may also have a positive ANCA test by indirect immunofluorescence (see Box 1). Although asthma is a typical early feature of EGPA, all forms of AAV can present with manifestations relating to small vessel vasculitic lesions and dysfunction of any organ[148]. A variety of organ systems and tissues are affected in AAV, albeit at different frequencies in GPA, MPA and EGPA (Figure 6).

Necrotizing or granulomatous lesions can affect the ears, nose and throat (ENT) tract, and cause symptoms of chronic rhinitis, sinusitis or laryngitis. Similar processes in the respiratory tract, also including pulmonary capillaritis, present with shortness of breath, cough, and haemoptysis due to pulmonary haemorrhage (Figure 6). Cavitating lung nodules can be present. Ophthalmological manifestations include granulomatous orbital or retroorbital masses, anterior segment inflammation, retinal vasculitis or optic neuritis. A purpural or petechial rash is most common, with necrotizing dermal vasculitis and other non-vasculitic skin rashes also occurring. Kidney involvement usually presents as rapid-progressive glomerulonephritis with haematuria, proteinuria and hypertension. Interstitial nephritis without glomerular involvement occurs but is not common. The peripheral nervous system is typically affected by mononeuritis multiplex, due to focal vasculitis of the vasa nervorum.

EGPA is characterised by the near-universal presence of asthma, often for years prior to the onset of eosinophilia and eosinophilic tissue inflammation, and difficult to control asthma not infrequently persists even after treatment of EGPA. A subset of EGPA patients do exhibit frank vasculitis. EGPA affected tissues are similar to those affected to GPA and MPA, at different frequencies (Figure 6). In particular, cardiomyopathy due to eosinophilic myocarditis is not uncommon in EGPA and can be life-threatening. Some of the differences in the manifestations of EGPA and MPA/GPA, for example urticaria and eosinophilic pneumonia, align with its characteristic eosinophil-dominated inflammation.

Some patients present with GPA or MPA limited to a single organ, such as the kidneys, ENT tract or lungs, which may represent the early stages of AAV. However, in MPO-ANCA$^+$ patients isolated renal disease or isolated pulmonary fibrosis is not infrequent. The recognition of MPO-ANCA$^+$ pulmonary fibrosis, that many be the sole manifestation of disease, as a feature of AAV has been of some interest[149]. It may be more common in Japan[150,151], though it occurs in diverse geographical locations. MPO-ANCA associated pulmonary fibrosis may result from chronic low-grade pulmonary inflammation, but this is not clear. A minority of MPO-ANCA$^+$ patients with MPA also have anti-glomerular basement membrane antibodies and exhibit a hybrid disease phenotype[152], whereas people with systemic lupus erythematosus or systemic sclerosis can be MPO-ANCA$^+$ and develop some features of AAV, especially the vasculitic pattern of glomerulonephritis[153-155]. As initial clinical presentations are diverse and often nonspecific, AAV is an infrequent but important differential diagnosis for many conditions across many medical disciplines. AAV can remain undiagnosed for months or years until ANCA testing is performed. In view of the rarity of AAV and the existence of mimics of vasculitis, the diagnosis should be reviewed periodically, particularly in cases of inadequate response to treatment or if not all disease manifestations are consistent with AAV.

Children with AAV can develop a similar range of clinical features to adults. Constitutional, ENT, renal and pulmonary manifestations are most commonly found at presentation[15]. However, some features may be more common in children. A French Vasculitis Study Group Registry based case control study, with most children having GPA, found that children were more likely to have fever at onset than adults[156]. Rates of renal involvement were similar, but myalgia and peripheral neuropathy were less common. Children were more likely to relapse than adults and more frequently accrued damage, especially ENT damage, over time[15,156].

[H2] Clinical syndromes and antigenic specificity

MPA and GPA are strongly associated with MPO-ANCA and PR3-ANCA, respectively, whereas EGPA can be either ANCA^{+} (mostly MPO-ANCA) or ANCA^{-} (Table 1). Global variations in clinical manifestations reflect the relative rates of MPA (MPO-AAV) and GPA (PR3-AAV) discussed in Epidemiology (above), with for example, clinical features associated with MPA being more common in East Asia. Given the presence of overlapping signs and symptoms but also clear clinical differences (described in Table 1 and Box 2), another approach to disease classification is by the autoantigen involved (that is, PR3-AAV and MPO-AAV), although this approach also has limitations: ANCA can be negative, MPO-ANCA can be false positive in patients without vasculitis[157], assay standardization is lacking, and not all countries have ready access to high quality assays. Nonetheless, genetic and other studies demonstrate that the clinical differences between PR3-AAV and MPO-AAV are greater than those between GPA and MPA[36,158], indicating that from a pathogenetic perspective, antigen specificity is important. Furthermore, post hoc analyses of a large multicentre study suggest that PR3-ANCA^{+} patients may respond better to the biologic rituximab than to the immunosuppressants cyclophosphamide and azathioprine, whereas these treatments seem to be equally effective in MPO-ANCA^{+} patients[159]. ANCA specificity also predicts differences in long-term prognosis: PR3-ANCA^{+} patients are at higher risk of relapse than MPO-ANCA^{+} patients[160]. In EGPA, the presence or absence of ANCA in patients defines its two subtypes. Most patients with EGPA are ANCA-, but approximately 40% are (or have been) ANCA positive, almost always MPO-ANCA. Clinically, renal involvement and peripheral nerve involvement are more common in ANCA^{+} patients, with cardiomyopathy and possibly pulmonary infiltrates being more common in those who are ANCA^{-} [42,43].

[H2] Biomarkers

ANCAs are unique markers that support the classification and diagnosis of GPA, MPA and EGPA. The indirect immunofluorescence test has been the initial screening test for ANCA, but high-quality immunoassays are preferred[161] (Box 1). The ANCA test is useful in monitoring: patients with persistently elevated ANCA, a reappearance of ANCA or an increase in ANCA level have an increased likelihood of relapse, though restarting or intensifying therapy based on ANCA alone is not recommended. This aligns with an association between earlier relapse and a higher frequency of memory B cells[162], while a higher plasmablast percentage during remission is also predictive of relapse[163]. The acute-phase markers C-reactive protein and erythrocyte sedimentation rate are of limited use in evaluating disease activity due to their lack of

specificity. Other disease activity biomarkers, including urinary soluble CD163, are under evaluation for use in assessing disease activity but await validation for routine clinical use[164-166].

[H2] Assessment of disease activity and chronic damage

Patients with AAV should have access to medical specialists with expertise in the complex care of vasculitis, ideally in a multidisciplinary context. Where needed, early referral to specialists experienced in assessing specific organ systems involved in AAV improves the quality of disease assessment. Managing patients at, or in collaboration with a dedicated vasculitis center provides opportunities to participate in clinical trials. Disease assessments in AAV should target activity, damage, prognosis and function or QOL[167], Validated tools to assess disease activity include the Birmingham Vasculitis Activity Score (BVAS) and the Five Factor Score (FFS). The BVAS comprises ten systems (one general, eight organ-specific and one open) and is used in clinical research to assess disease activity, remission, response to therapy and flare[168]. Only items that are newly present or worsening over the preceding four weeks are recorded. Disease states of active disease, remission, and refractory disease are defined as follows: a BVAS score of 0 represents remission, ≥1 represents active disease, and refractory disease is active disease despite treatment. Consensus definitions have been recommended by the European League Against Rheumatism (EULAR) for disease activity states, including remission, response, refractory disease and relapse which can be useful for clinical trials and studies[169]. The 1996 FFS is based on serum creatinine, proteinuria, cardiomyopathy, gastrointestinal involvement, and central nervous system involvement, and has been validated for MPA and EGPA but not GPA. The revised 2009 FFS includes serum creatinine, age (>65 years), cardiomyopathy, gastrointestinal involvement and absence of ENT manifestations (GPA and EGPA only) but this version requires validation[170]. To assess chronic damage, both from the disease itself and from treatments such as glucocorticoids, the Vasculitis Damage Index (VDI) predicts mortality risk and scores 10 systems, namely musculoskeletal, skin and mucous membranes, ocular, ENT, pulmonary, cardiovascular, the peripheral vasculature, gastrointestinal, renal and neuropsychiatric systems, with an eleventh category for other systems[171].

The BVAS and VDI are approved by the Outcomes Measures in Rheumatology (OMERACT) group and EULAR as key outcome measures to record disease activity and damage, respectively, in clinical trials[172]. Measures of QOL are important in the assessment of AAV. Generic tools have thus far been used but AAV-specific instruments have been developed (see QOL section, below).

[H2] Association with cardiovascular events

An increased risk of a cardiovascular events has been documented in AAV patients[173]. Indeed, during 5-years of follow up of four European Vasculitis Study Group trials of GPA and MPA, 14% of patients suffered a cardiovascular event defined as cardiovascular death, stroke, myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention. PR3-ANCA was associated with a reduced cardiovascular risk compared to MPO-ANCA or negative ANCA status[174].

Dysfunction of the immune and coagulation systems contribute to an increased risk of venous thromboembolism[175], especially during active disease[176]. An increased incidence of venous thromboembolism, in both typical and atypical sites, and pulmonary embolism has also been reported in GPA, MPA and EGPA[177].

[H2] Role of imaging and biopsy

A chest X-ray helps dissect the underlying pathology in patients with pulmonary symptoms (Figure 6), although CT has a higher sensitivity in detecting pulmonary nodules, cavities and alveolar opacities, as well as masses in the retro-orbital space, paranasal sinuses and the mastoids[178]. Iodinated contrast agents are not required for these studies. High-resolution chest CT (HRCT) may be helpful for detecting interstitial pneumonia; a study of HRCT involving Japanese patients with MPA, all but three of whom had MPO-ANCA, demonstrated abnormalities in 93%, with 51% having interstitial pneumonia[151]. While dynamic expiratory CT and other modalities have been advocated as potentially useful in detecting subglottic stenosis or endobronchial disease[179], advanced imaging techniques may not be widely available or may only available as research tools.

The high diagnostic specificity for AAV of a positive ELISA test for MPO-ANCA or PR3-ANCA, may in the appropriate clinical setting, preclude the need for biopsies. However, renal, lung, skin or other tissue biopsy is often important in establishing the diagnosis and may, especially in the case of nasal biopsy, provide the first evidence for AAV, particularly GPA. In the appropriate clinical context, granulomatous rhinitis or pneumonitis, and ‘pauci-immune’ glomerulonephritis are more specific for AAV than dermal leukocytoclastic vasculitis. Ultrasound-guided percutaneous kidney biopsy, while not mandatory, in the presence of haematuria and/or proteinuria can help make an initial diagnosis of AAV. Kidney biopsy can also diagnose relapse, establish the degree of chronicity of nephritis, and in chronic disease may be useful in determining whether impaired kidney function and proteinuria is related to active

vasculitis or irreversible damage. Biopsy samples from patients with suspected AAV should be assessed by an experienced pathologist.

[H2] Pathology

Although sharing many features, the different forms of AAV show histopathological differences (Figure 7). Fibrinoid necrosis and inflammation of small vessels, sometimes accompanied by thrombosis, is the hallmark of acute injury in all forms of AAV[180]. In MPA, these features are present without other defining features, such as the granulomas in GPA or the prominent eosinophilic infiltrates in EGPA. Chronic lesions are characterized by transmural scarring with loss of the elastic internal lamina. Larger blood vessels can be affected, with leukocytic infiltrates and fibrinoid necrosis, as seen in polyarteritis nodosa. However, the involvement of larger vessels should not be interpreted as an 'overlap' with other forms of vasculitis when small vessel (capillary and arterioles) involvement is also present. While the histopathology of EGPA features necrotizing small-vessel vasculitis (as in GPA and MPA), an abundance of eosinophils is its defining feature. In the early stages of disease, eosinophilic infiltrates (but no necrosis) are present in tissues or in blood vessel walls, whereas in later stages of disease, eosinophils also surround the epithelioid cells within granulomas, and necrosis is present.

[H3] Renal involvement. In the kidneys, the characteristic lesion in AAV is segmental necrosis of glomerular capillary loops, with little or no deposition of immunoglobulin or complement, termed 'pauci-immune' focal necrotizing (and crescentic) glomerulonephritis. Different lesions in different glomeruli within the same biopsy specimen reveal the asynchronous nature of the vasculitic injury. Acute glomerular injury is characterized by segmental necrosis with extravasation of fibrin and erythrocytes into the urinary space, followed by proliferation of parietal glomerular epithelial cells forming a cellular crescent. Destruction of Bowman's capsule, the basement membrane surrounding the glomerulus, results from glomerular and periglomerular inflammation. These inflammatory changes lead ultimately to glomerulosclerosis that can be either segmental or global and represent the evolution of injury over days to months.

Glomerular lesions are used to stage renal disease in AAV by a histopathological classification[181], where the dominant lesion is linked to outcomes. There are four patterns of injury, namely sclerotic (≥50% globally sclerosed glomeruli, worst outcome), focal (≥50% normal glomeruli, best outcome), crescentic (≥50% cellular crescents, intermediate outcome)

and mixed (no single dominant type of lesion, outcome better than the sclerotic but worse than the crescentic class). In clinical settings, this classification has been validated by some but not all studies, especially with regard to prognosis in the crescentic and mixed classes[182]. The classification does not currently include the extent of tubulointerstitial lesions or renal function. A further classification system has been proposed that includes these factors, together with the proportion of normal glomeruli at biopsy[183].

Glomerular injury is often accompanied by inflammation of small arteries and a variable interstitial infiltrate around necrotic lesions, either glomeruli or blood vessels, in a granuloma-like pattern, but multinucleated giant cells are rarely seen. The presence of sarcoid type granulomas in renal biopsies should lead to consideration of other diagnoses, such as renal sarcoidosis or an allergic drug reaction.

[H3] Respiratory tract involvement. In GPA, upper and lower respiratory tract injury classically involves granulomatous inflammation. Small granulomas are composed of sometimes loose aggregates of epitheloid cells. The granulomatous inflammation often shows central necrosis containing nuclear fragments of granulocytes, is surrounded by a palisade of epithelioid cells and, in EGPA, by large numbers of eosinophils. Granulomatous inflammation and areas of necrosis are often confluent, with a 'geographic' appearance at low magnification. Multinucleated giant cells are almost invariably present and are pathognomonic for GPA or EGPA when seen in isolation in lung or upper airway biopsy samples, cytology specimens from bronchoalveolar lavage or nasal swabs taken when clinical features suggestive of AAV are present.

In the lungs, neutrophilic capillaritis is common to all forms of AAV. As vasculitic changes can be difficult to detect in small biopsy samples, samples should also be stained with trichrome and Elastica van Gieson for optimal detection of any disruption to alveolar or vessel walls, small areas of necrosis in arterioles and arteries, vascular inflammation, and characteristic scars affecting the full thickness of the vessel wall, which indicate past injury. Acute injury may consist of only non-specific inflammation or features resembling bronchiolitis obliterans and organizing pneumonia. However, signs of recurrent alveolar haemorrhage with extravasation of erythrocytes, variable numbers of siderophages or small areas of fibrin, necrosis or micro-abscesses are suggestive of AAV. In the nose, necrotizing granulomatous inflammation in GPA can cause severe soft tissue destruction, including of the nasal cartilage. Large ulcers with denuded epithelium can be seen. Granulomatous inflammation is also a feature of nasal

involvement in EGPA, sometimes with eosinophilic necrosis but more often containing epithelioid cell aggregates surrounded by a dense eosinophil infiltrate.

[H3] Other organ and tissue involvement. Similar vasculitic changes are found in other tissues, such as the heart, brain or gastrointestinal tract. In the gut, the finding of otherwise unexplained necrosis or haemorrhagic infarction should prompt extensive examination of mesenteric vessels for vasculitis. Although most often seen in isolation, dermal leukocytoclastic vasculitis can represent systemic disease. Involvement of the peripheral nervous system as mononeuritis or mononeuritis multiplex is due to ischaemia caused by vasculitic inflammation of the vasa nervorum[184].

[H2] Prognosis

The 5-year survival rates for AAV have been steadily rising to around 70–80% over the past 40–50 years, following the introduction of immunosuppressant therapies, increasing know-how in the their use, and the introduction of ANCA testing, which are promoting earlier diagnosis and improvements in supportive care[185]. Data also suggest that there are ongoing improvements in mortality and end-stage kidney disease rates over the past decades in the USA[186,187]. Globally, AAV mortality rates, based on World Health Organisation International Classification of Diseases, 10th Revision (ICD-10) data are falling[188]. These data, though imperfect include mortality rates from many countries, and suggest similar age-standardised mortality rates in North America and Europe, with lower rates in Latin America and higher rates in Oceania. Data from Asia and Africa were limited.

Initial clinical factors influencing outcomes include older age, severity of renal dysfunction, the presence of pulmonary haemorrhage (in some series), and disease activity measured by BVAS[185]; the findings on renal biopsy reflect severity of renal dysfunction and correlate with outcomes[181]. The 2009 FFS can also be applied to prognosis, since four factors are associated with a poor prognosis (age, renal insufficiency, cardiac involvement, and gastrointestinal manifestations, where each is accorded +1 point); the fifth factor, ENT manifestations, is associated with a better outcome and the absence of ENT symptoms scores +1 point[170]. Ongoing factors influencing survival include infectious burden, development of first relapse within one year and the amount of chronic damage measured by the vasculitis damage index (VDI)[174]. As the VDI encompasses both disease and treatment-related damage, the risks of immunosuppressant drugs and glucocorticoids will also have an impact. Finally, other factors seem to influence the likelihood of relapse, currently quoted as ~50% by five years after

711 diagnosis; these include a diagnosis of GPA, presence of PR3-ANCA and upper or lower
712 respiratory involvement[189].
713

[H1] Management

Following diagnosis, disease assessment in AAV should consider activity and damage, for which assessment tools are available (see Assessment of disease activity and chronic damage section above), prognosis (see above), and function or QOL (described below). Broadly speaking, therapy can be divided into a phase aiming to induce remission with more intense therapy and a subsequent period where the goal is to maintain remission (Figure 8; clinical trials in GPA and MPA are summarized in Table 2). The goal of induction therapy is to achieve remission by 3 months that is sustained. Later remission, early relapsing or refractory disease is associated with worse outcomes[190].

Treatment should be initiated as soon as a diagnosis of AAV is at least probable and appropriate safety investigations have been performed, as delays in diagnosis and treatment lead to worse outcomes. Initiation of treatment, especially in the setting of severe renal or lung disease, should not be delayed obtaining a biopsy, as several days of treatment usually does not markedly reduce the diagnostic yield of a biopsy.

[H2] Remission induction

Prior to initiation of therapy there should be an assessment of any coexisting infection and any risk of infection, including screening for chronic viral infections, immunodeficiency, and for the risks of glucocorticoids, such as diabetes mellitus, osteoporosis, and psychiatric disorders.

[H3] Glucocorticoids. Oral glucocorticoids (such as prednisone, prednisolone and others) are commenced when a diagnosis of AAV seems probable. These drugs exert a rapid effect. The initial dose for severe disease is 1 mg/kg daily of prednisone (or equivalent). The PEXIVAS trial demonstrated that a regimen that rapidly reduces the dose to 20 mg daily by 7 weeks and 5 mg daily by 19 weeks is as effective and safer than more traditional, higher-dose regimens[191]. Glucocorticoids are the major modifiable cause of adverse events during the induction period and lower-dose regimens reduce severe infection rates. There is no consensus for glucocorticoid dosing in non-severe disease and lower initial doses may be used. The RITAZAREM trial demonstrated that patients with relapsing disease respond well to lower initial doses, such as 0.5 mg/kg/day, whether or not they had severe disease[192]. Intravenous pulse methylprednisolone (total dose 1–3 g) at the initiation of therapy for severe disease is conventionally administered, but its benefits and harms have not been adequately studied.

[H3] Other immunosuppressive or immunomodulating drugs. The combination of glucocorticoids with either cyclophosphamide or rituximab is the current standard of care for induction of remission for severe disease, although as further evidence supporting the efficacy of rituximab emerges, it is becoming the preferred induction agent for many patient subgroups, such as children and adults for whom the preservation of fertility is important, PR3-ANCA$^+$ patients and in relapsing disease. However, rituximab is more expensive and globally is not as available as cyclophosphamide. Cyclophosphamide dosing is either by intermittent intravenous pulse treatments or by a daily oral dose. Doses are reduced for increasing age and renal impairment; either regimen is usually discontinued after 3–6 months, with subsequent initiation of therapy to maintain remission. Close monitoring is essential to minimize the risk of myelotoxicity. Intravenous regimens deliver ~50% of the cumulative dose compared to daily oral, with similar remission rates, but lower cyclophosphamide exposure is associated with a higher subsequent relapse risk[193,194].

In two randomized trials, rituximab was non-inferior to cyclophosphamide for induction of remission and, in a post-hoc analysis of the RAVE trial, superior for patients with PR3-ANCA$^+$ or relapsing disease[159,195,196]. These trials used 375 mg/m^2, weekly for four doses, although two 1,000 mg doses (two-week interval) is also widely used. There is a paucity of comparative data on the use of either cyclophosphamide or rituximab in patients with low GFR (for example, <20 ml/min), with a lower dose of cyclophosphamide together with rituximab being used in the RITUXVAS trial[197]. The use of this combination is controversial and may confer an additional risk of infection[198].

For non-severe disease, alternative immunosuppressive agents to cyclophosphamide, such as methotrexate and mycophenolate mofetil, are equivalent to cyclophosphamide in terms of remission rates at 6 months but have higher subsequent rates of relapse and greater accrual of damage, especially for PR3-ANCA disease. Methotrexate has been recommended for patients with no threat of organ-damaging disease, although longer term outcomes (such as relapse and damage accrual) are worse than with cyclophosphamide[199]. Such patients are uncommon and often require later use of cyclophosphamide or rituximab for control of more severe or relapsing disease. The MYCYC trial found similar responses for MPO-ANCA$^+$ patients between mycophenolate mofetil and cyclophosphamide, at both 6 and 18 months[200], and two other small randomized trials support a role for this agent as an alternative for this subgroup.

[H3] Adjunctive therapy. Although smaller studies demonstrate that use of plasma exchange is associated with reduced risk of end-stage kidney disease for patients with a

781 serum creatinine >500 μmol/l at diagnosis[201], the results of the large PEXIVAS trial indicate
782 that plasma exchange should not be routinely recommended for GPA or MPA with nephritis
783 or lung haemorrhage[191]. Whether specific subgroups, such as those that are oliguric at
784 presentation or with hypoxic respiratory failure, benefit from plasma exchange requires
785 further study. In one study, high-dose intravenous immunoglobulin (2 g/kg total dose)
786 improved disease control of AAV refractory to usual therapy[202] and can be considered when
787 conventional agents are contraindicated, such as in the setting of severe infection.
788
789 ***[H2] Therapy to maintain remission***
790 The goals of maintenance therapy are to prevent relapse, to minimize the risk of
791 comorbidities and drug toxicity, and to manage the consequences of organ damage, such as
792 chronic kidney disease. Many patients with AAV require prolonged low-dose glucocorticoids
793 (prednisone ≤10 mg daily) to maintain remission, even if also treated with rituximab or an
794 oral immunosuppressive drug.
795 In the MAINRITSAN and RITAZAREM trials of interval treatment, rituximab was
796 superior to azathioprine[192,203]. These findings are consistent with previous observational data
797 and are driving a revision of guidelines. Azathioprine, methotrexate or mycophenolate
798 mofetil, with or without oral glucocorticoids, can be used after cyclophosphamide to maintain
799 remission in AAV. The optimal duration for treatment with these agents is uncertain, with the
800 REMAIN trial supporting 3–4 years of treatment regardless of ANCA subtype or
801 positivity[204]. The MAINRITSAN trial results indicate that following use of
802 cyclophosphamide in patients with new-onset disease, a reduction in relapse rates occurs with
803 use of rituximab (500 mg every six months over 2 years) compared with azathioprine.
804 MAINRITSAN3 showed that following the initial two years of treatment, a further two years
805 of rituximab treatment also reduced relapse rates[205]. The RITAZAREM trial confirmed and
806 extended these observations in a cohort of patients with relapsing disease in whom remission
807 was re-induced with rituximab and glucocorticoids, with maintenance rituximab at 1000 mg
808 every four months over two years[192,206]. Both the MAINRITSAN trial results and
809 observational data point to an increase in relapse risk after rituximab withdrawal, compared
810 with continuing treatment, with a mean time to flare of two years after the last rituximab
811 dose[207].
812 There remains widespread use of oral immunosuppressive drugs after induction of
813 remission with cyclophosphamide, at least until first relapse. The use of either CD19 counts

or serum ANCA levels to guide redosing of rituximab is controversial; a randomized trial comparing fixed-interval to biomarker-based dosing showed similar efficacy of these dosing regimens and reduced frequency of redosing, but more relapse when based on biomarkers[208].

Several factors have been shown to alter the risk of relapse in AAV, including disease phenotype (GPA relapses more than MPA), ANCA subtype (patients with PR3-ANCA relapse more than patients with MPO-ANCA), a history of previous relapses, the presence of ENT disease, and the absence of severe renal disease[207]. Following induction therapy, persisting or the return of ANCA positivity, *S. aureus* infection, and lower cyclophosphamide exposure are linked to increased risk of relapse, but confirmation of these findings and testing in a clinical trial setting are needed prior to routine application to practice. As withdrawal of therapy appears to increase risk of relapse, patient-level factors to consider around drug withdrawal are the likely consequences of relapse (for example, end-stage kidney disease in a patient with chronic kidney disease), adherence to monitoring, access to expert advice, and patients' views on the risks of relapse and ongoing drug exposure.

[H2] Treatment of relapses of GPA and MPA

Continued regular monitoring of patients with AAV after induction of remission enables early detection of relapses with less advanced symptomatology than at presentation and reduced delay. When a patient is considered to be having a relapse, a review of the primary diagnosis and vasculitis mimics such as infection, malignancy or recreational drug use, should be excluded. Non-adherence to prescribed medications is also often a concern. One-third of relapses are severe with consequences for renal and patient survival. Treatment of relapse follows the same principles as for initial therapy, but rituximab is preferred in view of superior responses in the RAVE trial in relapsing patients and the beneficial effects seen in the RITAZAREM trial[192,195,196].

[H2] Treatment of refractory disease

Refractory disease in AAV has been defined as a failure to achieve full control of the vasculitis-related disease activity by six months, progressive disease within the first three months or relapse despite adequate ongoing therapy for maintenance of remission. It is important to differentiate true 'failure' of a medication from non-adherence, disease damage or mimics of vasculitis. This is most relevant in respiratory tract disease in which comprehensive assessment and treatment of any infection should accompany the evaluation of the vasculitis. An increase in glucocorticoid dose, such as use of intravenous

methylprednisolone, is used in severe disease relapse but prolonged use of high-dose oral glucocorticoids should be avoided due to the associated risks. Switching from cyclophosphamide to rituximab can be considered. Adjunctive therapies to consider are plasma exchange or intravenous immunoglobin (discussed above).

[H2] Treatment of EGPA

The approach to patients with EGPA with severe disease is similar to that in GPA and MPA (Table 3). Treatment strategies for EGPA vary according to disease manifestations and severity, and concomitant manifestations of asthma should be managed assertively. The Five Factor Score is used to stratify people with EGPA, and the presence of substantial renal involvement (severe proteinuria or impaired kidney function), cardiomyopathy, gastrointestinal involvement, or central nervous system involvement indicates a need for more intensive treatment, such as a cyclophosphamide and glucocorticoid regimen analogous to that used in GPA and MPA. Although one trial failed to demonstrate a benefit of oral immunosuppressive drugs in non-severe disease[209], these agents are widely used in an attempt to reduce the high glucocorticoid requirement typical for this disease. The anti-IL-5 monoclonal antibody mepolizumab is a further therapeutic option that has demonstrated effects on airways and allergic manifestations[143]. In a randomised clinical trial, mepolizumab was useful in most patients, especially for asthma and sinonasal disease, either by maintaining sustained remission, reducing relapse rates or substantially reducing the dosage or duration of glucocorticoid therapy[210]. Rituximab can also be used in EGPA, but its efficacy in EGPA is less well established than for GPA and MPA, particularly for EGPA ANCA$^-$ patients, who show frequent relapse of asthma and sinonasal disease despite continued use of rituximab[211].

[H2] Monitoring disease activity

Clinical assessment and investigation follow the goals of maintenance outlined above, namely early identification of return of disease activity, screening for drug toxicity, and management and recognition of comorbidities. Serum creatinine measurement and urine analysis to detect haematuria and proteinuria should be undertaken regularly to assess disease activity and kidney function. Additional elements include patient education and psychosocial support. Lower baseline IgG levels are associated with increased risk of immunodeficiency after rituximab treatment. IgG levels should be checked periodically after treatment and falling levels should influence the decision on repeat dosing. Routine CD19 counts (a

measure of B cell levels) are not required but may be informative in patients with incomplete response to rituximab or early relapse. Microbiological assessment of the nasopharynx and infection control with topical antiseptic agents or antibiotics may improve symptomatic management. More intensive monitoring may be required for organ-specific issues, such as bronchoscopy in tracheo-bronchial disease, repeat renal biopsy in advanced renal impairment with persisting urinary abnormalities, and cardiac imaging (echocardiography and MRI) in cases of cardiac involvement

[H2] Comorbidities and treatment effects

Infection is the most frequent serious problem in the first year of treatment for AAV. Routine prophylaxis against *Pneumocystis jirovecii* pneumonia with sulfamethoxazole-trimethoprim (or alternative agents) is recommended and this treatment may also reduce the frequency of other bacterial infections. Independent of its value in *Pneumocystis jirovecii* prophylaxis, there is not enough evidence to recommend routine use of long-term sulfamethoxazole-trimethoprim in PR3-ANCA^{+} patients to prevent disease relapse. Avoidance of severe drug-induced leukopenia is crucial. Rituximab-induced immunodeficiency and any case of recurrent infection requires further immunological assessment. Cases of hypoimmunoglobulinaemia with frequent infections may prompt use of replacement immunoglobulin[212]. Routine vaccination against influenza and pneumococcal infection is recommended for all patients, although serological responses may be impaired, especially following rituximab treatment.

Venous thromboembolism should be treated with anti-coagulation agents, although these can be problematic in the setting of pulmonary haemorrhage[213]. The risk of cardiovascular events is markedly raised in patients with more extensive disease, those without PR3-ANCA, and in the presence of renal impairment[173,214]. There is no current advice concerning reducing these risks that is specific to patients with AAV, although careful attention to management of hypertension and hyperlipidaemia is recommended.

Cyclophosphamide and other oral immunosuppressive drugs are associated with an increased risk of malignancies, particularly non-melanoma skin cancer and urothelial malignancy[215,216]. The rates of these cancers are falling with reduced immunosuppressant exposure, especially to cyclophosphamide, and the increased use of rituximab[217]. The relative risk of malignancy increases with therapy duration, so screening for haematuria in patients exposed to cyclophosphamide and for skin malignancy should be lifelong. Prophylaxis

against gastric toxicity is often prescribed with high dose glucocorticoids, that also increase the risk of osteoporosis[218].

The management of organ damage in patients with AAV requires sub-specialist intervention by those with appropriate experience, in co-ordination with the primary physician overseeing the treatment of the vasculitis. Examples include surgical correction of lacrimal duct obstruction, middle ear disease, nasal collapse and subglottic or endobronchial stenosis[219]. Renal transplantation is generally successful in AAV, although opportunistic infections may be more common than in transplant recipients without AAV, reflecting the prior burden of immunosuppressive therapy for AAV. Recurrence of vasculitis in the renal graft occurs in 2% of transplant recipients with AAV and can lead to graft failure. Long-term patient survival is similar to that of all causes of end-stage renal disease[220].

[H1] Quality of Life

Patients are well aware of the challenges they face in managing AAV and self-report substantial impact on QOL from AAV itself as well as the burden of treatment and treatment-related toxicities (Box 4). The evolution in immunotherapeutics has converted AAV into a chronic disease and in consequence, patient priorities have realigned. Rather than focus on the spectre of major organ damage, patients rank QOL domains, such as fatigue and pain, as the greatest disease priorities[221].

There can be key differences between patient and clinician perceptions of these priorities. For example, although patients and clinicians both rank weight gain as a major concern about glucocorticoid treatment, patients frequently cite 'moon face' and other effects on appearance as highly concerning, whereas clinicians tend to not consider these effects to be as important as the risk of infection. A closer assessment of patient reported QOL will provide an opportunity for better alignment of patient and clinician priorities.

Characterization of a national cohort indicated that patients with AAV experienced substantially poorer levels of physical and mental QOL compared to matched controls in the general population (physical QOL: OR 7.0, 95% CI 4.4–11.1; mental QOL: OR 2.5, 95% CI 1.7–3.6), even though the vast majority (80%) of patients had achieved disease remission[5].

Modern induction agents certainly result in noticeable improvements in QOL, but gains are modest and patient QOL rarely returns to normal levels[195]. Several factors may explain this situation. First, high-dose glucocorticoids remain integral to standard care but they have multiple toxic effects, including on QOL domains such as mental health[222], which should be assessed using, for example, the Glucocorticoid Toxicity Index[223]. Second, almost all studies of QOL in patients with AAV have used generic questionnaires, including the 36-item Short Form Health Survey (SF-36), the EuroQol-5 Dimension (EQ-5D) and the Health Assessment Questionnaire, which may not capture AAV-specific issues.

The OMERACT Vasculitis Working Group developed a 29-item tool, the AAV-PRO questionnaire [224,225], covering six domains (organ-specific symptoms, systemic symptoms, treatment side effects, social and emotional effect, concerns about the future and physical function), following patient qualitative interviews to address this unmet need. The AAV-PRO is being integrated into ongoing randomized controlled trials. Similarly, the Patient-Reported Outcomes Measurement Information System (PROMIS), covers fatigue, physical functioning and pain interference. Both PRO systems assess function and QOL, are complementary and require further validation, but they offer options to ensure patients' perspectives are considered when assessing disease activity in AAV[224,225].

Impairments in QOL are the result of multiple factors, not only active inflammatory disease but also disease damage, although they seem to be primarily related to psychosocial factors, such as fatigue and dysfunctional coping strategies[5] and skeletal dysfunction. Persistently high levels of fatigue that does not change after treatment occurred in some patients in a SF-36 vitality domain sub-analysis of the MYCYC and RITUXIVAS studies[226]. Furthermore, there were marked disparities in physical QOL, including reduced knee extension (76%) among patients with AAV compared with healthy controls. This reduced knee extension was associated with impaired SF-36 Physical Component Score, as were metrics of pre-existing muscle strength[227].

Since QOL differs for each patient, QOL can also be helpful in developing more personalized treatment approaches. Studies examining whether physical activity improves fatigue in patients with AAV are underway[228]. As disease assessment in AAV should include function or QOL[167], reliable PRO tools are crucial not only for monitoring individual patients but also for high quality assessment of the impact of AAV and the success of its therapies.

[H1] Outlook

Substantial progress has been made in understanding and treating AAVs. GPA, MPA and EGPA have gone from diseases with a high mortality within 1–2 years of the onset of symptoms to chronic conditions that require lifelong specialist management. However, major challenges remain. AAVs are still responsible for substantial morbidity and mortality, both from the diseases themselves and from their treatments. Most treatments are fairly non-specific and come with undesirable immune and metabolic adverse effects. Furthermore, the optimal duration of therapy is uncertain, in part because of a lack of reliable predictors of relapse. More effective management of AAV in the future will rely on a better understanding of the clinical aspects of the disease and of disease-causing processes, together with the development of effective biomarkers to better define disease activity and predict relapse. More precise, effective and less toxic treatments require better knowledge, continued recognition of unmet clinical need, and additional strategic and successful well-designed international collaborative clinical trials. These efforts must be combined with more explicit recognition of important patient-centred outcomes, both in trials and in clinical practice. EGPA, as an even less common form of AAV with different clinical features to GPA and MPA, poses great challenges. In EGPA, even more than in GPA and MPA, multidisciplinary and international collaborations are required to improve the lives of people with this disease. Table 4 summarizes some of the emerging therapies and biomarkers in AAV.

Better diagnostic and classification criteria of AAV will assist understanding, clinical studies and improvements in patient care. The near-complete DCVAS has developed data-driven classification criteria for systemic vasculitides and should provide improved standardized criteria. Furthermore, while EGPA is clearly a distinct disease entity, for GPA and MPA the relationships and overlap between the syndromic classifications (GPA and MPA), and the presence of autoreactivity to either PR3 or MPO must be more clearly understood to aid progress in understanding, in clinical trial design and in management strategies. These efforts are not only important for improved induction therapies, but also for defining treatment duration and the management of relapse.

Epidemiologically, there is inadequate data pertaining to EGPA in general, as well as a clear need to define the occurrence of all AAV types in Africa and South Asia. A better definition of the nature and burden of disease is likely to improve clinical care and outcomes, while more detailed understanding of the epidemiological associations will inform disease pathogenesis. The recognition that AAV is an autoimmune condition and the role of ANCAs in effecting injury have been major advances. Nonetheless, the complexity of AAV and the

inadequacies of current therapies demand a more detailed understanding of pathogenesis. Many questions remain. Can the understanding of the genetics of AAV, including EGPA, lead to pathway-directed therapies, either via new therapies or by repurposing existing therapeutics? Why are only some ANCAs pathogenic – and if we understand this, can we measure specific ANCA subtypes to develop more effective biomarkers? As there is substantial deposition of ANCA antigens in affected tissues, why is immunoglobulin deposition not more prominent? Why are some organs and tissues preferentially affected? Why do some individuals lose tolerance to PR3 or MPO, whereas most do not, when these neutrophil proteins are frequently released in an immunologically 'dangerous' infectious and inflammatory context? Can immunological tolerance be re-established by antigen-specific immunomodulation? Although much is known about events in the acute effector phase of injury, key events in more chronic disease and the role of T and B cell memory are unclear. Better understanding of these issues has the potential to move the goalposts in developing treatments that induce long lasting remission and tolerance.

Key uncertainties in the care of patients with AAV include the optimal duration and intensity of maintenance therapy in an individual patient, and a lack of biomarkers that signal relapses. Better biomarkers, either singly or in combination, to predict severity and relapse risk would lead to a more precise treatment approach. Emerging biomarkers include urinary sCD163, which could be useful in determining renal relapse, with or without other markers[164,229]. Following from observations that the risk of relapse in a patient with AAV is associated with an 'active' T cell signature associated with the reduced expression of genes associated with T cell exhaustion[136], prospective clinical trials are underway to determine whether markers of this signature can inform treatment intensity. Other potential biomarkers are emerging and are undergoing further evaluation[165].

The potential for complement inhibition (by targeting the C5a receptor) is one of several therapeutic strategies aimed at limiting neutrophil activation. Complement inhibition therapies could reduce or replace the current reliance on glucocorticoids in induction therapy regimens, as in phase II and III trials of C5aR inhibition[110,111]. Glucocorticoids are a pillar of maintenance therapy for many patients and this reliance needs to be mitigated. In EGPA, further clinical trials in IL-5/IL-5R blockade will hopefully improve therapeutic options in this disease. Much attention has justifiably been given to ANCA–neutrophil mediated events in AAV, but the more selective inhibition of the underpinning T and B cell autoimmunity also has potential in inducing and maintaining remission. The goal in the treatment of AAV is not only to supress disease, but also to restore tolerance. Currently, there are no clear markers of tolerance to reassure clinicians

and patients when ceasing immunosuppression and that can be used as surrogate markers in trials of new tolerogenic, curative therapies. Whereas tolerogenic strategies that have been applied to other diseases might be suitable for AAV, outcome measures in AAV are unclear, although at least in the case of MPO, progress has been made in defining key epitopes.

A multidisciplinary approach and patient engagement would result in a more integrated treatment strategy and improved outcomes in these complex multisystem diseases. Clinicians and patients should work together in a clinical setting to increase involvement of patients in their own care and treatment decisions. There are several dimensions to this issue. The educational needs of patients newly diagnosed with AAV are high, and the rarity of the conditions makes meeting these needs complicated. In the clinical trial environment, the use of PRO measures, such as AAV-PRO, should be mandatory. Interventional trials including outcome measures that focus on improving physical and mental QOL are just beginning[228]. AAVs are challenging and complex conditions but, with an integrated, collaborative approach that includes considerable patient involvement, great progress can be made in improving the lives of people with these diseases.

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Author contributions

All authors contributed to all sections of the Primer, with A.R.K. coordinating the project.

Competing interests

A.R.K. is Chair of the board of the Australian and New Zealand Vasculitis Society and has been a consultant for CSL Limited and Visterra. N.B. has received research funding from Vifor and GSK and speaking fees from Roche and Vifor. E.B. received consultancy and speaker fees from Roche which were paid to her employer. D.J. has been a consultant for ChemoCentryx, InflaRx, and Insmed. P.L. holds founding equity in and receives consultation fees from PredictImmune Ltd. P.M has been a consultant for AbbVie, Biogen, CSL Behring, Genzyme, Insmed, Janssen, Kiniska and Sparrow, received research funding and consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, ChemoCentryx, Genentech/Roche, GSK and InflaRx, and grant support from Kypha. U.S. has been a consultant for AstraZeneca, Insmed and ChemoCentryx and has received research funding from Genentech, Bristol-Myers Squibb, ChemoCentryx, and GSK. The remaining authors declare no competing interests.

Display items

Table 1. Comparisons of the three syndromic presentations of AAV

	GPA	MPA	Eosinophilic GPA
Incidence[a]	0.4–11.9 cases per 1 million person-years	0.5–24.0 cases per 1 million person-years	0.5–2.3 cases per 1 million person-years
Prevalence[a]	2.3–146.0 cases per 1 million persons	9.0–94.0 cases per 1 million persons	2.0–22.3 cases per 1 million persons
Age of onset (years)	45–65	55–75	38–54
Male: Female	1:1	1:1	1:1
CHCC 2012 updated definition[144]	Necrotizing granulomatous inflammation, usually involving the upper and lower respiratory tract; necrotizing vasculitis affecting predominantly small-to-medium vessels (such as capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common.	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (such as capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract; necrotizing vasculitis predominantly affecting small to medium vessels; associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.
Frequency of ANCA	PR3-ANCA: 65–75% MPO-ANCA: 20–30% ANCA$^-$: 5%	PR3-ANCA: 20–30% MPO-ANCA: 55–65% ANCA$^-$: 5–10%	PR3-ANCA: <5% MPO-ANCA: 30–40% ANCA$^-$: 55–65%
Key innate immune cell	Neutrophil	Neutrophil	Eosinophil
Relapse rate	Higher than MPA (or MPO-AAV)	Lower than GPA (or PR3-AAV)	Relapse is frequent

ANCA, anti-neutrophil cytoplasmic antibody; CHCC, Chapel Hill Consensus Conference; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.

Table 2. Key clinical trials of therapies for GPA and/or MPA

Name	Population	Intervention	Key result	Other findings
Induction therapy				
CYCLOPS[193,194]	Newly diagnosed GPA or MPA, renal involvement, ANCA^{+a} or ANCA^{-} if biopsy	IV versus oral CYC, plus GCs	IV non-inferior to oral CYC in inducing remission, ~50% cumulative dose with IV vs oral CYC	Decreased relapse with oral CYC (HR 0.50) at long-term follow up
CORTAGE[230]	New diagnosis, age ≥65 years[b]	IV-CYC (maximum 6 x 500 mg, every 2-3 weeks) plus 9 months GCs versus IV CYC (~5.5g) plus 26 months GCs	Similar remission rates	Fewer serious adverse events with lower dose CYC and GCs
RAVE[195,196]	GPA or MPA newly diagnosed or relapsing, ANCA^{+}, SCr <353 μmol/l	RTX versus oral CYC, then AZA	RTX non-inferior to CYC. RTX may be better for relapsing AAV	Similar short-term adverse effects, similar relapse rates with single-dose RTX
RITUVAS[197,231]	GPA or MPA newly diagnosed, renal involvement, ANCA^{+}	2 doses IV-CYC, then RTX versus IV-CYC	Equivalent outcomes	Similar relapse rates

MEPEX[201,232]	GPA or MPA with biopsy proven glomerulonephritis, SCr >500 μmol/l, $ANCA^+$ or $ANCA^-$	PLEX versus IV-MP as add on to CYC and GCs	PLEX superior in rates of dialysis independence at 3 months and renal survival at 12 months	Long-term outcomes similar
PEXIVAS[191]	GPA or MPA newly diagnosed or relapsing with renal involvement (eGFR <50 ml/min/1.73 m^2) or pulmonary haemorrhage, $ANCA^+$	a) PLEX as add on to CYC or RTX and GCs b) Low-dose GCs versus high-dose, plus RTX or CYC	a) PLEX not superior b) low-dose GCs non-inferior, with fewer serious infections	Effects similar across subgroups
CLEAR[110]	Phase II, newly diagnosed or relapsing GPA or MPA with renal involvement, $ANCA^+$	Avacopan and reduced GCs or no GCs, versus GCs, plus RTX or CYC	Avacopan not inferior	Avacopan: faster reduction in proteinuria, better QOL indices with no GCs
ADVOCATE[111,233]	Phase III, newly diagnosed or relapsing GPA or MPA, $ANCA^+$	Avacopan versus GCs, plus RTX or CYC then AZA	Avacopan non inferior to GCs, superior for sustained remission at one year.	Less GCs-related toxicity

IVIg[202]	Active GPA or MPA, >2 months CYC and GCs, $ANCA^+$	CYC and GCs versus add-on IV-Ig (single dose 2 g/kg)	Response: 14/17 IV-Ig, 6/17 placebo	Effects did not extend beyond 3 months
NORAM[199,234]	Newly diagnosed GPA or MPA, less severe disease	MTX (20–25 mg weekly) versus oral CYC	MTX non-inferior for remission induction	MTX less effective for extensive or pulmonary disease; relapse more frequent with MTX
MYCYC[200]	New diagnosis of GPA or MPA, eGFR >15 ml/min/1.73 m^2	IV-CYC versus MMF (2–3 g daily)	MMF non-inferior for remission induction	Increased relapse with MMF, especially PR3-AAV
Maintenance therapy				
CYCAZAREM[23][5]	New diagnosis GPA or MPA, SCr <500 μmol/l, $ANCA^+$ or $ANCA^-$ if biopsy	Induction oral-CYC or GCs 3–6 months (to remission), then CYC 1.5mg/kg daily versus AZA to 12 months	Similar relapse rates	Relapse more common in GPA than MPA
WEGENT[236,237]	GPA or MPA in remission, initially treated with IV CYC and GCs, $ANCA^+$ or $ANCA^-$ if biopsy	AZA versus MTX	Similar relapse rates and toxicity	Long-term outcomes similar

IMPROVE[238]	GPA or MPA newly diagnosed, in remission, $ANCA^+$	MMF versus AZA	Relapse more common with MMF (HR 1.69)	Similar adverse event rates
REMAIN[204]	GPA or MPA in remission 18–24 months post diagnosis, $ANCA^+$ or $ANCA^-$ with biopsy	AZA or GCs for 48 months versus withdrawal by 24 months	Relapse higher with withdrawal (OR 5.96)	More serious adverse events in continuation group
MAINRITSAN[203,239]	GPA or MPA in remission after CYC and GCs, $ANCA^+$	RTX (500 mg, every six months) versus AZA	Relapse higher with AZA at 28 months (HR 6.61)	Similar rates of adverse events Decreased relapse rate at long-term follow up
MAINRITSAN2[208]	GPA or MPA, in remission, $ANCA^+$ and $ANCA^-$	Scheduled RTX versus RTX tailored to B cell return and/or ANCA	No difference in relapse rates	Tailored RTX arm received fewer infusions
MAINRITSAN3[205]	GPA or MPA, sustained remission, 2 years after RTX maintenance therapy	No additional treatment (placebo) versus 2 further years of RTX	Relapse higher with placebo: 26% versus 4% (HR 7.5)	No increase in adverse events with extended RTX
RITAZAREM[192,206]	Relapsed GPA or MPA re-induced with RTX and GCs, in remission, $ANCA^+$	RTX (1 g every 4 months) versus AZA	RTX superior in preventing relapse (HR 0.36)	No increase in adverse events with RTX

WGET[240]	GPA with active disease, ANCA$^+$ or ANCA$^-$	Standard therapy[c] (pre-RTX era) versus add-on etanercept (TNF inhibitor)	No difference in relapse rates	6/89 etanercept-treated patients developed solid organ tumours
Metzler et al.[241]	GPA, complete or partial remission	LEF versus MTX	Relapses: MTX 13/28, LEF 6/26 patients	LEF: 19% withdrawal with adverse effects at 30 mg dose
BREVAS[242]	GPA or MPA in remission 26 weeks after induction, ANCA$^+$	AZA and low-dose GCs versus add-on belimumab	No improvement with belimumab, but low relapse rate in placebo group	Recruitment lower than planned due to change in clinical practice
Stegeman et al.[243]	GPA in remission, ANCA$^+$ or ANCA$^-$	Standard therapy[c] (pre-RTX era) versus add-on co-trimoxazole	Fewer upper airways relapses with co-trimoxazole	Fewer infections with co-trimoxazole

[a] ANCA$^+$ refers to a positive test at any time, not ANCA$^+$ at the time of entry into study.

[b] Study also included polyarteritis nodosa (10 patients) and EGPA (14 patients), of the 104 patients.

[c]Several treatment pathways were available, depending on the severity and activity of disease and other factors, but usually involved either MTX + GCs, then taper and try to cease GCs; or oral CYC and GCs, then MTX or AZA taper and try to cease GCs.

AAV, ANCA-associated vasculitis; AZA, azathioprine; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GCs, glucocorticoids; GPA, granulomatosis with polyangiitis; FFS, Five Factor Score; HR, hazard ratio; LEF, leflunomide; MMF,

mycophenolate; MPA, microscopic polyangiitis; MTX, methotrexate; OR, odds ratio; PLEX, plasma exchange; PR3, proteinase 3; RTX, rituximab; SCr, serum creatinine; TNF, tumour necrosis factor.

Table 3. Key clinical trials of therapies for EGPA

Trial	Population	Intervention (*n*)	Key result	Other findings
Ribi et al.[244]	Treatment failure or relapse on GCs alone, limited disease, 1996 FFS = 0	GCs and IV-CYC (10) versus GCs and AZA (9)	No significant differences in remission; CYC 5/10, AZA 7/9	Most remained on GCs
Puéchal et al.[209,245]	New diagnosis, limited disease, 1996 FFS = 0, included other AAV	GCs (25) versus add-on AZA (26)	No effect on combined endpoint of remission induction and relapse	No change in exacerbations of asthma/rhinosinusitis. Long-term outcomes similar
MIRRA[143,210]	Relapsing or refractory EGPA, stable GC dose (7.5–50 mg)	GCs (68) versus add-on SC-mepolizumab every four weeks for 52 weeks (68)	Mepolizumab effective, mainly in allergy related manifestations	Post hoc analysis sugg >75% of patients deriv benefit
Guillevin et al.[246]	Non-severe EGPA (included PAN)	GCs versus add-on PLEX (18 in total)	No benefit, results grouped together with patients with PAN	Reflects historical grouping of disease
Guillevin et al.[247]	Severe EGPA (included PAN)	IV-CYC and GCs (6) versus add-on PLEX (8)	No benefit, results grouped together with patients with PAN	Reflects historical grouping of disease

AAV, ANCA-associated vasculitis; AZA, azathioprine; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; FFS, Five Factor Score; GCs, glucocorticoids; PAN, polyarteritis nodosa; PLEX, plasma exchange; SC, subcutaneous.

Table 4. Selected potential new management strategies and biomarkers in AAV[a]

	Potential strategy	Stage of development
Treatments		
Complement inhibition	Avacopan (small-molecule C5a receptor antagonist)[110]	Phase III trial completed (NCT02994927)[111]
SYK inhibition	Small-molecule inhibitors[248]	Pre-clinical model proof of concept studies (MPO-AAV)
Eosinophils and Th2 cells in EGPA	Direct or indirect targeting of eosinophils and T_H2 cells[b], for example anti-IL-5R (benralizumab), Th2 and eosinophil chemokines	Non-inferiority clinical trial comparing mepolizumab with benralizumab (NCT04157348)
BAFF inhibition	Belilumab[242] as add on to rituximab	Phase II trial in progress (NCT03967925)
Co-stimulatory signal blockade	Abatacept[249]	Phase II trial in progress (NCT02108860)
T cell or T_H cell defining cytokine inhibition	Monoclonal antibodies, for example ustekinumab (anti-IL-12p40)[121,218]	Pre-clinical model proof of concept studies published (MPO-AAV)[121,250]
Tolerogenic therapies	Peptide and antigen tolerogenic platforms	Pre-clinical model proof of concept studies published[251] (MPO-AAV)
Biomarkers		
Renal activity or flare	Urinary soluble CD163 with or without other biomarkers (for example, soluble CD25, CCL2)[164,229]	Further clinical studies for biomarker utility
Overall risk of flare	Markers of T cell activity and exhaustion in AAV[135,136]	Trials of 17 gene qPCR stratification for prognosis in other diseases [252]
Impending flare	$CD5^+$ B cells[253],	Clinical studies, NCT03906227

[a]Only those for which a rationale has been established are included.

[b]In addition to anti-IL-5 strategies already in clinical use.

BAFF, B cell-activating factor; EGPA, eosinophilic granulomatosis with polyangiitis; qPCR, quantitative polymerase chain reaction; SYK, spleen tyrosine kinase.

Figure legends

Figure 1. Small vessel vasculitis. a | The updated 2012 Chapel Hill Consensus Conference classification of vasculitis[144], which is based on the size of the main vessels that are affected. The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides, namely granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA), are small vessel vasculitides. **b |** Patterns of ANCA staining by indirect immunofluorescence. A cytoplasmic pattern of staining for ANCA (cANCA) is strongly associated with antibodies against PR3. A perinuclear pattern of staining for ANCA (pANCA) is seen with antibodies against several different proteins, but anti-MPO antibodies are most relevant for AAV. Part **a** is adapted with permission from [add publisher here with permission] (REF [144]). Scale bar = 10 μm.

Figure 2. Global epidemiology of ANCA-associated vasculitides. The map depicts studies that have examined the incidence of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) per 1 million individuals per year. There is substantial variation in the relative incidences of GPA and MPA between Europe and Asia, and an effect of latitude. The regions studied include Australia[254]; Canada[255]; Germany[256]; Greece[257]; Japan[258]; Lithuania[259], Turkey[260]; Peru[261]; Spain (Lugo)[262]; Spain (Malaga)[263]; Sweden[264]; United Kingdom[18]; USA (Minnesota)[2]; USA (Western Montana)[265]; and the West Bank[266].

Figure 3. Pathogenetic events in GPA and MPA. Simplified schematic showing events leading to acute tissue injury in two forms of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), namely granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Risk factors for loss of tolerance and disease (pink) include genetic and environmental factors, age, and infection or inflammation. These AAVs involve autoreactive elements (blue), including effector cell responses to the neutrophil proteins proteinase 3 (PR3) and myeloperoxidase (MPO) by autoreactive T cells and B cells, with the humoral response resulting in the production of ANCAs. The key steps in the effector phase (green) are neutrophil priming and activation by ANCA with subsequent neutrophil localisation to the microvasculature and injury. MPO and PR3 are deposited in and around the microvasculature of target tissues and effector T cells recognise these antigens, resulting in pro-inflammatory cytokine production and further recruitment of effector leukocytes. These responses lead to

tissue injury and endothelial damage (red). Less is known about the pathogenesis of the other form of AAV, namely eosinophilic GPA (EGPA), than for GPA and MPA.

Figure 4. Loss of tolerance and the generation of effector responses in GPA and MPA. Genetic risk factors in an ageing host combine with known or unknown environmental factors (possibly including silica, certain medications or drugs) and potentially infection to induce a loss of T and B cell tolerance to one of two clinically recognized neutrophil antigens, proteinase 3 (PR3) or myeloperoxidase (MPO). Autoantigen-specific T cells become activated and differentiate into T helper (T_H) cells, including T follicular helper (T_{FH}) cells that provide help to B cells, type 1 T helper (T_H1) cells and IL-17-producing T_H17 cells; an exhausted phenotype is associated with a lower risk of disease relapse. B cells differentiate into plasma cells and memory cells. Plasma cells secrete autoantibodies against PR3 (PR3-ANCA) or MPO-ANCA. Neutrophils are activated and primed by pro-inflammatory cytokines, pattern-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), and binding of C5a to the C5a receptor on neutrophils. ANCAs bind to neutrophils in an antigen-specific and Fcγ receptor (FcγR)-dependent fashion to neutrophils and monocytes. BAFF, B cell-activating factor; B_{reg} cells: regulatory B cells; NET: neutrophil extracellular trap; TLR: Toll-like receptor; TNF: tumour necrosis factor; T_{reg} cells: regulatory T cells. GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

Figure 5. Endothelial and tissue injury in GPA and MPA. Anti-neutrophil cytoplasmic antibody (ANCA)-activated, primed neutrophils localize to the endothelial cells in the microvasculature of the kidneys, respiratory tract and other tissues. Recruitment is mediated by adhesion molecules and chemokines. Adherent neutrophils induce endothelial injury by several mechanisms. They produce reactive oxygen species (ROS) and degranulate, releasing proteases and ANCA antigens. They generate neutrophil extracellular traps (NETs) and undergo cell death by NETosis. ANCA antigens released by neutrophils and when in a complex with major histocompatibility complex class II (MHC-II) or MHC-I can be recognized as antigenic peptides by effector T helper 1 (T_H1) cells, IL-17 producing T helper (T_H17) cells and $CD8^+$ T cells, at least in the case of myeloperoxidase (MPO). Antigen-presenting cells can include endothelial cells, intravascular monocytes and dendritic cells (DCs). Cytotoxic $CD4^+$ T cells expressing NKG2D recognize MHC-I-polypeptide-related sequence A (MICA), which is upregulated on activated endothelial cells and in granulomas. Mechanisms of extravascular tissue injury include

the extravasation of inflammatory leukocytes, the formation of B cell aggregates that may present ANCA antigens to T cells, produce pro-inflammatory cytokines and produce ANCA in situ. Tissue-resident and recruited DCs present antigen, whereas tissue-resident and recruited macrophages are pro-inflammatory and pro-fibrotic. These macrophages shed soluble CD163 (sCD163), which is a potential biomarker of disease activity. Leukocytes within granulomas contribute to inflammatory injury. Ag, antigen; DAMPs, danger-associated molecular patterns; FcγR, Fcγ receptor; ICAM1, intercellular adhesion molecule 1; PAMPs, pattern-associated molecular patterns; ROS, reactive oxygen species; TLR, Toll-like receptor; VCAM1, vascular cell adhesion protein 1.

Figure 6. Clinical features of AAV. a | Schematic showing the organs, organ systems and tissues that are affected in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs). The approximate relative frequency of involvement is also shown. **b |** Radiological features of sinonasal disease in AAV. Coronal CT images showing (left) destruction of the nasal septum, inferior turbinates and right middle turbinate (arrowheads) in a patient with newly diagnosed GPA; (right) chronic changes in sinonasal GPA showing simultaneous nasal septum destruction (white arrowhead) and neo-osteogenesis (black arrowhead). **b |** Radiological features of pulmonary hemorrhage in acute AAV. Chest X-ray (left) showing infiltrates and changes consistent with acute pulmonary haemorrhage; (right) transverse CT image showing acute pulmonary haemorrhage and "ground-glass" changes (*). =, rate of involvement approximately equal to; <, rate of involvement more frequent than; <<, rate of involvement substantially more frequent than; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis. [a]For EGPA, asthma and allergic manifestations are included in the frequency of involvement. Parts **b** and **c** courtesy of Dr Ken Lau and A/Prof Joanne Rimmer, Monash Health and Monash University.

Figure 7. Histopathology of AAV. a | Fibrinoid vessel wall necrosis (N) is the hallmark of AAV, accompanied by a 'granuloma-like' mixed inflammatory infiltrate (circled) composed of macrophages, lymphocytes, plasma cells and granulocytes in microscopic polyangiitis (MPA). **b |** Resolution of inflammation leads to transmural (<) fibrous scars (F) and substantial narrowing (*) or even complete occlusion of the vessel lumen. **c |** 'Geographic' necrosis (N) of confluent epithelioid granulomas in the lungs in granulomatosis with polyangiitis (GPA). Inset shows a subepithelial nasal granuloma in GPA, composed of loose aggregates of epitheloid cells

and giant cells. **d |** Epithelioid granulomas (circled) in eosinophilic GPA (EGPA) in the nose are more compact and are surrounded by eosinophils. **e |** Early lesions in the lung in MPA often only show neutrophilic capillaritis (C) and fibrinous exudates (*). **f |** Giant cells with sometimes 'smudged' appearing nuclei (>), neutrophilic granulocytes and nuclear debris (*) from neutrophils in epithelioid granulomas in the lungs in GPA. **g |** Necrosis of glomerular capillaries (N) is seen adjacent to an unaffected glomerulus (G) in MPA. **h |** Lesions of different age are seen with partial or circumferential crescents and variable destruction of the Bowman capsule (>) in MPA. **i |** Neutrophilic capillaritis (C) and multinucleated giant cells (GC) are characteristic features of GPA in the nasal mucosa. Staining methods are haematoxylin and eosin (parts **a**–**f**) acid fuchsin orange G (part **g**); Periodic acid–Schiff (part **h**) and Giemsa (part **i**)**.**

Figure 8. Management of GPA and MPA cases that present with organ or life-threatening manifestations. a | Current treatment approaches include an induction phase to induce remission, followed by a maintenance phase, then long-term follow up. **b |** Current induction treatment regimens for several diseases are centred on glucocorticoids (GCs), in combination with either cyclophosphamide (CYC) or rituximab (RTX). Intravenous GCs are often administered after treatment with high-dose oral prednisolone (or prednisone) at an initial dose of 50–75 mg. GC dose is tapered over several months, with the standard of care being the quicker taper used in the PEXIVAS trial[191]. The optimal duration of GC therapy in the maintenance phase of AAV is unclear, but GCs are often withdrawn over 4–36 months. CYC is recommended for induction, for between 3–6 months, and can be administered by intravenous pulse or daily oral therapy, with a switch to maintenance therapy at remission (3–6 months). Rituximab can also be given for induction therapy in 2–4 doses and is increasingly being used in preference to CYC. RTX is given for maintenance therapy, after induction with RTX or CYC. Oral immunosuppressive agents, including azathioprine (AZA), methotrexate (MTX) or mycophenolate mofetil (MMF), are alternatives for RTX for maintenance therapy. MTX or MMF are alternatives to CYC or RTX for induction therapy in non-organ threatening disease. **c |** Disease state corresponding with phase of therapy in parts **a** and **b**. Some patients do not respond to one of the standard induction regiments and develop refractory disease, whereas others relapse while on or after maintenance therapy is halted, and therefore require re-initiation of induction therapy.

Boxes

Box 1. Diagnostic testing methods in AAV

Most cases of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are characterized by anti-neutrophil cytoplasmic antibodies (ANCAs) directed against either proteinase 3 (PR3) or myeloperoxidase (MPO). Two methods have been used to detect these antibodies in clinical practice, namely indirect immunofluorescence (IIF) and various antigen-specific immunoassays, most commonly enzyme-linked immunosorbent assays (ELISAs).

Indirect immunofluorescence

This technique involves incubating diluted patient serum samples with ethanol-fixed and permeabilized neutrophils from healthy donors, which in some assays are pre-attached to glass slides. Bound ANCA is then detected using a fluorescent secondary anti-human IgG antibody, and the presence, titre and pattern of fluorescence are assessed by fluorescence microscopy. There are two primary patterns of fluorescence that are relevant to the diagnosis of AAV (Figure 1c):

- cANCA: a cytoplasmic pattern of ANCA staining, which is strongly associated with anti-PR3 antibodies (PR3-ANCA)
- pANCA: a perinuclear pattern of ANCA staining, which in AAV is strongly associated with anti-MPO antibodies (MPO-ANCA). The perinuclear pattern is a consequence of the ethanol fixation of neutrophils, as the highly cationic MPO localizes around the negatively charged cell nucleus after ethanol fixation.

Antigen-specific assays for PR3-ANCA and MPO-ANCA

The most commonly used assays are ELISAs specific for either PR3-ANCA or MPO-ANCA. Improvements in antigen-capture methods have resulted in better assay performance. In addition, several other types of solid-phase antigen-specific assays may be used to detect PR3-ANCA and MPO-ANCA[161].

Approaches to ANCA testing when the diagnosis of AAV (that is, GPA, MPA or EGPA) is suspected are informed by consensus statements, but there is substantial variation in practice[267]. With improved immunoassay performance, the approach recommended by an international consensus statement[161] after a large multicentre study[268] is to use antigen-specific assays for PR3-ANCA and MPO-ANCA as the initial screening method when AAV is

suspected, with IIF only performed if these assays are negative. Approaches based on 1999 guidelines[269], which are still used in some diagnostic laboratories, involve a combination of IIF screening with specific PR3-ANCA and MPO-ANCA ELISAs for positive samples, or using both methods for each sample.

Although ANCAs are primarily associated with AAVs, a positive ANCA test by IIF occurs in other diseases, including:

- Infections, including infective endocarditis, where PR3-ANCA or MPO-ANCA can occur[270-272], an important differential diagnosis, as misdiagnoses result in unwarranted immunosuppression with life-threatening consequences. ANCA may be present in other chronic infections, including tuberculosis, and *Pseudomonas aeruginosa* infection in individuals with cystic fibrosis[273,274].
- Gastrointestinal tract diseases[273], including ulcerative colitis and liver disease, such as autoimmune hepatitis, primary biliary sclerosis, primary sclerosing cholangitis and viral hepatitis. The ANCA pattern in these conditions resembles, but differs from, the pANCA pattern and is described as atypical ANCA (aANCA). In ulcerative colitis, PR3-ANCA is present, but is uncommon.
- Other autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis (notwithstanding the co-existence of AAV or AAV-like features in a small minority of people with these diseases).
- Drug-associated AAV is associated not only with MPO-ANCA but also anti-lactoferrin and anti-neutrophil elastase antibodies.

Other proteins associated with a positive IIF ANCA test in these diseases include azurocidin, bactericidal/permeability increasing protein and cathepsin G. Their clinical utility is unproven and antigen-specific testing is not routinely performed in AAV. Besides PR3 and MPO, other antigens may be relevant to AAV, but are not currently tested for in routine clinical practice.

Box 2. Clinical features of the ANCA-associated vasculitides

Granulomatosis with polyangiitis (GPA)

Symptoms of systemic vasculitis, such as fever, weight loss, malaise and fatigue. Symptoms and signs of small vessel vasculitis, often in the ear, nose and throat (ENT) tract (nasal and oral ulcers and crusting, nose bleeds, nasal polyps, paranasal sinusitis, cartilaginous destructions with granulomas on biopsy, hearing impairment and otorrhea), the eyes (conjunctival injection, eye pain, diplopia, proptosis, uveitis and retroorbital mass), the airways and lungs (hoarseness, cough, dyspnoea, stridor, pleuritic pain, pulmonary nodules, infiltrates, cavities and haemorrhage with granulomatous inflammation on biopsy), the kidneys (urinary abnormalities, elevated serum creatinine with variable degrees of proteinuria and rapidly-progressing pauci-immune glomerulonephritis on biopsy), the peripheral nervous system (mononeuritis) and the skin (purpura, focal necrosis, ulcers and leukocytoclastic vasculitis on biopsy).

Microscopic polyangiitis (MPA)

Symptoms of systemic vasculitis, such as fever, weight loss, malaise, and fatigue. Symptoms and signs of small vessel vasculitis are as for GPA, but without granulomatous inflammation on biopsy. ENT tract manifestations are as in GPA but less frequent. The kidneys (rapidly progressing necrotizing pauci-immune glomerulonephritis) and the skin (necrotizing leukocytoclastic vasculitis) are commonly affected.

Eosinophilic granulomatosis with polyangiitis (EGPA)

Many but not all individuals with EGPA have clear features of vasculitis. Symptoms of systemic vasculitis include fever, weight loss, malaise, fatigue and lymphadenopathy. Small vessel vasculitis of skin, peripheral nervous system, kidneys, heart, and gastrointestinal tract occurs. Cardiac involvement, including cardiomyopathy, contributes considerably to mortality in EGPA. Asthma is a near universal feature of EGPA and usually precedes vasculitis. Pulmonary infiltrates and >10% eosinophilia in peripheral blood are common. ENT involvement is frequent, including serous otitis media, allergic rhinitis, nasal obstruction, recurrent sinusitis and nasal polyposis.

Box 3: Drug induced vasculitis

A variety of drugs are associated with ANCA$^+$ vasculitis, with at least some features of AAV. Propylthiouracil (PTU) and to a lesser degree some other antithyroid drugs is relatively commonly associated with MPO-ANCA, with some people developing an MPA-like vasculitis[275]. Other drugs, including hydralazine (an anti-hypertensive vasodilator), minocycline (a tetracycline antibiotic), and cocaine adulterated with the antihelminthic agent levamisole are associated with ANCA$^+$ vasculitis[276]. Leukotriene antagonists have been implicated in EGPA, though causality is unclear[277]. The therapeutic agents associated with ANCA$^+$ vasculitis have been listed in detail elsewhere[275]. The epidemiology of drug induced vasculitis largely reflects patterns and frequency of use of these drugs in different populations (for example, PTU is widely used in China, while cocaine/levamisole is more common in the USA).

Clinically, a pANCA pattern is most common, but concurrent pANCA and cANCA positivity is common in cocaine/levamisole induced disease. Autoantibody specificities include MPO-ANCA, as well as other, non-classical ANCA antigens such as lactoferrin and neutrophil elastase (Box 2)[275,276]. Patients are often younger. Clinical manifestations can mimic AAV but are often less severe. Skin involvement may be more prominent, variant in nature and severe, particularly with cocaine/levamisole, and neutropenia can be present in vasculitis secondary to PTU or cocaine/levamisole. Anti-nuclear antibodies may be present, and hydralazine and minocycline are both associated with a lupus-like phenotype.

The mechanisms that underpin drug induced vasculitis are unclear, though some clues exist. Levamisole and minocycline have immunomodulatory effects. PTU inhibits thyroid peroxidase that has sequence homology to MPO. Due to this homology, it alters the structure and function of MPO in rats[275,278]. Furthermore, PTU induces abnormal NET formation from human neutrophils *in vitro* and MPO-AAV *in vivo* in rats[279]. These data, as well as cocaine/levamisole's effects on NET formation[280] support abnormal or aberrant autoantigen exposure as a factor in the development of AAV.

Recognition of drug induced vasculitis via an appropriate index of clinical suspicion, obtaining a medication history and enquiring as to illicit drug use, potentially with urinary screening, is central to the management of these conditions. Ceasing the potential offending agent may itself result in improvement. However, immunosuppression may be required and severe, organ threatening disease can occur. Re-challenge with the suspected drug for diagnostic reasons is not recommended.

Box 4. A patient's experience of AAV

Being diagnosed with a rare and potentially life-threatening disease is something that no one expects to happen to them. Many patients with AAV have substantial delays in time to diagnosis and may have had serious hospitalizations and organ damage by the time they are diagnosed. But once the initial crisis is over, the ongoing work to achieve and maintain remission begins. It is important to note that AAV is typically a life-long chronic condition that will require constant vigilance by patients and their doctors. Fortunately, there have been new treatment options for AAV in recent years, especially new biologic therapies. However, these medications have little or no impact on the fatigue and pain caused by AAV. Thus, while patients may be 'in remission' with the help of ongoing immunosuppressive therapy, many of us still feel the relentless effects of this fatigue and pain on a daily basis. Patients also worry about the potential adverse effects from the treatments and the balancing of toxicity from the treatment against damage from the vasculitis itself. Better treatments for AAV are needed, especially less toxic substitutes for glucocorticoids. But also needed are better ways to measure disease activity, such as biomarkers that will distinguish our flares from symptoms caused by other things, such as treatment toxicity or infections. In addition, urgently needed are treatment options for symptoms that have a major impact on our quality of life, such as fatigue and pain, which often remain unaddressed. Greater patient input on setting treatment priorities will help focus attention on our unmet quality of life needs.

Jennifer Gordon, PhD. Dr. Gordon has EGPA and serves on the Vasculitis Foundation Vasculitis Patient-Powered Research Network.

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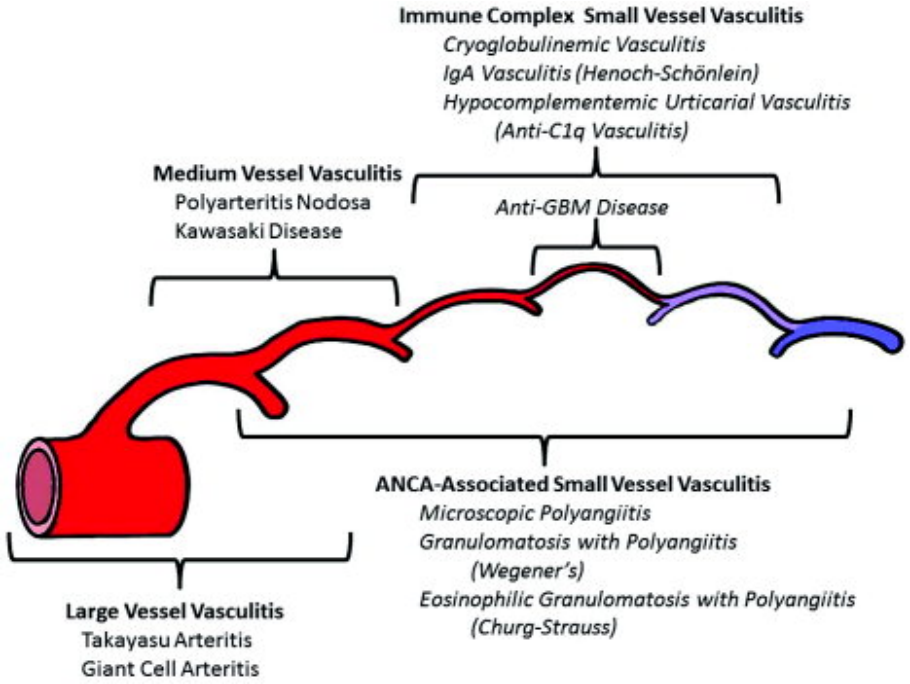
ToC blurb

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are autoimmune disorders characterized by inflammation and destruction of small blood vessels. In this Primer, the authors discuss the classification of AAVs and the pathogenetic mechanisms, diagnosis and treatment of these debilitating conditions.

Figure 1

a



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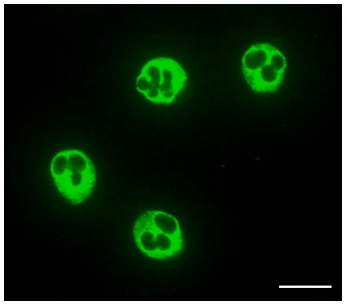
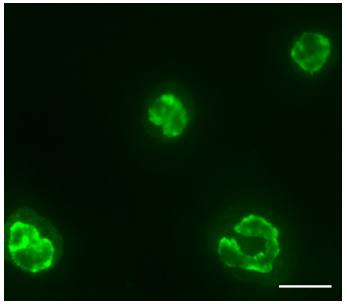


cANCA



pANCA

Figure 2

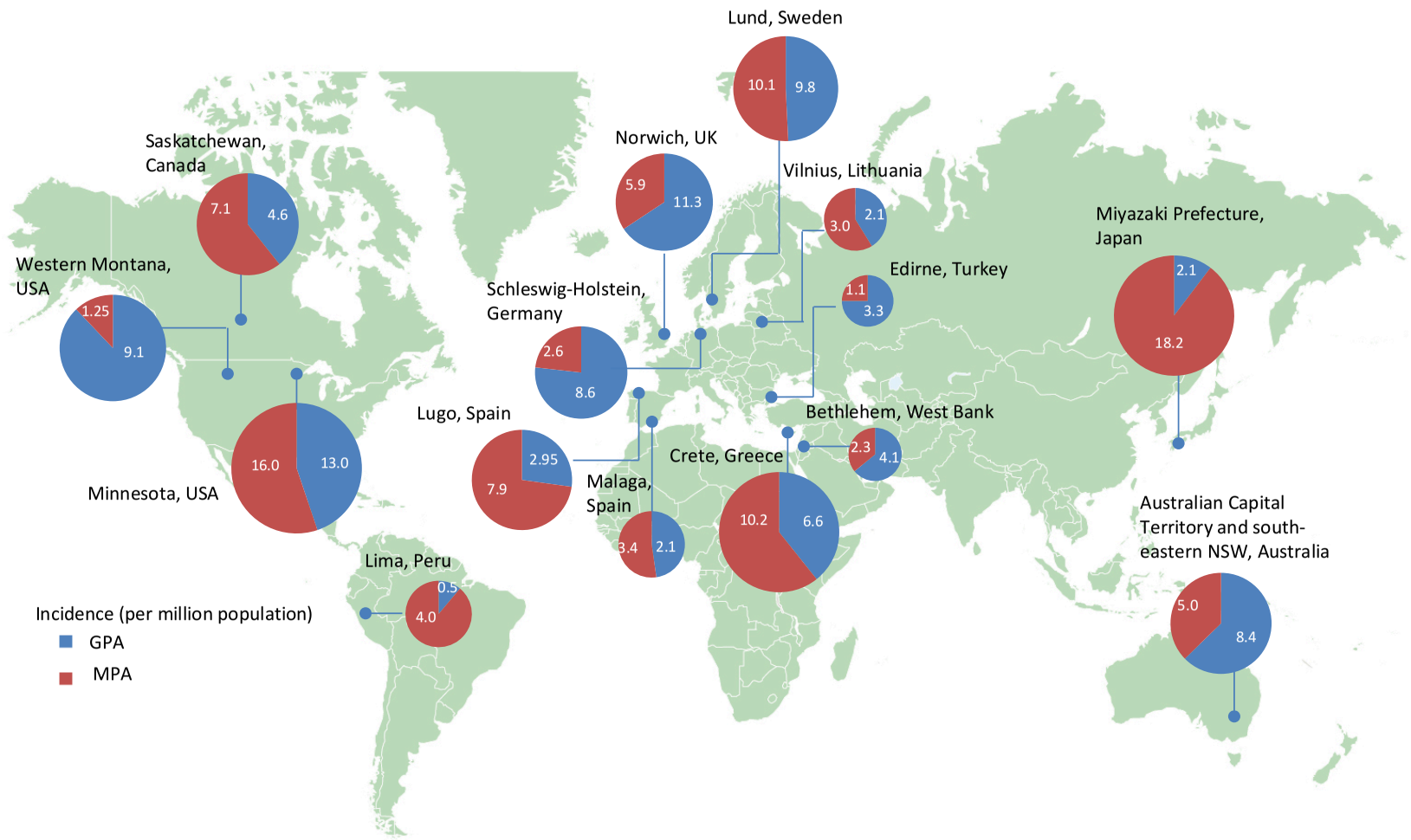

Lund, Sweden
10.1
9.8
Norwich, UK
5.9
11.3
Vilnius, Lithuania
3.0
2.1
Saskatchewan, Canada
7.1
4.6
Western Montana, USA
1.25
9.1
Schleswig-Holstein, Germany
2.6
8.6
Edirne, Turkey
1.1
3.3
Miyazaki Prefecture, Japan
2.1
18.2
Lugo, Spain
2.95
7.9
Bethlehem, West Bank
2.3
4.1
Crete, Greece
10.2
6.6
Malaga, Spain
3.4
2.1
16.0
13.0
Minnesota, USA
Lima, Peru
0.5
4.0
Australian Capital Territory and south-eastern NSW, Australia
5.0
8.4
Incidence (per million population)
GPA
MPA

Figure 3

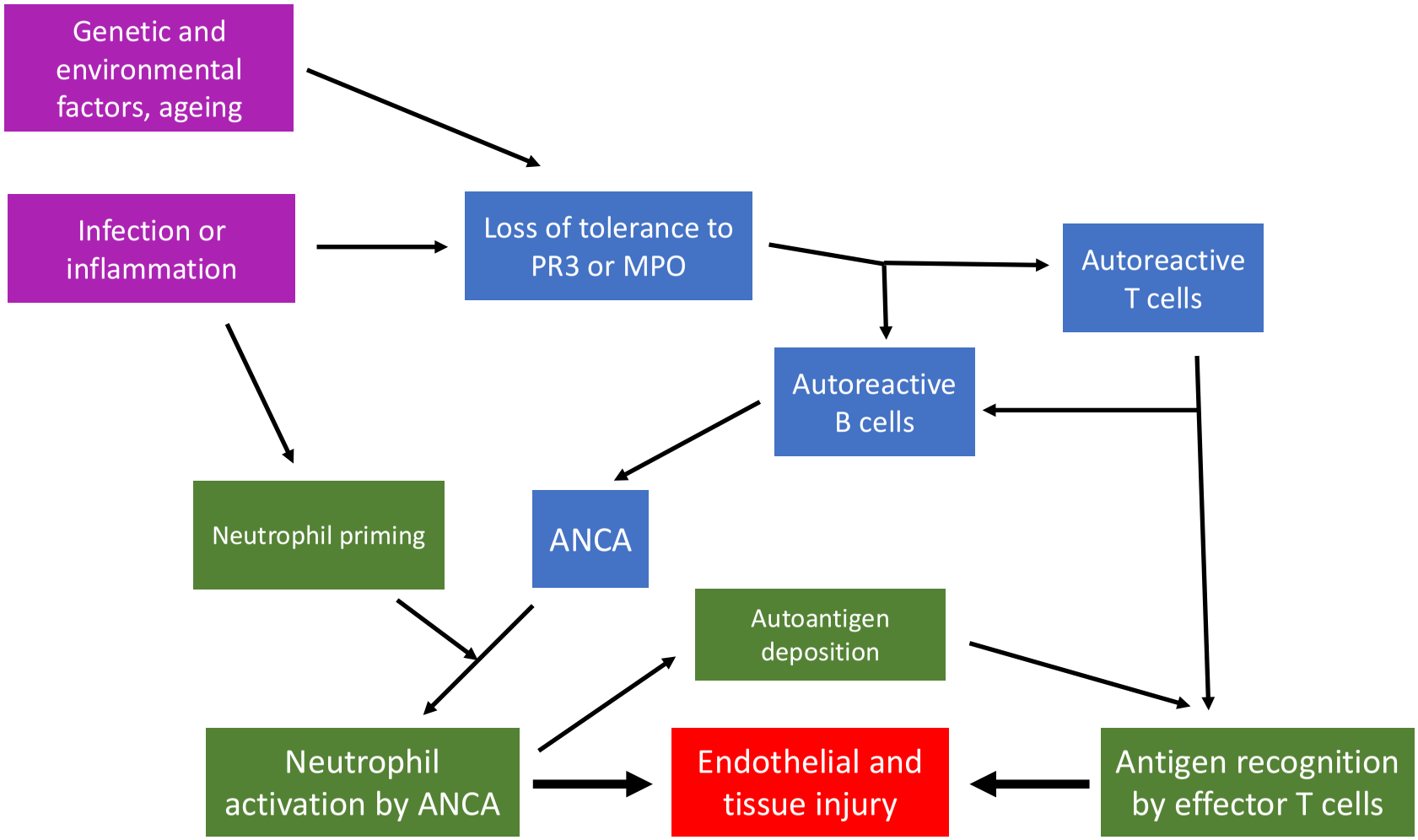

Genetic and environmental factors, ageing
Infection or inflammation
Loss of tolerance to PR3 or MPO
Autoreactive T cells
Autoreactive B cells
Neutrophil priming
ANCA
Autoantigen deposition
Neutrophil activation by ANCA
Endothelial and tissue injury
Antigen recognition by effector T cells

Figure 4

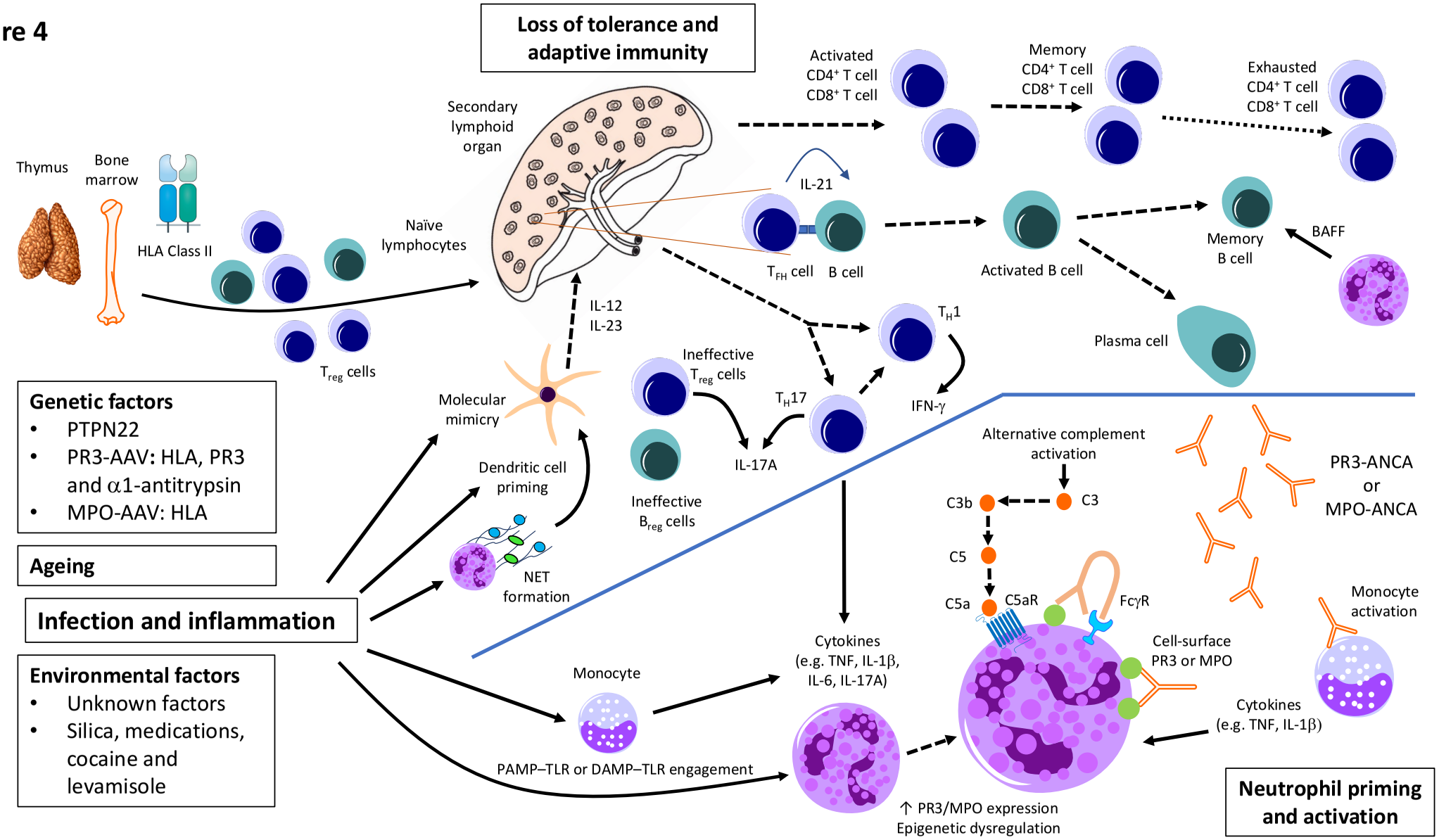

Loss of tolerance and adaptive immunity
Thymus
Bone marrow
HLA Class II
Naïve lymphocytes
Secondary lymphoid organ
Activated CD4+ T cell CD8+ T cell
Memory CD4+ T cell CD8+ T cell
Exhausted CD4+ T cell CD8+ T cell
IL-21
TFH cell
B cell
Activated B cell
Memory B cell
BAFF
Plasma cell
Treg cells
IL-12
IL-23
TH1
IFN-γ
Molecular mimicry
Ineffective Treg cells
TH17
IL-17A
Ineffective Breg cells
Dendritic cell priming
NET formation
Genetic factors
• PTPN22
• PR3-AAV: HLA, PR3 and α1-antitrypsin
• MPO-AAV: HLA
Ageing
Infection and inflammation
Environmental factors
• Unknown factors
• Silica, medications, cocaine and levamisole
Monocyte
PAMP–TLR or DAMP–TLR engagement
Cytokines (e.g. TNF, IL-1β, IL-6, IL-17A)
Alternative complement activation
C3b
C3
C5
C5a
C5aR
FcγR
Cell-surface PR3 or MPO
PR3-ANCA or MPO-ANCA
Monocyte activation
Cytokines (e.g. TNF, IL-1β)
↑ PR3/MPO expression
Epigenetic dysregulation
Neutrophil priming and activation

Figure 5

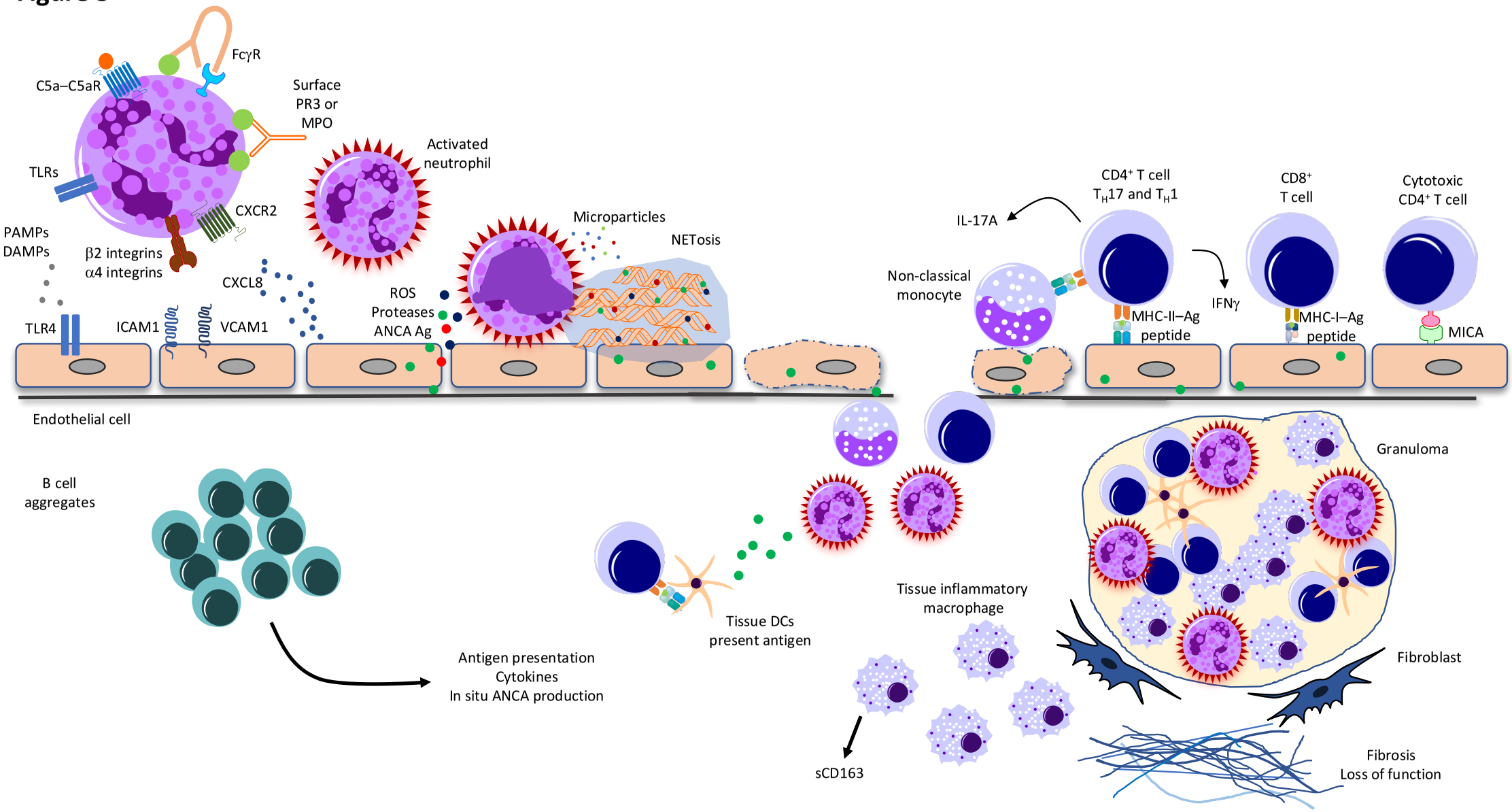

FcγR
C5a–C5aR
Surface PR3 or MPO
Activated neutrophil
TLRs
CXCR2
PAMPs DAMPs
β2 integrins α4 integrins
CXCL8
Microparticles
NETosis
ROS Proteases ANCA Ag
TLR4
ICAM1
VCAM1
Endothelial cell
CD4+ T cell TH17 and TH1
IL-17A
CD8+ T cell
Cytotoxic CD4+ T cell
Non-classical monocyte
IFNγ
MHC-II–Ag peptide
MHC-I–Ag peptide
MICA
Granuloma
B cell aggregates
Tissue DCs present antigen
Tissue inflammatory macrophage
Fibroblast
Antigen presentation
Cytokines
In situ ANCA production
sCD163
Fibrosis
Loss of function

Figure 6

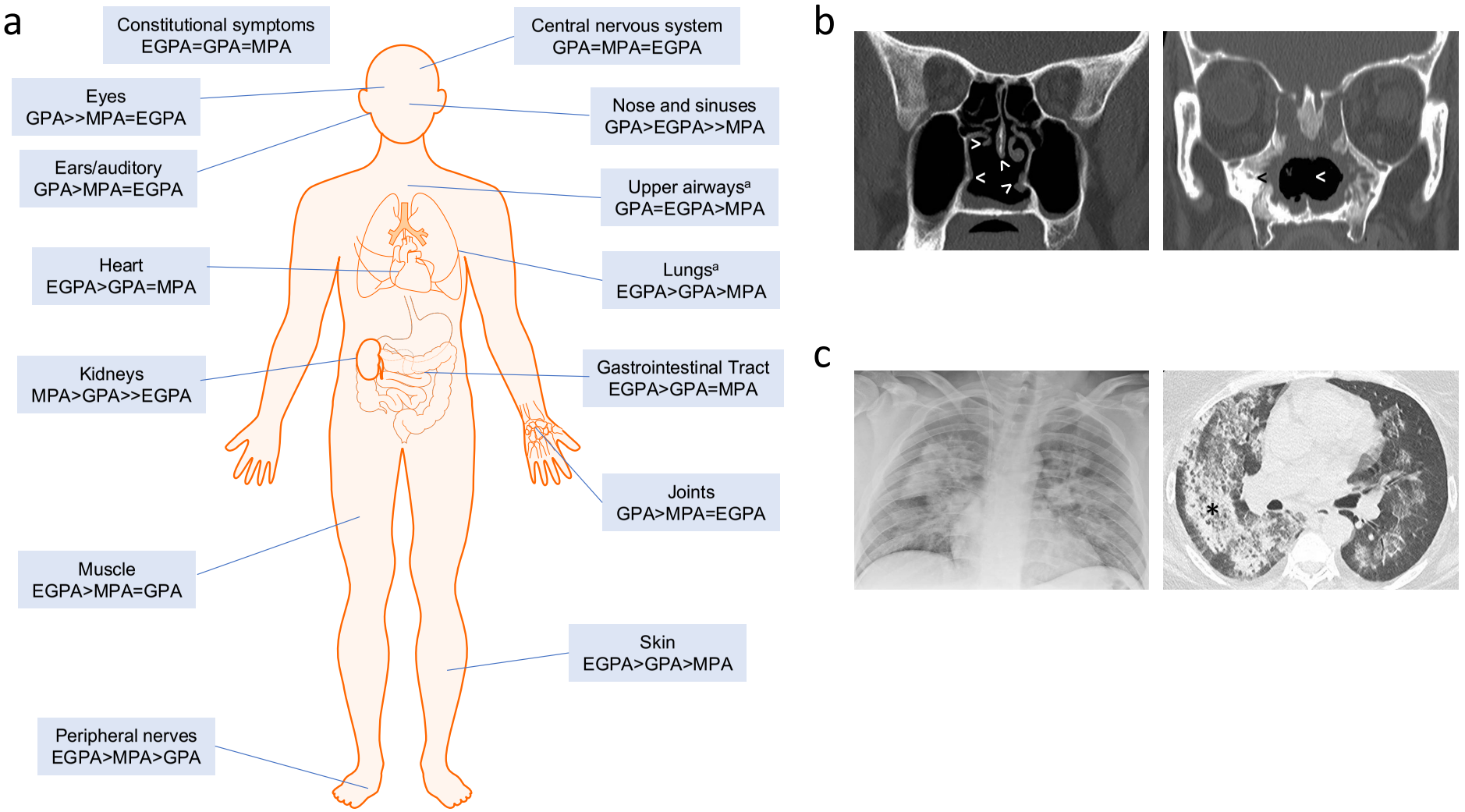

a
Constitutional symptoms
EGPA=GPA=MPA
Central nervous system
GPA=MPA=EGPA
Eyes
GPA>>MPA=EGPA
Nose and sinuses
GPA>EGPA>>MPA
Ears/auditory
GPA>MPA=EGPA
Upper airways[a]
GPA=EGPA>MPA
Heart
EGPA>GPA=MPA
Lungs[a]
EGPA>GPA>MPA
Kidneys
MPA>GPA>>EGPA
Gastrointestinal Tract
EGPA>GPA=MPA
Joints
GPA>MPA=EGPA
Muscle
EGPA>MPA=GPA
Skin
EGPA>GPA>MPA
Peripheral nerves
EGPA>MPA>GPA
b
c

Figure 7

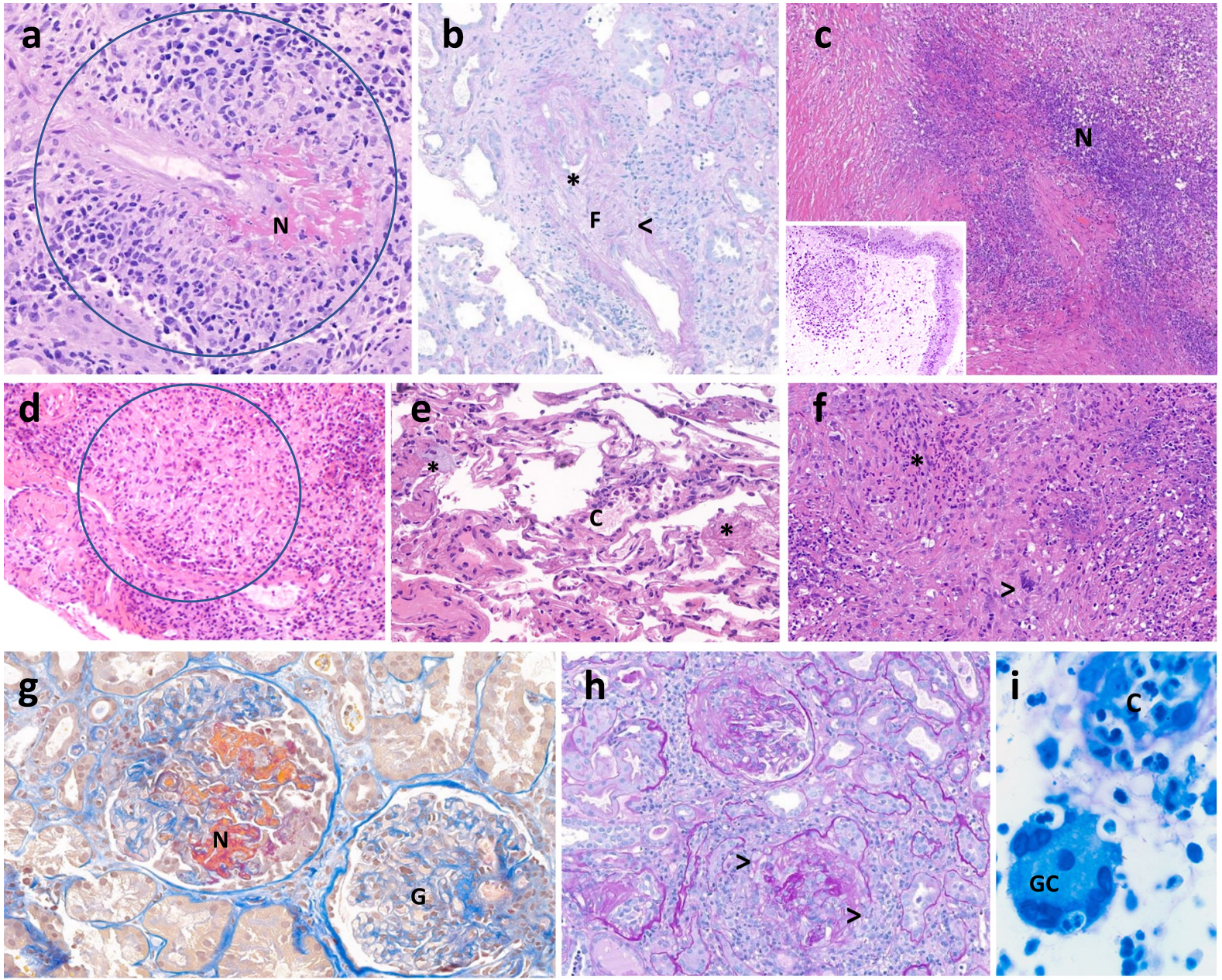
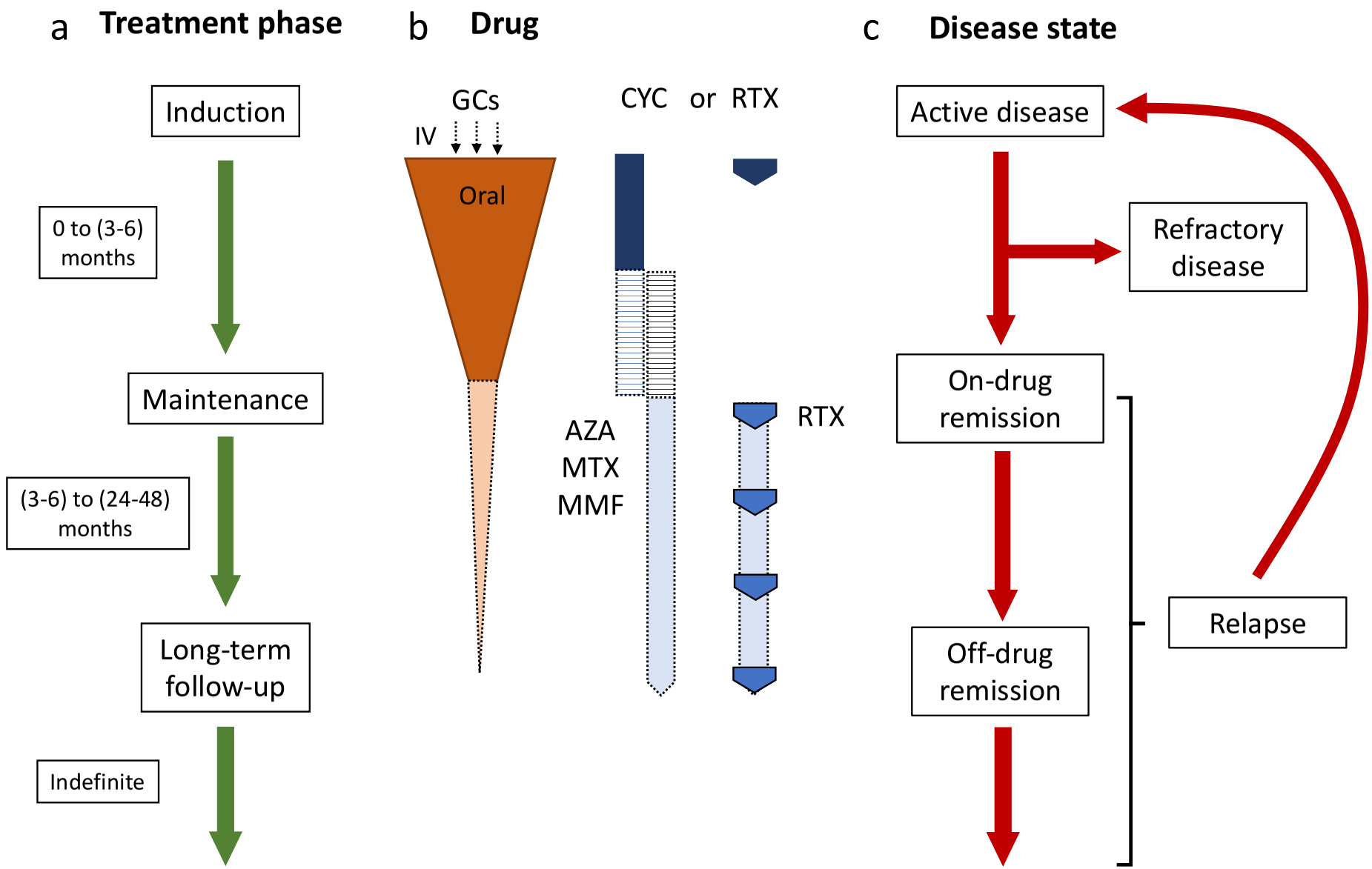


Figure 8


a Treatment phase
Induction
0 to (3-6) months
Maintenance
(3-6) to (24-48) months
Long-term follow-up
Indefinite
b Drug
GCs
IV
Oral
CYC or RTX
AZA
MTX
MMF
RTX
c Disease state
Active disease
Refractory disease
On-drug remission
Off-drug remission
Relapse