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# Antineutrophil Cytoplasmic Antibody-Associated Vasculitides and Respiratory Disease

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**Vasculitides associated with serum positivity for antineutrophil cytoplasmic antibodies (ANCAs) are a well-established subgroup affecting small- to medium-sized vessels that are commonly recognized as *ANCA-associated vasculitis*, which includes necrotizing granulomatous vasculitis (NGV) [formerly Wegener granulomatosis], microscopic polyangiitis (MPA), and Churg-Strauss syndrome. NGV usually starts as a granulomatous disease of the respiratory tract and progresses to systemic disease with proteinase 3 (PR3)-ANCA-associated vasculitis, suggesting an aberrant cell-mediated immune response to exogenous or endogenous antigens in the respiratory tract and resulting in granuloma formation. In NGV, granulomata may represent lymphoid structures ultimately responsible for PR3-ANCA production. In both NGV and MPA, necrotizing glomerulonephritis and necrotizing pulmonary capillaritis may well result from an injury orchestrated by ANCA. Untreated NGV and MPA normally are rapidly progressive and fatal. Pulmonary capillaritis with alveolar hemorrhage is a severe complication in patients with MPA and NGV. Because plasma exchange removes circulating ANCAs and other proteins from the blood, its use has been advocated in critical situations of severe renal and pulmonary involvement. However, no studies of plasma exchange in ANCA-associated vasculitis focused on pulmonary involvement have been reported. Dissecting the mechanisms of inflammation may identify molecular targets for future therapies in ANCA-associated vasculitis. Thus, biological agents are emerging as potential therapies in refractory cases. Notably, rituximab and infliximab have been trialed with apparent initial clinical success.**

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**Abbreviations:** AAV = antineutrophil cytoplasmic antibody-associated vasculitis; ANCA = antineutrophil cytoplasmic antibody; APACHE = acute physiology and chronic health evaluation; BVAS = Birmingham Vasculitis Activity Score; CSS = Churg-Strauss syndrome; LAMP = lysosomal membrane protein; MMF = mycophenolate mofetil; MPA = microscopic polyangiitis; MPO = antimyeloperoxidase antibody; NGV = necrotizing granulomatous vasculitis; PR3 = proteinase 3; TNF = tumor necrosis factor

Systemic vasculitides are uncommon life-threatening disorders in which vascular inflammation damages tissue through the occlusion or rupture of vessels. Vasculitides associated with serum positivity for antineutrophil cytoplasmic antibodies (ANCAs) affecting small- to medium-sized vessels are commonly recognized as *ANCA-associated vasculitis* (AAV). Although renal-limited vasculitis is closely associated with ANCAs, Wegener granulomatosis (because of reported ethical concerns and editorial policies,[1] we will use the term *necrotizing granulomatous vasculitis* [NGV] instead of *Wegener granulomatosis* throughout this article), microscopic poly-

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**Table 1—*Prevalence of ANCA Positivity in AAV***

| Variables | Anti-PR3 (c-ANCA), % | MPO (p-ANCA), % |
|---|---|---|
| Generalized NGV | 70–95 | 0–10 |
| Localized NGV | 40–50 | 0–10 |
| MPA | 10–20 | 30–80 |
| CSS | 0–10 | 30–75 |

Data were derived from the studies of Abdou et al,[93] Allenbach et al,[94] Sable-Fourtassou et al.[95] c-ANCA = cytoplasmic ANCA; p-ANCA = perinuclear ANCA.

angiitis (MPA), and Churg-Strauss syndrome (CSS) are systemic forms of AAV with potential pulmonary involvement.[2] ANCAs directed to proteinase 3 (PR3) are mainly detected in patients with NGV, whereas ANCA directed to antimyeloperoxidase antibodies (MPOs) are predominantly found in patients with MPA and CSS.[3] The prevalence of ANCA positivity in patients with AAV is shown in Table 1. Although NGV is characterized by systemic necrotizing small-vessel vasculitis associated with extravascular granuloma formation mainly involving the upper respiratory tract and lungs, MPA shows no clinical or pathologic evidence of granulomatous inflammation. Both diseases affect the kidneys and lungs through pauci-immune focal necrotizing glomerulonephritis and pulmonary capillaritis, respectively.[4] CSS is characterized by asthma and eosinophilic infiltrates or granulomatous nodules in the lungs. In this study, we evaluated the pathogenic and clinical aspects of pulmonary involvement in AAV and the current therapeutic options.

## Pathogenesis of AAV

### In Vitro *and* In Vivo *Models Studying the Pathogenic Role of ANCAs in Vasculitis*

The close clinical association between MPO-ANCA and PR3-ANCA and AAV, together with evidence from *in vitro* and animal models,[3,5] suggests that they play a critical role in the pathogenesis of vascular damage in patients with AAV. ANCA antigens are mainly located within the cytoplasmic granules of resting neutrophils, "sheltered" from circulating ANCAs. However, when neutrophils are primed by tumor necrosis factor (TNF)-α, other cytokines, or microbial products, MPO and PR3 traffic to the external leaflet of the neutrophil plasma membrane, facilitating ANCA binding.[5,6] This preliminary low-grade inflammation may occur *in vivo* due to infection.[7] *In vitro* studies[3,5] show an orchestrating role for ANCA in neutrophil-mediated vascular injury models. Individual baseline levels of PR3 surface expression in resting neutrophils vary widely, and higher degrees of PR3 surface expression are reported in patients with NGV,[8] possibly increasing the likelihood of PR3-ANCA binding.

ANCAs are believed to influence neutrophil-endothelial interactions. ANCAs induce changes in the neutrophil actin cytoskeleton, resulting in changes in shape and capillary sequestration and favoring adhesion to small-vessel endothelium.[9] Only when adhering to endothelium can ANCA-activated neutrophils release reactive oxygen species and lytic enzymes, including MPO and PR3, damaging vessel walls.[6,10] ANCA-activated neutrophils and monocytes also release proinflammatory cytokines, which activate and recruit more inflammatory cells, including monocytes and T cells, perpetuating deleterious immune responses.[11]

*In vivo* evidence for the pathogenic role of ANCAs comes from Xiao et al,[12] who administered murine anti-MPO IgG to Rag2−/− mice lacking functioning T or B lymphocytes, producing focal necrotizing glomerulonephritis without immune deposits (indistinguishable from human ANCA-associated glomerulonephritis), with damage to approximately 15% of glomeruli. In another murine experiment,[13] the administration of a rat homolog of interleukin-8 to human MPO-immunized rats led to increased leukocyte adherence and transmigration with microvasculature focal hemorrhage at chemokine application sites, confirming *in vitro* models showing that ANCAs promote neutrophil adhesion to the endothelium *in vivo*. Foucher et al[14] found that rats immunized with human MPO developed antibodies to human and rat MPO after 2 weeks. Single-lung perfusion with human neutrophil lysosomal extract containing MPO and proteolytic enzymes resulted in patchy inflammatory cell infiltrates throughout the pulmonary parenchyma and occasional granuloma-like lesions, giant cells, and foci of alveolar hemorrhage. There is no convincing *in vivo* evidence of PR3-ANCA pathogenicity in these settings.

### *Granuloma Development in NGV: The Role of the Respiratory System*

NGV usually starts as a granulomatous disease of the respiratory tract and progresses to systemic disease with PR3-ANCA-associated vasculitis,[15] suggesting an aberrant cell-mediated immune response to exogenous or endogenous antigens in the respiratory tract, resulting in granuloma formation.[16] Cell types in NGV granulomas include PR3+ cell clusters (neutrophils and monocytes) surrounded by antigen-presenting cells and abundant T-helper type 1 CD4+CD28− effector memory T cells and maturing B and plasma cells, suggesting neoformation of lymphoid-like tissue. There are alterations in the differentiation of T cells,[17] which display features of

effector memory T cells.[18] As a major source of T-helper type 1 cytokines, CD4+CD28− T cells are thought to be the driving force of granuloma formation.[19,20] Abdulahad et al[21] found that patients with NGV in remission have an expanded number of regulatory T cells with a defective suppressor function, which may explain the development of NGV and its relapsing nature.

NGV granulomas may represent lymphoid structures the cellular components of which would ultimately be responsible for PR3-ANCA production. Voswinkel et al[22] found B lymphocyte-rich follicle-like aggregates in granulomatous NGV lesions. Exposure of the immune system to the complementary peptide of PR3 may produce antibodies to this peptide that generate anti-idiotype antibodies that cross-react with PR3.[23] PR3-encoding gene complementary sequences have been identified in *Staphylococcus aureus* infections, the nasal carriage of which is associated with NGV, supporting the role of infectious agents as triggering factors of PR3 autoimmunity.[22]

### *Uncertainties and Gaps: ANCA-Negative Vasculitis*

Although the evidence for a pathogenic role for ANCAs, mainly MPO-ANCAs, is striking, various questions remain. For instance, some patients who are negative for ANCAs fit the phenotype for MPO-ANCA-associated pauci-immune necrotizing glomerulonephritis. One study[24] found that the histologic findings and prognosis in patients with ANCA-negative pauci-immune glomerulonephritis are comparable with those of patients with ANCA-positive disease. Neutrophil cell infiltration in tissues occurs independently of circulating ANCAs in patients with ANCA-negative disease and, thus, may involve unidentified autoantibodies or T-cell-dependent mechanisms.[25] In patients with NGV, patients remain more frequently negative for ANCAs in the limited form (*ie*, upper airways) of the disease. However, ANCAs are usually detected on the progression of disease to the systemic vasculitic stage.[26] Another counterargument is that MPO-ANCAs are not useful to monitor patients with MPO-AAV.[27]

Kain et al[28] recently provided a novel molecular explanation for the origin and development of pauci-immune focal necrotizing glomerulonephritis, showing that infection by fimbriated bacteria can trigger cross-reactive autoimmunity to a previously characterized ANCA antigen, lysosomal membrane protein (LAMP)-2, resulting in the production of autoantibodies that activate neutrophils, damage human microvascular endothelium *in vitro*, and cause segmental necrotizing glomerulonephritis in rats. Together with reports that MPO-ANCAs cause pauci-immune focal necrotizing glomerulonephritis in mice,[12] it is possible that MPOs-ANCAs act synergically with anti-LAMP-2 antibodies to cause injury. Alternatively, anti-LAMP-2 antibodies might alter the role of LAMP-2 in the presentation of cytoplasmic antigens, such as MPO and PR3, leading to the synthesis of antibodies against these proteins. Of 84 patients with biopsy-proven active pauci-immune necrotizing glomerulonephritis, 70 patients (83%) had positive enzyme-linked immunosorbent assay results for classic ANCA, 38 for MPO-ANCA, 39 for PR3-ANCA, and 7 for both antigens.[28] However, 78 patients (93%) had antibodies to human LAMP-2, which may explain the negativity for PR3-ANCAs and MPO-ANCAs in some patients with typical AAV.

## Clinical Forms of Lung Disease in AAV

Table 2 shows the spectrum of respiratory abnormalities found in patients with AAV. The recent European League Against Rheumatism recommendations[27] for the management of primary small- and medium-vessel vasculitis classified AAV in different disease patterns, according to the extension and severity of the disease. These patterns were localized, (upper respiratory tract disease, lower respiratory tract disease, or both with no other systemic involvement or constitutional symptoms), early systemic (no organ-threatening or life-threatening disease), generalized (renal or other organ-threatening disease, with serum creatinine $< 500$ μmol/L [5.6 mg/dL]), severe (renal

**Table 2—*Airway Abnormalities in AAV***

| Condition | Abnormality |
|---|---|
| NGV | |
| Otorhinolaryngologic | Endobronchial granulomatous inflammation;<br>Granulomatous nasal or paranasal inflammation; and<br>Subglottic stenosis |
| Pulmonary | Symptomatic and asymptomatic pulmonary nodules and infiltrates;<br>Pleuritis and pleural effusion;<br>Pulmonary arterial hypertension; and<br>Pulmonary fibrosis |
| MPA | |
| Pulmonary | Symptomatic and asymptomatic pulmonary infiltrates;<br>Pleuritis and pleural effusion;<br>Pulmonary hemorrhage and alveolitis;<br>Pulmonary fibrosis; and<br>Pulmonary arterial hypertension |
| CSS | |
| Otorhinolaryngologic | Allergic rhinitis;<br>Nasal polyposis and obstruction; and<br>Recurrent sinusitis |
| Pulmonary | Asthma; and<br>Infiltrates and nodules |

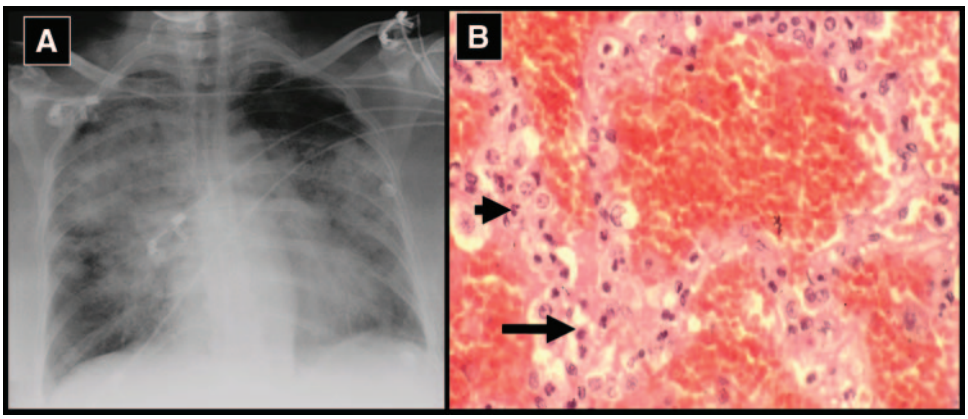


FIGURE 1. *A*: chest roentgenogram with posteroanterior view of a patient with NGV who was admitted to the hospital ICU with diffuse pulmonary hemorrhage and respiratory failure. *B*: lung biopsy specimen showing severe alveolar capillaritis with alveolar hemorrhage. Observe the thickened interalveolar septum with infiltrates of mononuclear cells (long arrow) and neutrophils (short arrow) [hematoxylin-eosin, original ×60].

or other vital organ failure, with serum creatinine levels > 500 μmol/L [5.6 mg/dL]), and refractory (progressive disease not responsive to glucocorticoids and cyclophosphamide).

Classic forms of NGV primarily involve the upper and lower respiratory tracts and kidneys.[29] However, NGV is limited to the upper respiratory tract or lungs in 25% of cases, with necrotizing granulomatous inflammation developing in patients that leads to chronic sinusitis, subglottic stenosis, orbital pseudotumor, and pulmonary nodules or infiltrates. Tracheobronchial disease is almost exclusive to patients with NGV and usually is associated with involvement of the supraglottic territories, pulmonary parenchyma, and other structures. Common symptoms include hoarseness, cough, dyspnea, stridor, wheezing, and hemoptysis due to cavitated pulmonary parenchymal lesions, alveolar hemorrhage, bronchiectasis, and blood from supraglottic airways.[30] Lung nodules or infiltrates are apparent in 85% of patients with NGV,[29] whereas transient and patchy pulmonary infiltrates have been reported in 38 to 77% of patients with CSS.[31] However, asthma is the predominant symptom in CSS, occurring in > 95% of patients and usually preceding vasculitis by a mean time of 3 to 4 years.[31] Other common forms of airway involvement in patients with CSS include nasal obstruction, recurrent sinusitis, and nasal polyposis.[31] As other vasculitic elements appear (*eg*, neuropathic or systemic involvement), asthma severity as well as bronchial, nasal, and sinusal exacerbations may increase. Prolonged glucocorticoid treatment of asthma may partially or totally mask the clinical signs of untreated CSS.

Pulmonary involvement manifested as alveolar capillaritis-induced diffuse alveolar hemorrhage is reported in 25 to 55% of patients with MPA. Alveolar hemorrhage is increasingly recognized as a prominent pulmonary manifestation of NGV, occurring in around 5% of cases and occasionally as the initial finding.[3] When accompanied by glomerulonephritis, it is considered to be a form of pulmonary-renal syndrome. Lung biopsy specimens reveal intra-alveolar and, frequently, interstitial RBCs (Fig 1).[3] Often, there is pauci-immune hemorrhagic necrotizing alveolar capillaritis without evidence of granulomatous inflammation or prominent large-vessel lesions.[32] Clinical features in patients with both MPA and NGV range from asymptomatic pulmonary infiltrates to hemoptysis, pleural effusion, and alveolar hemorrhage.[4,33] A few cases[34–36] present with interstitial lung involvement mimicking idiopathic pulmonary fibrosis, which may result from repeated alveolar hemorrhage due to pulmonary capillaritis.[3]

Pulmonary functional alterations described in AAV include restrictive and obstructive patterns. The most frequent functional abnormality is a reduced lung carbon monoxide diffusing capacity, which may increase markedly when an active alveolar hemorrhage is present. In cases of diffuse interstitial involvement, a clear restrictive pattern is observed. Airflow obstruction is typical in asthma due to CSS. An altered flow-volume loop may be useful in the diagnosis of lesions causing obstruction of the large airways, such as subglottic or main bronchial stenosis in patients with NGV.[30]

## PROGNOSIS OF PULMONARY COMPLICATIONS OF AAV

AAV is potentially life threatening. Although outcomes differ, untreated NGV and MPA are normally

rapidly progressive and fatal. MPA mortality is highest in the first year after diagnosis, whereas NGV mortality increases progressively, perhaps reflecting the nature of the underlying disease.[37] When glucocorticoids and other immunosuppressants are administered, patient survival improves dramatically, and > 90% of patients achieve remission at 6 months.[38] However, relapse rates remain at around 50%,[39] and severe vital organ-threatening damage and treatment-related adverse effects develop in approximately 25% of patients.[40] About 10% of patients with AAV are refractory to standard immunosuppressant combination therapies and are at high risk for death.[41,42] Features associated with high AAV mortality include age > 60 years, renal and pulmonary involvement (for NGV and MPA), cardiac involvement (for CSS), and a high disease activity index, as assessed by the Birmingham Vasculitis Activity Score (BVAS).[37]

A recent study[43] comparing two large cohorts of French and American patients with AAV found that age was a predictor of treatment resistance, whereas PR3-ANCA positivity and lung involvement were predictors of relapse in both groups. Age and pulmonary infections were independent predictors of death in a study[44] of 234 patients with AAV (MPA, 147 patients; NGV, 69 patients; CSS, 3 patients; and renal-limited vasculitis, 15 patients), in which 99 patients (42%) were > 65 years of age (mean [± SD] age, 72 ± 5.6 years). Older patients had more severe pulmonary involvement, including pulmonary infiltration, interstitial fibrosis, and mechanical ventilation at presentation, and a higher risk of secondary pulmonary infection during follow-up, which was indeed more frequent in patients with pulmonary interstitial fibrosis.[44]

Alveolar hemorrhage is the main cause of hospitalization[45] and hospital ICU admission[46] in cases of AAV with pulmonary complications. A study[45] that analyzed clinical outcomes in 65 patients hospitalized for AAV found that respiratory failure, hemoptysis, smoking, and acute renal failure were strong predictors of hospital ICU admission, and 28-day mortality was increased in patients requiring ICU transfer, mechanical ventilation, or blood transfusions. Similarly, alveolar hemorrhage was the main reason for hospital ICU admission in another study[46] of 38 patients with severe small-vessel vasculitis (NGV, 19 patients; MPA, 16 patients; CSS, 1 patient; and CNS vasculitis, 2 patients), and the 28-day mortality rate was 11% due mainly to septic shock. Patients who died had higher initial severity and multiorgan system failure scores, including acute physiology score and acute physiology and chronic health evaluation [APACHE] III score.

Patients with CSS seem to have a better prognosis, although severe complications, such as myocardial vasculitis and renal and CNS involvement, occur in a considerable number of patients.[31] The French Vasculitis Study Group[47] proposed the "five factor score," a prognosis index for CSS that includes the following items: severe GI tract disease (bleeding, perforation, infarction, or pancreatitis); renal involvement (serum creatinine level ≥ 1.58 mg/dL); proteinuria (≥ 1 g/d); heart disease (infarction or heart failure); and CNS involvement. Having any factor adversely affects outcomes.[33]

## Treatment

### *Treating Pulmonary Complications*

Table 3 shows the therapeutic options for AAV and indications according to the results of clinical trials. Therapy with glucocorticoids in combination with other immunosuppressants, such as cyclophosphamide or methotrexate, are the current mainstay of AAV treatment.[42] Cotrimoxazole therapy has shown benefit when coadministered with the standard immunosuppressant therapy for remission maintenance of patients with NGV and upper respiratory tract disease.[48]

The therapeutic options for pulmonary manifestations of AAV depend on the type of complication and the concomitant vasculitic features when pulmonary lesions are discovered. Pulmonary nodules or limited infiltrates may or may not be accompanied by constitutional symptoms or upper airway involvement, especially in patients with NGV and CSS, and patients should be treated with regimens for limited or early systemic disease, including glucocorticoids and methotrexate for induction remission, and azathioprine or methotrexate for remission maintenance (Tables 3, 4). In cases of pulmonary nodules with involvement of vital organs, such as the kidneys, intensive treatment, assessed by the renal function, should be administered. High doses of glucocorticoids and cyclophosphamide are recommended; plasma exchange also should be considered. Plasma exchange has been advocated in critical situations with severe renal and pulmonary involvement because it removes circulating ANCAs and other proteins from the bloodstream (Table 4).

The treatment of pulmonary capillaritis and alveolar hemorrhage in patients with MPA and NGV remains empiric, and, apart from ventilatory support when indicated, patients should be treated according to the schema for severe renal involvement (Table 4). Despite early treatment with high-dose glucocorticoids, overall mortality remains high. Although reports[49,50] have emphasized the utility of plasma exchange in NGV patients with alveolar hemorrhage (mainly with those with pulmonary-renal syndrome), no studies of plasma exchange in patients with AAV

**Table 3—*Therapeutic Agents for AAV***

| Agent* | Type of Study† | Comments |
|---|---|---|
| Azathioprine[38] | RCT | Standard agent used to maintain remission |
| Cotrimoxazole[48] | RCT | Reduce risk of respiratory tract relapses in limited forms given concomitantly with glucocorticoids |
| Cyclophosphamide[96] | RCT | Standard agent used to induce remission in generalized and severe disease |
| 15-Deoxyspergualin[84]‡ | Prospective uncontrolled | Good alternative for treatment of refractory NGV; high rate of adverse side effects (mainly leukopenia) |
| IV Ig[92] | RCT | Only one RCT in AAV; good response in patients with refractory NGV and MPA during first 3 months |
| Infliximab[40,60–62] | Open-label trials | Useful alternative therapy for refractory AAV |
| Leflunomide[75] | RCT | Good alternative as maintenance therapy |
| Methotrexate[97] | RCT | Good alternative to cyclophosphamide in patients with NGV and MPA with localized forms or non-life-threatening disease; limited efficacy as induction therapy |
| MMF[82] | Prospective uncontrolled | Good alternative as maintenance treatment; little information as induction therapy |
| Plasma exchange[51] | RCT for renal vasculitis | Good results in renal vasculitis and life-threatening disease situations, such as alveolar hemorrhage |
| Rituximab[69,73] | Prospective long term | Good response mainly for vasculitis-related symptoms; partial or unsatisfactory response for granulomatous lesions |

RCT = randomized controlled trial.
*Presented in alphabetical order.
†The best evidence available is collected.
‡15-Deoxyspergualin has not been approved by the US Food and Drug Administration or the European Medicines Agency.

have focused on pulmonary involvement. The best evidence has come from a randomized trial[51] of plasma exchange as adjunct therapy in 137 patients with severe renal vasculitis who received high doses of IV methylprednisolone (n = 67) or plasma exchange (n = 70) [Methylprednisolone or Plasma Exchange for Severe Renal Vasculitis (or MEPEX) trial]. Plasma exchange was associated with increased renal recovery, a risk reduction for end-stage renal disease, and reduced dialysis dependency compared with methylprednisolone, supporting its use in patients with AAV and renal failure. Anecdotal reports[52,53] have shown good results with the administration of recombinant coagulation factor VIIa in cases of alveolar hemorrhage in patients with CSS and MPA.

The management of subglottic disease remains challenging. For new-onset subglottic stenosis, medical treatment for localized disease is indicated. However, in cases with severe tracheobronchial disease, some authors[30] have recommended therapy with systemic glucocorticoids and cyclophospha-

**Table 4—*Treatment of AAV According to Disease Extension and Severity***

| Disease State | Treatment Recommendation | NGV and MPA Remission Induction Level of Evidence/Grade of Recommendation* | Remission Maintenance Treatment Recommendation | Level of Evidence/Grade of Recommendation* |
|---|---|---|---|---|
| Localized disease | Steroids ± cotrimoxazole | 2b/B | Steroids ± cotrimoxazole | 1b/A |
| Generalized non-organ-threatening disease | Methotrexate + steroids | 1b/A | Methotrexate + steroids | 2b/B |
| Generalized organ-threatening disease | Pulse cyclophosphamide + steroids | 1a/A | Azathioprine + steroids | 1b/A |
| Diffuse pulmonary hemorrhage | High-dose of cyclophosphamide + pulse methylprednisolone | 5/D | Azathioprine + steroids | 5/D |
| | Cyclophosphamide + steroids + plasma exchange | 4/C | Azathioprine + steroids | 5/D |
| CSS | | | | |
| Five-factor score ≥ 1 | Cyclophosphamide + steroids | 1a/A | | |
| Five-factor score = 0 | Steroids | 1a/A | | |

Adapted from Bosch et al.[42]
*Level of evidence and grade of recommendation according to Oxford Centre for Evidence-Based Medicine[98] definitions.

mide, regardless of the severity of other organ manifestations. On the other hand, Hoffman et al[54] showed that the efficacy of local procedures, such as intralesional methylprednisolone injections and mechanical or balloon dilations, eliminate the need for new tracheotomies in almost all patients with NGV and subglottic stenosis. Silicone-coated stent implantation can be used as a good alternative,[55] and in cases of fixed subglottic stenosis, intraluminal dilation, laser resection, or laryngotracheoplasty may be required.[30] Finally, in patients with critical airway stenosis who are unresponsive to medical measures and dilation therapies, tracheostomy provides long-term relief.[30] Therapy with inhaled glucocorticoids has shown benefits when the dosage of oral glucocorticoids is tapered to $< 30$ mg/d.[30]

### *New Medications for AAV*

Selective targeting of the immune mechanisms involved in vascular inflammation has the potential to effectively treat AAV while leaving host defense mechanisms relatively intact. More pathogenesis-oriented therapies could overcome current therapeutic defects by ablating key immune pathways with less toxicity.[56] Although not exclusive to pulmonary involvement, currently used and experimental biological agents and new therapies are described in the following section.

### *Biological Agents*

*Anti-TNF-α Blockers: In vitro* and *in vivo* evidence shows a central role of anti-TNF-α in AAV pathogenesis. TNF-α mediates granuloma formation in patients with NGV, and is increased in serum and vasculitic foci in those with active disease, with a return to normal levels during remission.[57] TNF-α inhibition may be beneficial in patients with AAV, as animal models[13,58] have shown that anti-TNF-α antibodies prevent and even strongly attenuate ANCA-induced focal necrotizing glomerulonephritis. However, clinical trials with anti-TNF-α agents (adalimumab, etanercept, and infliximab) in patients with AAV have not consistently shown a benefit. Etanercept showed disappointing results in maintaining remission in a randomized, placebo-controlled trial[58] of 180 patients with NGV. In the same trial,[59] etanercept administered with cyclophosphamide increased the risk of cancer beyond that observed with cyclophosphamide therapy alone. Therapy with infliximab has shown satisfactory remission rates (around 80%) and low relapse rates (around 15%) in several open-label trials[40,60–62] in patients with refractory AAV. Josselin et al[63] evaluated long-term outcomes in 15 patients with refractory systemic necrotizing vasculitides (NGV, 10 patients; MPA, 1 patient; rheumatoid arthritis vasculitis, 3 patients; and cryoglobulinemia, 1 patient) treated with infliximab (mean duration, 8 months). By day 45, 11 patients were in remission (BVAS, 0), and BVAS scores were reduced by $> 50\%$ in the remaining 4 patients. During follow-up, 5 patients achieved sustained remission; however, 10 patients relapsed at a median of 13 months, 3 of whom were still receiving infliximab. Adalimumab has been successfully tested[64–66] in patients with several vasculitides, but there are no reports on its efficacy in patients with AAV. Randomized studies with infliximab and adalimumab in patients with refractory AAV are required.

*Rituximab:* Rituximab, a chimeric human and mouse monoclonal antibody that specifically depletes CD20+ B cells, has demonstrated potential for the treatment of B-cell-mediated autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus. The rationale for using rituximab in the treatment of AAV is based on its effective depletion of CD20-expressing precursors of ANCA-producing plasma cells.

Rituximab was first successfully used in a patient with chronic, relapsing NGV.[67] Prospective open-label studies[68–70] and retrospective studies[71,72] have investigated rituximab as remission-induction therapy in patients with refractory or relapsing NGV (and MPA and CSS[69]) in combination with glucocorticoids[68,71,72] or cyclophosphamide.[69,70] Overall, at a dose of 375 mg/m$^2$ in 4 weekly courses, rituximab has shown promising results in refractory cases.[68,69,71,72] However, contradictory results were observed in patients with granulomatous lesions (*eg*, pulmonary nodules and retro-orbital masses). Rituximab was effective in eight cases[72] of limited NGV unresponsive to three immunosuppressive agents but showed no benefit in other small series.[70,71]

In these preliminary studies, rituximab-induced total depletion of circulating B cells at 1 month and ANCA titers generally decreased or became negative. Some patients experienced complete remission with no correlation with ANCA titers.[69,70,73] Relapse rates ranged from 10 and 64%[68,69] and frequently were preceded by a rise in ANCA titers and circulating B-cell recovery within 6 to 12 months.[71,73]

More conclusive data depend on the final results of two large, ongoing, multicenter randomized trials of AAV. The Rituximab for the Treatment of NGV and MPA (or RAVE) trial (ClinicalTrials.gov identifier NCT00104299) is a prospective, multicenter, double-blind, placebo-controlled trial designed to establish the capacity of rituximab (compared to cyclophosphamide) to induce complete remission during the first 6 months after randomization. Dur-

ing the remission maintenance phase, all participants received therapy with oral azathioprine until month 18. The Rituximab for ANCA-Associated Renal Vasculitis (or RITUXVAS) trial is a phase II/III randomized clinical trial (EudraCT No. 2005–003610-15) that compares a rituximab-based regimen to standard care (combined regimen with cyclophosphamide for induction and azathioprine for remission maintenance) in 44 patients with ANCAs and renal involvement due to active NGV, MPA, or renal-limited vasculitis. Long-term B-lymphocyte depletion seems to be a promising approach to remission maintenance therapy in patients with refractory AAV (especially for vasculitis-related features) and is associated with a few adverse events.

*Abatacept:* With regard to AAV, there are no published reports on abatacept, which is a recombinant fusion protein with activity as a selective costimulation modulator that interferes with the interaction between antigen-presenting cells and T lymphocytes, and inhibits the activity of T lymphocytes. The Abatacept in AAV (or ABAVAS) trial (ClinicalTrials.gov identifier: NCT00482066) is an ongoing, prospective, double-blind, placebo-controlled trial assessing relapse rates of > 24 months in 112 patients with acute AAV presenting at first diagnosis or relapse. Patients will receive standard therapy with methotrexate and glucocorticoids and 12 months of therapy with abatacept or placebo.

### *Other Therapies*

Leflunomide, a prodrug the active metabolite of which inhibits a mitochondrial enzyme, has shown good results as remission maintenance therapy in patients with NGV.[74,75] However, its use should be contemplated carefully because of its safety profile.

Uncontrolled studies have suggested that mycophenolate mofetil (MMF) may be useful as induction therapy in AAV,[76,77] even in patients who do not tolerate cyclophosphamide.[78,79] A nonblinded clinical trial[80] compared MMF therapy with intermittent cyclophosphamide pulses as induction treatment in 35 patients with AAV and moderate renal involvement. At month 6, BVAS scores were much lower in the MMF group, with more patients achieving complete remission and recovery of renal function. MMF also has been used for remission maintenance in patients with NGV after inducing remission with cyclophosphamide and glucocorticoids, with conflicting results.[81,82] The results of the ongoing MMF vs Cyclophosphamide (or MYCYC) randomized clinical trial (EudraCT No. 2006–001663-33) and the completed MMF vs Azathioprine for Maintenance Therapy in AAV (or IMPROVE) trial (ClinicalTrials.gov identifier: NCT00307645), which was designed to define the optimal induction and maintenance therapy for AAV in patients with MMF, are awaited.

Because activated CD4 T cells producing T helper type 1 cytokines seem to play a crucial role in AAV, there is a rationale for the use of T-lymphocyte-blocking therapies, such as antithymocyte globulin. In a prospective, uncontrolled trial,[83] a 10-day regimen of antithymocyte globulin induced remission in 13 of 15 patients with NGV.

15-Deoxyspergualin is an antiproliferative drug with effects on lymphocyte and macrophage function and neutrophil production. In an open-label study[84] of 44 patients with refractory NGV, 45% of patients achieved complete remission after a median duration of 78 days, and around 40% of patients relapsed. Severe treatment-related side effects, which rarely led to treatment discontinuation, developed in one-half of the patients. The authors concluded that 15-deoxyspergualin may be a good alternative therapy for patients with refractory NGV, although it is not approved by the US Food and Drug Administration or the European Medicines Agency.

Patients with CSS have been treated with interferon-α since the 1990s because of its capacity to suppress the immune responses of overreactive T helper type 2 cells and their inhibitory effect on eosinophil effector functions.[3] There have been no systematic studies of the effectiveness of therapy with interferon-α.[85–87] Long-term use has been associated with leukoencephalopathy,[88] which might limit its use in patients with CSS.

IV Igs have demonstrated clear benefits in Kawasaki disease.[89] Uncontrolled series[90,91] have suggested some beneficial effects in AAV patients. The only randomized controlled trial[92] of IV Ig therapy showed a significant decrease in clinical and laboratory vasculitic activity in most patients (82%) in the IV Ig group during the first 3 months, but there were no subsequent differences between therapy with IV Ig and placebo.

## Conclusions

Pulmonary involvement in patients with AAV is frequent. Depending on the nature of the lesions (nodules, infiltrates, or alveolar hemorrhage), patients may require different therapeutic approaches. In addition to glucocorticoids and other immunosuppressant agents, biological agents are emerging as potential therapies in refractory cases, although only rituximab and infliximab have been trialed with apparent initial clinical success. The results of ongoing and concluded trials are eagerly awaited. Dissect-

ing inflammatory mechanisms may identify molecular targets for future therapies in AAV. If safety concerns are overcome, a pathogenesis-based strategy might involve the combined use of agents directed to specific complications or situations in patients with AAV.

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## References

1 Rosen MJ. Dr. Friedrich Wegener, the ACCP, and history. Chest 2007; 132:739–741
2 Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides: proposal of an international consensus conference. Arthritis Rheum 1994; 37:187–192
3 Bosch X, Guilabert A, Font J. Antineutrophil cytoplasmic antibodies. Lancet 2006; 368:404–418
4 Lhote F, Cohen P, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome. Lupus 1998; 7:238–258
5 Falk RJ, Terrell RS, Charles LA, et al. Anti-neutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals *in vitro*. Proc Natl Acad Sci U S A 1990; 87:4115–4119
6 Jennette JC, Xiao H, Falk RJ. Pathogenesis of vascular inflammation by anti-neutrophil cytoplasmic antibodies. J Am Soc Nephrol 2006; 17:1235–1242
7 Kallenberg CG. Antineutrophil cytoplasmic autoantibody-associated small-vessel vasculitis. Curr Opin Rheumatol 2007; 19:17–24
8 Schreiber A, Busjahn A, Luft FC, et al. Membrane expression of proteinase 3 is genetically determined. J Am Soc Nephrol 2003; 14:68–75
9 Tse WY, Nash GB, Hewins P, et al. ANCA-induced neutrophil F-actin polymerization: implications for microvascular inflammation. Kidney Int 2005; 67:130–139
10 Kallenberg CG, Heeringa P, Stegeman CA. Mechanisms of disease: pathogenesis and treatment of ANCA-associated vasculitides. Nat Clin Pract Rheumatol 2006; 2:661–670
11 Day CJ, Hewins P, Savage CO. New developments in the pathogenesis of ANCA-associated vasculitis. Clin Exp Rheumatol 2003; 21:S35–S48
12 Xiao H, Heeringa P, Hu P, et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. J Clin Invest 2002; 110:955–963
13 Little MA, Smyth CL, Yadav R, et al. Antineutrophil cytoplasm antibodies directed against myeloperoxidase augment leukocyte-microvascular interactions *in vivo*. Blood 2005; 106:2050–2058
14 Foucher P, Heeringa P, Petersen AH, et al. Antimyeloperoxidase-associated lung disease: an experimental model. Am J Respir Crit Care Med 1999; 160:987–994
15 Bacon PA. The spectrum of Wegener's granulomatosis and disease relapse. N Engl J Med 2005; 352:330–332
16 Sarraf P, Sneller MC. Pathogenesis of Wegener's granulomatosis: current concepts. Expert Rev Mol Med 2005; 7:1–19
17 Voswinkel J, Muller A, Lamprecht P. Is PR3-ANCA formation initiated in Wegener's granulomatosis lesions? Granulomas as potential lymphoid tissue maintaining autoantibody production. Ann N Y Acad Sci 2005; 1051:12–19
18 Lamprecht P, Mueller A, Gross WL. CD28-T cells display features of effector memory T cells in Wegener's granulomatosis [letter]. Kidney Int 2004; 65:1113
19 Komocsi A, Lamprecht P, Csernok E, et al. Peripheral blood and granuloma CD4(+)CD28(-) T cells are a major source of interferon-γ and tumor necrosis factor-α in Wegener's granulomatosis. Am J Pathol 2002; 160:1717–1724
20 Csernok E, Trabandt A, Muller A, et al. Cytokine profiles in Wegener's granulomatosis: predominance of type 1 (Th1) in the granulomatous inflammation. Arthritis Rheum 1999; 42:742–750
21 Abdulahad WH, Stegeman CA, Limburg PC, et al. CD4-positive effector memory T cells participate in disease expression in ANCA-associated vasculitis. Ann N Y Acad Sci 2007; 1107:22–31
22 Voswinkel J, Mueller A, Kraemer JA, et al. B lymphocyte maturation in Wegener's granulomatosis: a comparative analysis of VH genes from endonasal lesions. Ann Rheum Dis 2006; 65:859–864
23 Preston GA, Pendergraft WF III, Falk RJ. New insights that link microbes with the generation of antineutrophil cytoplasmic autoantibodies: the theory of autoantigen complementarity. Curr Opin Nephrol Hypertens 2005; 14:217–222
24 Eisenberger U, Fakhouri F, Vanhille P, et al. ANCA-negative pauci-immune renal vasculitis: histology and outcome. Nephrol Dial Transplant 2005; 20:1392–1399
25 Cunningham MA, Huang XR, Dowling JP, et al. Prominence of cell-mediated immunity effectors in "pauci-immune" glomerulonephritis. J Am Soc Nephrol 1999; 10:499–506
26 Carrie S, Fenton PA. Necrobacillosis: an unusual case of pharyngotonsillitis. J Laryngol Otol 1994; 108:1097–1098
27 Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2008; 68:310–317
28 Kain R, Exner M, Brandes R, et al. Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis. Nat Med 2008; 14:1088–1096
29 Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992; 116:488–498
30 Polychronopoulos VS, Prakash UB, Golbin JM, et al. Airway involvement in Wegener's granulomatosis. Rheum Dis Clin North Am 2007; 33:755–775, vi
31 Pagnoux C, Guilpain P, Guillevin L. Churg-Strauss syndrome. Curr Opin Rheumatol 2007; 19:25–32
32 Bosch X, Lopez-Soto A, Mirapeix E, et al. Antineutrophil cytoplasmic autoantibody-associated alveolar capillaritis in patients presenting with pulmonary hemorrhage. Arch Pathol Lab Med 1994; 118:517–522
33 Guillevin L, Pagnoux C, Mahr A, et al. The Five-Factor Score (FFS) revisited: a tool to assess the prognoses of polyarteritis nodosa (PAN), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS) and Wegener's granulomatosis (WG) based on 1108 patients from the French Vasculitis Study Group (FVSG) [abstract]. Arthritis Rheum 2008; 58(suppl):S906
34 Nada AK, Torres VE, Ryu JH, et al. Pulmonary fibrosis as an unusual clinical manifestation of a pulmonary-renal vasculitis in elderly patients. Mayo Clin Proc 1990; 65:847–856
35 Gaudin PB, Askin FB, Falk RJ, et al. The pathologic spectrum of pulmonary lesions in patients with anti-neutrophil cytoplasmic autoantibodies specific for anti-proteinase 3 and anti-myeloperoxidase. Am J Clin Pathol 1995; 104:7–16

36 Gómez-Puerta J, Espinosa G, Morla R, et al. Pulmonary alveolitis as a presenting manifestation of microscopic polyangiitis successfully treated with mycophenolate mofetil. Clin Exp Rheumatol 2009; 27:166–167
37 Luqmani RA, Flossmann O. Outcome in small-vessel systemic vasculitis. J Rheumatol 2006; 33:1224–1227
38 Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003; 349:36–44
39 Langford CA. Treatment of ANCA-associated vasculitis. N Engl J Med 2003; 349:3–4
40 Booth A, Harper L, Hammad T, et al. Prospective study of TNFα blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol 2004; 15:717–721
41 Hellmich B, Lamprecht P, Gross WL. Advances in the therapy of Wegener's granulomatosis. Curr Opin Rheumatol 2006; 18:25–32
42 Bosch X, Guilabert A, Espinosa G, et al. Treatment of antineutrophil cytoplasmic antibody associated vasculitis: a systematic review. JAMA 2007; 298:655–669
43 Pagnoux C, Hogan SL, Chin H, et al. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. Arthritis Rheum 2008; 58:2908–2918
44 Chen M, Yu F, Zhang Y, et al. Antineutrophil cytoplasmic autoantibody-associated vasculitis in older patients. Medicine (Baltimore) 2008; 87:203–209
45 Holguin F, Ramadan B, Gal AA, et al. Prognostic factors for hospital mortality and ICU admission in patients with ANCA-related pulmonary vasculitis. Am J Med Sci 2008; 336:321–326
46 Khan SA, Subla MR, Behl D, et al. Outcome of patients with small-vessel vasculitis admitted to a medical ICU. Chest 2007; 131:972–976
47 Guillevin L, Le Thi Huong D, Godeau P, et al. Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients. Br J Rheumatol 1988; 27:258–264
48 Stegeman CA, Tervaert JW, de Jong PE, et al. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis: Dutch Co-Trimoxazole Wegener Study Group. N Engl J Med 1996; 335:16–20
49 Iwatani H, Uzu T, Kakihara M, et al. A case of Wegener's granulomatosis with pulmonary bleeding successfully treated with double filtration plasmapheresis (DFPP). Clin Exp Nephrol 2004; 8:369–374
50 Sugimoto T, Deji N, Kume S, et al. Pulmonary-renal syndrome, diffuse pulmonary hemorrhage and glomerulonephritis, associated with Wegener's granulomatosis effectively treated with early plasma exchange therapy. Intern Med 2007; 46:49–53
51 Jayne DR, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007; 18:2180–2188
52 Heslet L, Nielsen JD, Levi M, et al. Successful pulmonary administration of activated recombinant factor VII in diffuse alveolar hemorrhage. Crit Care 2006; 10:R177
53 Betensley AD, Yankaskas JR. Factor VIIa for alveolar hemorrhage in microscopic polyangiitis. Am J Respir Crit Care Med 2002; 166:1291–1292
54 Hoffman GS, Thomas-Golbanov CK, Chan J, et al. Treatment of subglottic stenosis, due to Wegener's granulomatosis, with intralesional corticosteroids and dilation. J Rheumatol 2003; 30:1017–1021
55 Solans-Laque R, Bosch-Gil J, Canela M, et al. Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis. Lupus 2008; 17:832–836
56 Sarraf P, Kay J, Friday RP, et al. Wegener's granulomatosis: is biologic therapy useful? Curr Rheumatol Rep 2006; 8:303–311
57 Noronha IL, Kruger C, Andrassy K, et al. *In situ* production of TNF-α, IL-1 beta and IL-2R in ANCA-positive glomerulonephritis. Kidney Int 1993; 43:682–692
58 Huugen D, Xiao H, van Esch A, et al. Aggravation of anti-myeloperoxidase antibody-induced glomerulonephritis by bacterial lipopolysaccharide: role of tumor necrosis factor-α. Am J Pathol 2005; 167:47–58
59 Stone JH, Holbrook JT, Marriott MA, et al. Solid malignancies among patients in the Wegener's Granulomatosis Etanercept Trial. Arthritis Rheum 2006; 54:1608–1618
60 Lamprecht P, Voswinkel J, Lilienthal T, et al. Effectiveness of TNF-α blockade with infliximab in refractory Wegener's granulomatosis. Rheumatology (Oxford) 2002; 41:1303–1307
61 Booth AD, Jayne DR, Kharbanda RK, et al. Infliximab improves endothelial dysfunction in systemic vasculitis: a model of vascular inflammation. Circulation 2004; 109:1718–1723
62 Booth AD, Jefferson HJ, Ayliffe W, et al. Safety and efficacy of TNFα blockade in relapsing vasculitis. Ann Rheum Dis 2002; 61:559
63 Josselin L, Mahr A, Cohen P, et al. Infliximab efficacy and safety against refractory systemic necrotising vasculitides: long-term follow-up of 15 patients. Ann Rheum Dis 2008; 67:1343–1346
64 Seymour MW, Home DM, Williams RO, et al. Prolonged response to anti-tumour necrosis factor treatment with adalimumab (Humira) in relapsing polychondritis complicated by aortitis. Rheumatology (Oxford) 2007; 46:1738–1739
65 Ahmed MM, Mubashir E, Hayat S, et al. Treatment of refractory temporal arteritis with adalimumab. Clin Rheumatol 2007; 26:1353–1355
66 Tato F, Rieger J, Hoffmann U. Refractory Takayasu's arteritis successfully treated with the human, monoclonal anti-tumor necrosis factor antibody adalimumab. Int Angiol 2005; 24:304–307
67 Specks U, Fervenza FC, McDonald TJ, et al. Response of Wegener's granulomatosis to anti-CD20 chimeric monoclonal antibody therapy. Arthritis Rheum 2001; 44:2836–2840
68 Keogh KA, Ytterberg SR, Fervenza FC, et al. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. Am J Respir Crit Care Med 2006; 173:180–187
69 Smith KG, Jones RB, Burns SM, et al. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: remission, relapse, and re-treatment. Arthritis Rheum 2006; 54:2970–2982
70 Aries PM, Hellmich B, Voswinkel J, et al. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. Ann Rheum Dis 2006; 65:853–858
71 Brihaye B, Aouba A, Pagnoux C, et al. Adjunction of rituximab to steroids and immunosuppressants for refractory/relapsing Wegener's granulomatosis: a study on 8 patients. Clin Exp Rheumatol 2007; 25:S23–S27
72 Seo P, Specks U, Keogh KA. Efficacy of rituximab in limited Wegener's granulomatosis with refractory granulomatous manifestations. J Rheumatol 2008; 35:2017–2023
73 Stasi R, Stipa E, Del Poeta G, et al. Long-term observation of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. Rheumatology (Oxford) 2006; 45:1432–1436

74 Metzler C, Fink C, Lamprecht P, et al. Maintenance of remission with leflunomide in Wegener's granulomatosis. Rheumatology (Oxford) 2004; 43:315–320
75 Metzler C, Miehle N, Manger K, et al. Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. Rheumatology (Oxford) 2007; 46:1087–1091
76 Lin S, Shan L, Mingcai Q. A case of Wegener's granulomatosis treated with mycophenolate mofetil. Nephron 2002; 92:959
77 Waiser J, Budde K, Braasch E, et al. Treatment of acute c-ANCA-positive vasculitis with mycophenolate mofetil. Am J Kidney Dis 1999; 34:e9
78 Joy MS, Hogan SL, Jennette JC, et al. A pilot study using mycophenolate mofetil in relapsing or resistant ANCA small vessel vasculitis. Nephrol Dial Transplant 2005; 20:2725–2732
79 Stassen PM, Cohen Tervaert JW, Stegeman CA. Induction of remission in active anti-neutrophil cytoplasmic antibody-associated vasculitis with mycophenolate mofetil in patients who cannot be treated with cyclophosphamide. Ann Rheum Dis 2007; 66:798–802
80 Hu W, Liu C, Xie H, et al. Mycophenolate mofetil versus cyclophosphamide for inducing remission of ANCA vasculitis with moderate renal involvement. Nephrol Dial Transplant 2008; 23:1307–1312
81 Langford CA, Talar-Williams C, Sneller MC. Mycophenolate mofetil for remission maintenance in the treatment of Wegener's granulomatosis. Arthritis Rheum 2004; 51:278–283
82 Nowack R, Gobel U, Klooker P, et al. Mycophenolate mofetil for maintenance therapy of Wegener's granulomatosis and microscopic polyangiitis: a pilot study in 11 patients with renal involvement. J Am Soc Nephrol 1999; 10:1965–1971
83 Schmitt WH, Hagen EC, Neumann I, et al. Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): an open study in 15 patients. Kidney Int 2004; 65:1440–1448
84 Flossmann O, Baslund B, Bruchfeld A, et al. Deoxyspergualin in relapsing and refractory Wegener's granulomatosis. Ann Rheum Dis 2009; 1125–1130
85 Tatsis E, Schnabel A, Gross WL. Interferon-α treatment of four patients with the Churg-Strauss syndrome. Ann Intern Med 1998; 129:370–374
86 Simon HU, Seelbach H, Ehmann R, et al. Clinical and immunological effects of low-dose IFN-α treatment in patients with corticosteroid-resistant asthma. Allergy 2003; 58:1250–1255
87 Termeer CC, Simon JC, Schopf E. Low-dose interferon alfa-2b for the treatment of Churg-Strauss syndrome with prominent skin involvement. Arch Dermatol 2001; 137:136–138
88 Lamprecht P, Till A, Steinmann J, et al. Current state of biologicals in the management of systemic vasculitis. Ann N Y Acad Sci 2007; 1110:261–270
89 Nagashima M, Matsushima M, Matsuoka H, et al. High-dose gammaglobulin therapy for Kawasaki disease. J Pediatr 1987; 110:710–712
90 Jayne DR, Lockwood CM. Intravenous immunoglobulin as sole therapy for systemic vasculitis. Br J Rheumatol 1996; 35:1150–1153
91 Levy Y, George J, Fabbrizzi F, et al. Marked improvement of Churg-Strauss vasculitis with intravenous gammaglobulins. South Med J 1999; 92:412–414
92 Jayne DR, Chapel H, Adu D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. QJM 2000; 93:433–439
93 Abdou NI, Kullman GJ, Hoffman GS, et al. Wegener's granulomatosis: survey of 701 patients in North America: changes in outcome in the 1990s. J Rheumatol 2002; 29:309–316
94 Allenbach Y, Seror R, Pagnoux C, et al. High frequency of venous thromboembolic events in Churg-Strauss syndrome, Wegener's granulomatosis and microscopic polyangiitis but not polyarteritis nodosa: a systematic retrospective study on 1130 patients. Ann Rheum Dis 2009; 68:564–567
95 Sable-Fourtassou R, Cohen P, Mahr A, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. Ann Intern Med 2005; 143:632–638
96 de Groot K, Muhler M, Reinhold-Keller E, et al. Induction of remission in Wegener's granulomatosis with low dose methotrexate. J Rheumatol 1998; 25:492–495
97 Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005; 352:351–361
98 Oxford Centre for Evidence-Based Medicine. Levels of evidence and grades of recommendation. Available at: http://www.cebm.net/levels_of_evidence.asp. Accessed May 21, 2007

# Antineutrophil Cytoplasmic Antibody-Associated Vasculitides and Respiratory Disease

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