ANCA-Associated Vasculitis

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Introduction

The systemic vasculitides are a group of rare and life-threatening diseases characterized by inflammation of blood vessel walls and adjacent tissues.[1-4] The end result of this inflammatory response is necrosis, stenosis, and thrombosis of vascular channels leading to ischemia, infarction or hemorrhage in affected organs. These disorders should be considered in any patient with multisystem organ dysfunction or persistent constitutional complaints. Some of the primary vasculitides are associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA).[5-10] These disorders include Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and the Churg-Strauss syndrome (CSS).[11-18] They occur at a rate of approximately 1-3 per 100,000, with CSS being the least common.[19-25] While each of these conditions has been associated with characteristic "patterns" of organ involvement, and particular laboratory and histopathologic findings, there is actually considerable overlap between them.[6, 18, 26-29] In some cases, it is impossible to tell them apart. They are all idiopathic, pauci-immune forms of predominantly small vessel vasculitis (mainly affecting arterioles, capillaries and venules) that have the potential to target any organ in the body.[3, 30, 31] They are best considered "variations on a theme" of a single disease entity, ANCA-associated systemic vasculitis (AASV).[32, 33]

Clinical Features

Wegener's Granulomatosis

Patients with AASV often present with constitutional symptoms including fever, weight loss, malaise, fatigue, arthralgias and myalgias.[34-36] WG additionally features involvement of the upper and lower respiratory tract, as well as the kidneys.[14, 34, 37, 38] Sinonasal disease presenting as chronic nasal congestion, recurrent sinus infections or epistaxis is common at presentation, and ultimately develops in 90%.[34, 37, 39, 40] Examination may reveal nasal crusting, ulceration, septal perforation and, occasionally, saddle nose deformity. Other important head and neck manifestations include serous otitis, sensorineural hearing loss and ocular disease.[39, 41-44] Ocular abnormalities have been identified in 15-50% of patients during the course of the disease.[34, 37, 44-47] Findings range from proptosis caused by retroorbital inflammatory pseudotumors, to scleritis, uveitis, optic neuritis or occlusion of the central retinal vessels. Oral ulcers and gingivitis may also be seen.

Pulmonary disease is identified in 65-85% of patients with WG.[34, 37, 48] Nodules, masses or alveolar infiltrates, often cavitating, are the most common radiographic abnormalities (figure 1).[34, 37, 40, 49, 50] Computed tomography is more sensitive than plain chest radiography for detecting abnormalities in these patients.[49, 51, 52] Cough, pleurisy or hemoptysis may be seen, but such symptoms are absent in one third.[34] Pleural effusions occur in 20%.[40, 49-51, 53]

The most immediately life-threatening complication of AASV is diffuse alveolar hemorrhage (DAH).[54-57] This occurs in 5-10% of patients with WG and carries a 25% mortality risk.[34, 58-60] Pulmonary hemorrhage typically produces dyspnea, hemoptysis and bilateral airspace disease (ground glass opacities or frank consolidation).[54, 56, 61, 62] The diagnosis is confirmed by bronchoalveolar lavage demonstrating increasingly bloody return upon instillation of serial saline aliquots.[63, 64]

Granulomatous inflammation and scarring may lead to subglottic or endobronchial stenosis.[65-67] Subglottic stenosis occurs in 15% of WG patients and may produce dyspnea, hoarseness, or no symptoms at all.[68, 69] Management usually involves mechanical dilatation with corticosteroid injection, or sometimes tracheostomy.[69]

Cutaneous involvement is seen in up to half of patients during the course of their disease.[34, 37, 41, 70, 71] Palpable purpura, associated with leukocytoclastic vasculitis, is the most

common lesion.[72] Digital ischemia, skin nodules, pyoderma gangrenosum-like lesions and even livido reticularis may also be seen in patients with AASV.[71-73]

Colonic or small bowel ulceration may occur due to mesenteric vasculitis, and lead to abdominal pain, diarrhea, gastrointestinal bleeding or perforation.[74-80] Clinically significant gastrointestinal involvement in seen in fewer than 15% of WG patients, although more have evidence of disease at autopsy.

Neurologic complications develop in 20-50% of patients with WG, usually later in the disease course.[34, 37, 40, 81-84] Peripheral neuropathies, particularly mononeuritis multiplex, and cranial neuropathies are most common, but stroke, seizure, cerebritis and meningitis can be seen.

Renal involvement in WG is usually asymptomatic until severe impairment in glomerular filtration occurs.[34, 37, 85] Proteinuria, hematuria and red blood cell casts characteristic of glomerulonephritis (GN) are seen on urinalysis, along with elevations in blood urea nitrogen and serum creatinine. Although it ultimately develops in between 50 and 90% of WG patients, only about 20% have glomerulonephritis at the time of presentation.[33, 34, 37, 48] Consequently, only one patient in five will have the classic triad of WG when they first come to medical attention. This, and a lack of physician familiarity with other systemic disease manifestations, may be an important factor contributing to delays in diagnosis and treatment initiation.

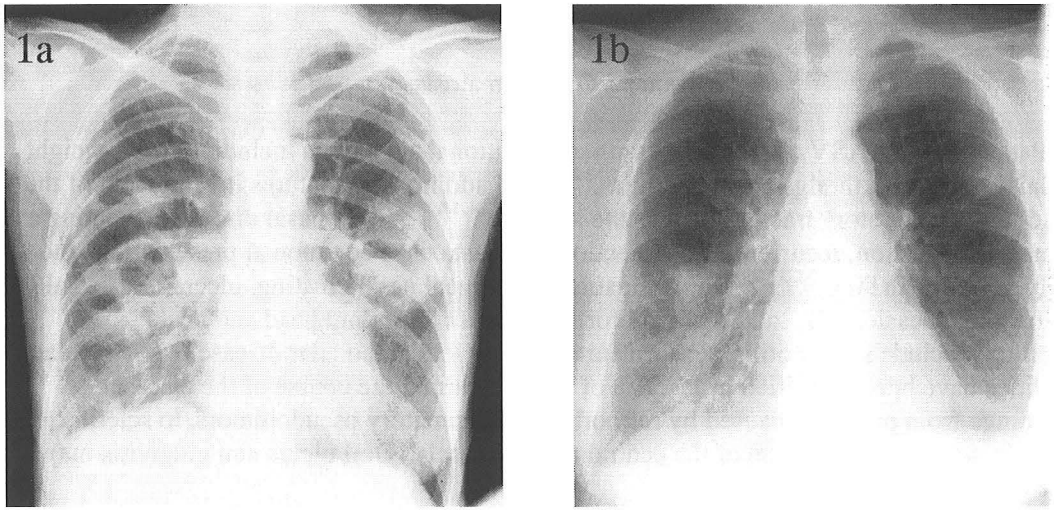

Figure 1. Typical plain film patterns in two subjects with Wegener's granulomatosis. Figure 1a demonstrates multiple, bilateral cavitating masses in a patient with chronic sinusitis, cough and hemoptysis. Figure 1b shows bilateral nodular opacities and a right lower lobe alveolar infiltrate. This patient had a history of epistaxis and dry cough, and presented with acute renal failure.

Microscopic Polyangiitis

MPA is one of the most common small vessel vasculitides.[13, 86] All of the clinical complications of vasculitis noted above can also occur in microscopic polyangiitis, with the exception of cavitating lung opacities and the granulomatous upper airway disease.[30] Relative to WG, renal involvement is reported even more frequently (80-100%), and is more often evident at initial presentation.[3, 13, 87-89] Microscopic hematuria and/or proteinuria are almost always present, even in the few patients with a normal serum creatinine level.[3, 87] Diffuse alveolar hemorrhage is usually an ANCA-associated condition, and MPA is a more frequent cause than WG.[88, 90-92] Between 10% and 40% of MPA patients develop this complication (figure 2).[13, 87, 93, 94] Constitutional complaints are more frequent compared to WG, and may be present for several

months before a diagnosis is secured.[13, 35, 87, 95] About one half of MPA patients have skin disease, typically palpable purpura.[13, 87, 95] Ocular pathology, sinusitis, epistaxis and oral ulcers occur, but less frequently than in WG.[11, 13, 92] The destructive upper airway disease characteristic of WG does not occur, however. Abdominal pain and gastrointestinal bleeding are twice as common in MPA as in WG.[87, 96] The reported frequency of central and peripheral nervous system disease in MPA is quite variable.[13, 87, 95-97]

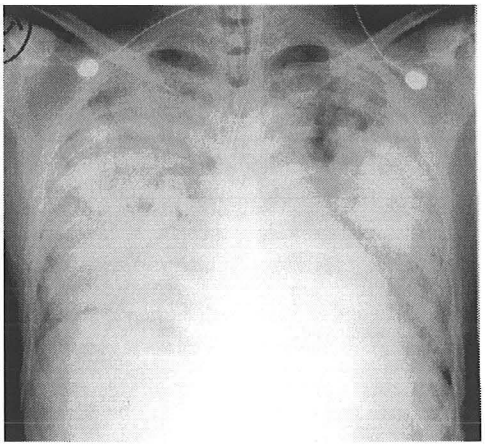

Figure 2. Microscopic polyangiitis. Diffuse alveolar hemorrhage presenting as hemoptysis and acute respiratory failure in a 24 year old man with necrotizing, crescentic glomerulonephritis. The patient was ANCA positive with a perinuclear pattern. Anti-MPO antibodies were also present. The plain film reveals extensive, bilateral airspace disease that cleared completely within two weeks following pulse corticosteroid treatment and plasma exchange.

Churg Strauss Syndrome

Churg Strauss syndrome is diagnosed when asthma and prominent eosinophilia are seen along with a necrotizing vasculitis.[16, 38, 98-100] Asthma, which is uncommon in other vasculitic syndromes, is almost universally present here.[98, 101-103] The organs most commonly involved in CSS include the lungs, skin, nervous system, heart, GI tract and kidneys (table 1).[99, 100, 104] Chest films often reveal patchy alveolar infiltrates at the time of presentation, and computed tomography can detect additional more subtle findings such as ground glass opacities.[101, 105-109] As in chronic eosinophilic pneumonia, symmetrical peripheral alveolar consolidation resembling the "photographic negative of pulmonary edema" may be seen (figure 3a). Nodular opacities may also be identified, but unlike WG, they rarely cavitate. Diffuse alveolar hemorrhage occurs in CSS, but much less commonly than in MPA or WG.[99] Thirty percent have pleural involvement.[110] Enlargement of the cardiac silhouette is not uncommon (figure 3b).

Table 1. Approximate frequency of various organ involvement in patients with ANCA-associated small vessel vasculitis.

	WG	MPA	CSS
Eye/ENT	90%	30%	65%
Pulmonary	75%	30%	60%
Renal	80%	95%	35%
Cutaneous	50%	50%	65%
Gastrointestinal	15%	30%	50%
Nervous system	35%	35%	70%
Cardiac	<5%	<5%	40%
Musculoskeletal	35%	65%	50%
Constitutional symptoms	40%	70%	70%

In many individuals, chronic rhinosinusitis and nasal polyposis are present for years prior to the onset of asthma.[89, 98] Patients often transition from this prodromal phase to one with simple

tissue eosinophilia that may involve any organ.[111] Asthma becomes increasingly difficult to control.[16] Marked elevations in serum IgE are common.[98, 103] Finally, the vasculitic phase appears, usually coincident with the development of constitutional symptoms.[112] Paradoxically, the asthmatic component may enjoy significant remission during this phase of the disease, only to return after disease remission is achieved.[89, 99]

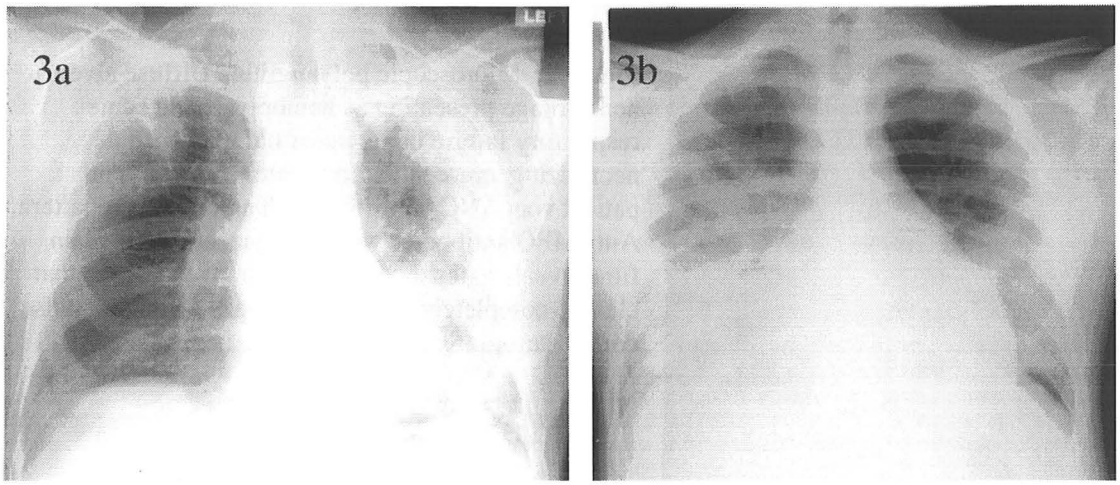

Figure 3. Plain chest radiographs in two patients with Churg Strauss syndrome. 3a) peripheral, axillary predominant consolidation, a finding classic for chronic eosinophilic pneumonia, that is sometimes also seen in CSS. 3b) chest film of a patient with a two year history of asthma and long-standing allergic rhinitis with nasal polyposis. He presented with dyspnea, orthopnea, abdominal pain and marked eosinophilia. He had a pericardial effusion, an ejection fraction of 35%, mononeuritis multiplex, and bilateral, basilar predominant airspace disease with eosinophilic pneumonia (but no vasculitis) by surgical lung biopsy.

Palpable purpura or subcutaneous nodules are seen in two thirds.[73, 98, 113, 114] Gastrointestinal involvement ranging from an eosinophilic gastroenteritis to mesenteric ischemia, and producing abdominal pain, bleeding, ulceration or perforation, is seen in about 50% of patients at some point in the disease course.[98, 101, 115-119] Peripheral neuropathies, usually mononeuritis multiplex, develop in 65-75%.[89, 98, 120, 121] CSS is the form of vasculitis most strongly associated with neurologic impairment. Central nervous system involvement leading to psychiatric disturbances, hemorrhage, infarction or seizures has also been reported in up to 25%.[82, 98, 120, 122] Cerebral bleeding was responsible for 16% of deaths in the series by Lanham and colleagues.[98] Involvement of the heart is also common in CSS, and is the leading cause of disease-related death.[98, 102, 123, 124] It may manifest as congestive heart failure from eosinophilic myocarditis, pericardial effusion or myocardial infarction due to coronary vasculitis.[98, 125-127] Although renal disease is less frequent, less severe and easier to treat in CSS relative to the other AASVs, it is hardly inconsequential.[98, 102, 128] Renal abnormalities including proteinuria, hematuria, or renal insufficiency were identified in 84% of 19 patients by Clutterbuck and colleagues.[129] Four of these patients had a serum creatinine level above 6 mg/dl, and three had nephrotic syndrome. In Lanham's series, renal failure was responsible for 18% of CSS deaths.[98]

Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

ANCA are autoantibodies that react with a variety of proteins within the cytoplasmic granules of neutrophils and monocytes.[130] While strongly associated with small vessel vasculitis,

ANCA may be seen in a number of other conditions that may appear on the differential diagnosis of AASV.[131] These include collagen vascular disease, certain infections, inflammatory bowel disease, some fibrotic lung conditions and lymphoproliferative disorders.[5, 132-136] A consensus statement released in 1999 recommended ANCA testing for patients with glomerulonephritis, alveolar hemorrhage, cutaneous vasculitis, chronic sinusitis or otitis, retro-orbital mass, unexplained peripheral neuropathy, or subglottic stenosis.[132] A positive ANCA with one or more of these clinical features indicates a greater than 90% probability of a pauciimmune small vessel vasculitis.[137]

ANCA are detected by indirect immunofluorence (IIF) staining of alcohol fixed neutrophils exposed to patient sera. Two major patterns may be identified: perinuclear (p-ANCA) and cytoplasmic (c-ANCA). IIF alone lacks specificity, so ELISA assays are performed on positive sera to confirm the antigen involved.[138] In AASV, that antigen is almost always proteinase 3 (PR3) or myeloperoxidase (MPO). c-ANCA staining is usually associated with anti-PR3 antibodies and are present in 65-90% of Wegener's granulomatosis patients.[139-142] p-ANCA are classically associated with anti-MPO antibodies and MPA or CSS.[3, 4, 10, 17, 99, 143] Approximately 70% of CSS patients and 80% of MPA patients have positive ANCA assays.[115, 144] Occasionally, patients with MPO antibodies show a cytoplasmic IIF pattern, and patients with PR3 antibodies demonstrate a perinuclear pattern.[145, 146] One large study was done to assess ANCA sensitivity and specificity in WG and MPA.[144] The sensitivity of the various assays in WG patients was: c-ANCA 64%, p-ANCA 21%, anti-PR3 66%, and anti-MPO 24%. In MPA, the sensitivities were: p-ANCA 58%, c-ANCA 23%, anti-MPO 58%, and anti-PR3 26%. The specificity of these assays for idiopathic small vessel vasculitis, in general, were: c-ANCA 95%, p-ANCA 81%, anti-PR3 87%, and anti-MPO 91%. The diagnostic specificity of the c-ANCA/anti-PR3 and p-ANCA/anti-MPO combinations was 99%.[144]

ANCA titers are often high at presentation and during disease exacerbations, and low or absent when the vasculitis is quiescent.[141, 142, 147] Antibody levels typically decline with treatment, and an increase in ANCA titer often precedes clinical relapse.[8, 132, 148-150] In a meta-analysis by Tervaert and colleagues, however, clinical relapse occurred in only 94 out of 197 patients with rising ANCA titers; and 157 disease flares were preceded by a rising ANCA titer in only 81 instances.[151] This suggests about a 50% sensitivity and specificity in the relationship between changing antibody levels and disease activity. A rising c-ANCA titer accompanied by a rising anti-PR3 titer may indicate a higher probability of disease flare in WG, but the two do not necessarily occur simultaneously.[88] Stegeman and co-workers also found that anti-PR3 and anti-MPO levels were useful for predicting relapse in AASV.[152] Patients with MPO-ANCA more frequently have persistent antibody elevations despite clinical remission.[88, 150, 153] It does appear, however, that those with persistently high titers are more prone to disease relapse.[154]

Some clinical differences have been noted between patients with PR3-ANCA and those with MPO-ANCA.[155] Patients with anti-PR3 antibodies have more eye, ear and upper respiratory tract involvement, granuloma formation, and a higher relapse rate.[9, 156] Patients with PR3-ANCA also tend to have more active renal lesions and experience more rapid declines in renal function compared to MPO-ANCA patients, but the long-term renal outcome is essentially the same.[9, 157]

Histopathology and the Need for Biopsy in AASV

Whether the presence of ANCA in certain clinical settings can replace biopsy as a diagnostic tool is debatable. Some suggest that the presence of MPO- or PR3-ANCA with glomerulonephritis abrogates the need for biopsy confirmation.[158] Others believe that the treatments employed in these disorders are too toxic to be used without first obtaining tissue, and that other useful prognostic information can be gleaned at least from examination of renal tissue.[17] When certain characteristic patterns of organ involvement are combined with the

presence of anti-MPO or PR3 antibodies, the diagnosis of AASV is virtually assured. A more specific diagnosis may require examination of biopsy material, but that information may have little impact on the ultimate approach to treatment.

Many times, even examination of biopsy material only reveals "supportive" evidence that still must be interpreted in the light of other clinical and serologic parameters. For example, the histopathologic hallmarks of WG are vasculitis (involving the small and medium sized arteries), granulomatous inflammation and tissue necrosis (fig 4a). Renal biopsies in WG patients, however, typically reveal only a segmental, necrotizing and crescentic glomerulonephritis with no direct evidence of vasculitis or granulomas (figure 4b).[55] Immunohistochemistry reveals few, if any, immune deposits (pauci-immune GN), but this does not distinguish WG from MPA or CSS. Renal biopsies are primarily useful for excluding immune complex-mediated GN, anti-basement membrane antibody disease and other causes of GN, and for projecting long-term renal outcome (based on the percentage of glomerular crescents). Upper airway biopsies are easy to perform, but reveal the "diagnostic" combination of granulomas and vasculitis in only one fifth of patients.[159] Surgical lung biopsies have the best overall diagnostic yield, but are harder to obtain.[55, 160] In patients presenting with diffuse alveolar hemorrhage, pulmonary capillaritis may be seen without any specific findings (i.e., granulomas) to suggest WG.[161, 162] Capillaritis is characterized by neutrophilic infiltration of alveolar septae with fibrinoid necrosis of alveolar walls leading to the extravasation of erythrocytes into alveolar spaces (figure 4c).[57, 58, 163, 164] Some of the neutrophils are apoptotic with pyknotic nuclei, and nuclear dust is often seen.[57, 58] This lesion is the pulmonary equivalent of the leukocytoclastic vasculitis in the skin that produces palpable purpura, and the glomerular capillaritis that leads to necrotizing, crescentic GN.[30, 162, 165] It may be seen in any of the ANCA-associated vasculitides, and in a variety of other autoimmune conditions as well.[58, 166-168]

MPA is not associated with granulomatous inflammation, but the histopathology is otherwise indistinguishable from WG.[11, 30, 87] MPA mainly involves small vessels, but can also involve medium sized arteries. Capillaritis and rapidly progressive necrotizing, crescentic GN are common (figure 4b and 4c).[87, 160, 169] In some cases, a more slowly progressive glomerulosclerosis may be seen.[88, 157, 170, 171] Skin, sural nerve and kidney biopsies are the most commonly employed biopsy sites because they are accessible.[11]

In CSS, the classic histopathologic findings include a necrotizing vasculitis involving small and medium sized vessels, granulomatous inflammation, and eosinophilic infiltration of blood vessel walls and tissues (figure 4d).[160, 172, 173] It is not essential, however, to see all of these features to make the diagnosis. The original patients described by Churg and Strauss had severe, systemic vasculitis.[172] More subtle presentations are now prevalent due to the common use of exogenous corticosteroids in problematic asthmatics.[111] In a retrospective study of 23 CSS patients, Reid and colleagues found that only four patients demonstrated all of the classic histologic findings of allergic angiitis and granulomatosis.[174] Eosinophilic infiltration of any organ should raise suspicion for CSS even in the absence of other findings.[111] Renal disease can be due to a pauci-immune GN or interstitial nephritis.[99, 128, 129, 175] In the appropriate clinical setting, a positive ANCA with MPO (or occasionally PR3) specificity is good evidence for CSS even when vasculitis is not identified on biopsy.[15, 111]

Diffuse alveolar hemorrhage occurs rarely in CSS, but subclinical alveolar bleeding may be very common in all of the ANCA-associated vasculitides.[55, 99, 176-179] Hemosiderin-laden macrophages (indicating prior leakage of red blood cells into the alveolar spaces) were identified in bronchoalveolar lavage fluid from 53% of WG and CSS patients in one study, compared to only a small percentage of patients with collagen vascular disease.[179] At autopsy, capillaritis has been reported in 40% of MPA patients and 31% of WG patients.[55, 177]

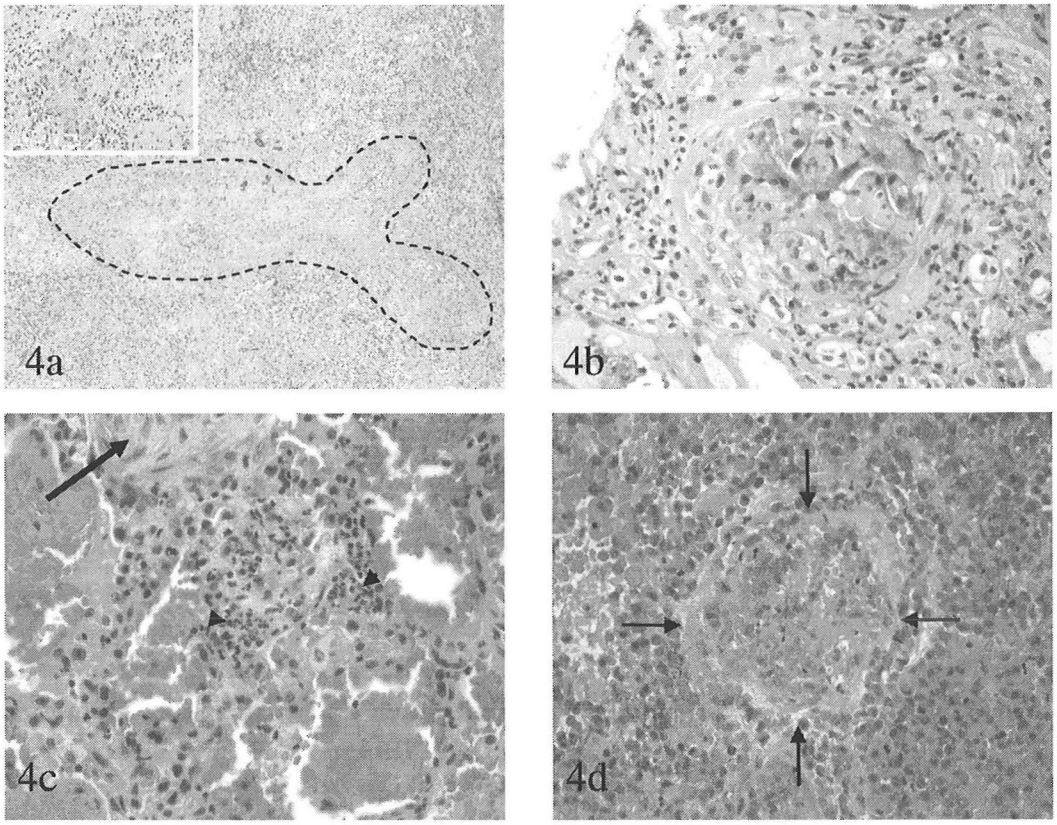

Figure 4. Histopathology of ANCA-associated vasculitis. 4a) necrotizing granulomatous vasculitis in a lung biopsy from a patient with WG. The dotted line outlines the vessel. There is infiltration of the vessel by a poorly formed granuloma (inset). Necrosis is visible in the upper right field. 4b) necrotizing and crescentic glomerulonephritis. 4c) lung biopsy from a patient with microscopic polyangiitis and diffuse alveolar hemorrhage. The specimen shows capillaritis with collections of neutrophils and nuclear debris within the alveolar septae (arrowheads). The adjacent airspaces are filled with blood. A focus of organizing pneumonia is also visible (arrow). 4d) Necrotic small vessel (arrows) in a patient with CSS. The vessel is infiltrated by numerous eosinophils. The adjacent alveolar spaces are filled with blood and eosinophils.

Pathogenesis of AASV

Anti-neutrophil cytoplasmic antibodies participate directly in the pathogenesis of small vessel vasculitis, which is illustrated in figure 5.[162, 180-183] In order to be fully activated by ANCA, the various effector cells in AASV (neutrophils, monocytes, lymphocytes, eosinophils and endothelial cells) must first be primed by proinflammatory cytokines. Studies have shown that circulating IL-6, IL-8 and TNF-α levels are increased in patients with active disease, but not during remission.[130, 184, 185] TNF-α and IL-1 levels are high at sites of active vascular inflammation as well.[186] It has been suggested that infection may play a role in the development of vasculitis simply by increasing TNF-α levels and facilitating leukocyte priming.[7, 180] ANCA, themselves, have also been shown to stimulate the production of proinflammatory cytokines like IL-1, IL-8, monocyte chemoattractant protein-1 (MCP-1) and leukotrienes.[187-191] ANCA-binding activates cytokine-primed neutrophils causing a respiratory burst and the release of lysosomal enzymes.[35] Neutrophils must first adhere to endothelium, however, before ANCA can fully

activate them.[192] ANCA facilitate this process as well by upregulating adhesion molecule expression (β2 integrins, ICAM-1, VCAM-1).[7, 193-197]

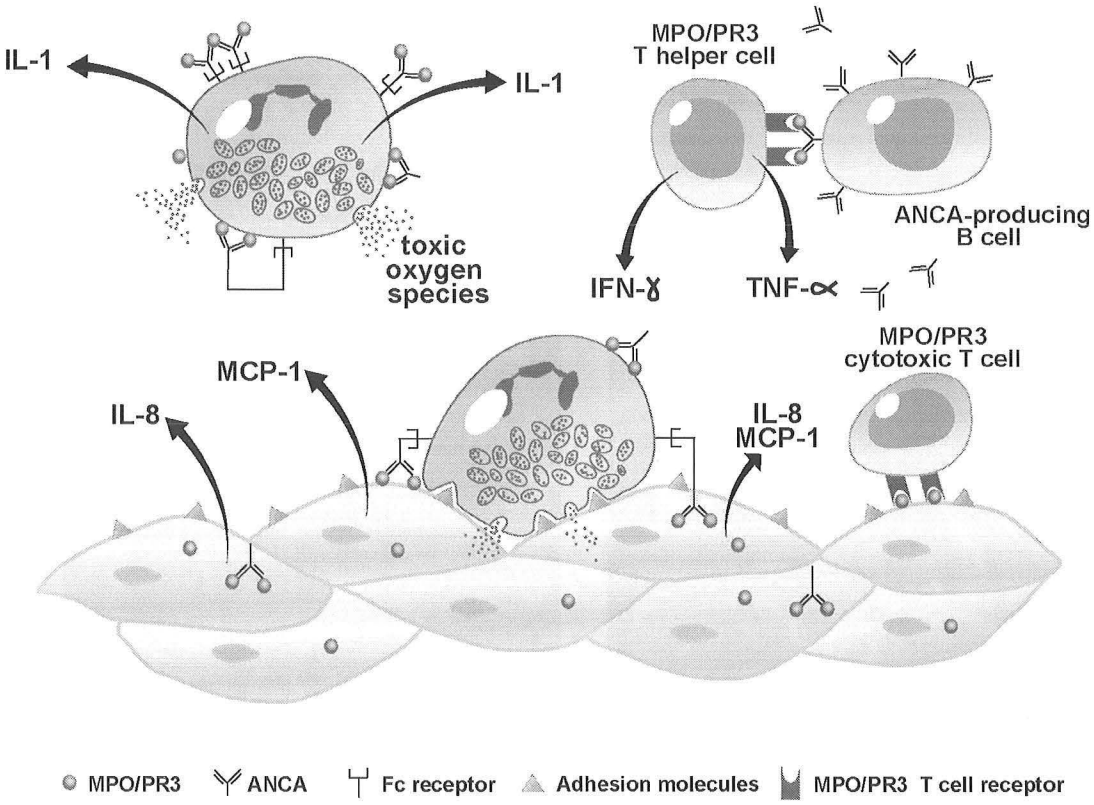

Figure 5. Schematic of major cellular and humoral events contributing to the pathogenesis of AASV. ANCA bind to, and activate, neutrophils and endothelial cells, augmenting the respiratory burst in PMNs, and leading to the elaboration of pro-inflammatory cytokines like IL-1, IL-8 and MCP-1. PR3 binding to endothelium has also been shown, *in vitro*, to elicit IL-8 and MCP-1 production, while also increasing endothelial apoptosis. ANCA promote antibody-dependent cellular cytotoxicity in the presence of neutrophils, contributing to endothelial injury. ANCA-specific T helper cells assist with B cell production of autoantibodies, and release additional cytokines that promote neutrophil and monocyte activation. Cytotoxic T cells with specificity for ANCA target antigens also contribute to vascular injury.

After neutrophils degranulate, cytoplasmic antigens including MPO and PR3 can bind to the neutrophil membrane. When ANCA interact with these proteins, the degree of cellular activation, adhesion molecule expression and oxidant liberation increase.[196, 198-200] In the presence of cytokines, endothelial cells may also express PR3 on their cell surface.[201] Free cationic PR3 and MPO can also bind directly to the anionic endothelium after release by degranulation. ANCA binding then promotes antibody-dependent cellular cytotoxicity in the presence of neutrophils.[202-207]

ANCA also trigger signal transduction pathways within primed endothelial cells that lead to impairment of endothelial barrier function.[208] IL-8 inhibits the transendothelial migration of neutrophils, which may result in additional bystander injury to the vascular surface.[162, 209] Injured and activated endothelial cells release even more proinflammatory substances that attract T cells and monocytes, leading to further damage and, in some cases, granuloma formation.[162]

Several lines of evidence in animal models have confirmed the pathogenicity of ANCA. When MPO antibodies are induced in mice, the animals develop necrotizing glomerulonephritis.[210, 211] Even in knockout mice that have no functioning lymphocytes, the infusion of anti-MPO antibodies produces a pauci-immune necrotizing, crescentic GN.[180, 212] When rats are immunized with human MPO, they develop cross-reactive MPO antibodies leading to pulmonary hemorrhage and necrotizing, crescentic GN.[213]

Apoptosis of neutrophils is associated with translocation of the normally sheltered PR3 and MPO antigens to the cell surface, but the ability of ANCA to induce neutrophil activation of these cells is actually decreased.[214, 215] Still, apoptosis may play a key role in the pathogenesis of AASV. Primed neutrophils exposed to ANCA undergo dysregulated apoptosis.[162] These cells fail to express an important consumption signal for scavenging phagocytes. Not only do more cells undergo programmed cell death, but they are cleared less efficiently as evidenced by the frequent appearance of cells with pyknotic nuclei and nuclear dust in biopsy specimens of capillaritis or leukocytoclastic vasculitis.[58] Their persistence in tissues may lead to continued inflammation or the actual induction of autoimmunity.[162, 215-220] In humans, dendritic cells, but not macrophages, have been shown to efficiently present antigen derived from apoptotic cells, stimulating a cytotoxic T cell response.[221] This may even be true for self-antigens. The clonal expansion of self-reactive T helper cells may facilitate the production of ANCA by B cells in this setting. In fact, when Brown Norway rats are injected with syngeneic apoptotic neutrophils (but not fresh neutrophils), they develop ANCA.[222] Interestingly, once ANCA are present, they further amplify neutrophil apoptosis, possibly creating a positive feedback loop and contributing to the development of AASV.[215, 223]

Under normal circumstances, there are few ANCA target molecules present on the cell surface of neutrophils or other cells. It appears, however, that most of the biological effects of ANCA occur via Fc receptor (FcR) dependent mechanisms.[191, 224-227] Certain FcR alleles, when engaged by ANCA, trigger a more intense oxidative burst,[225] and certain alleles have been associated with a greater risk of developing WG, and an increased rate of disease relapse.[228]

The role of anti-endothelial cell antibodies (AECA) in small vessel vasculitis is less clear. These antibodies have been reported to occur frequently in this setting by some authors, and uncommonly by others.[229-231] Under some circumstances, AECA may exert a direct cytotoxic effect on endothelial cells.[229, 232] AECA have also been shown to increase adhesion molecule expression and proinflammatory cytokine production by endothelial cells.[233] In CSS, AECA are found in patients with active and inactive disease.[234] They could simply represent an epiphenomenon related to endothelial cell damage.

The neutrophilic proteases targeted by ANCA are not merely degradative enzymes. They participate in complex biological functions including intracellular signaling.[235] PR3, for example, is linked to downregulation of myeloid differentiation. This process of feedback control may be defective in patients with ANCA, and contribute to excessive inflammation.[236] PR3, itself, has been shown to augment IL-8 and MCP-1 production by endothelial cells *in vitro*.[237-239] PR3 can also induce apoptosis in endothelial cells, leading to further vascular damage.[235, 240, 241] It is also found in normal lung, and is upregulated in alveolar tissue of patients with WG.[242] Within an individual, PR3 may be present on the cell membrane of some neutrophils, but absent on others. The size of the membrane PR3+ subset can range from 0-100% of the cells, but is constant in each person.[243] Patients with a high membrane PR3+ phenotype may be more likely to develop AASV.[243-245] Certain PR3 (or MPO) polymorphisms may also result in enhanced immunogenecity contributing to more autoantibody production.[236]

PR3 activity in normally limited by serum anti-proteases like α1-antitrypsin.[246] For MPO, normal scavenging appears to involve ceruloplasmin.[247] Interestingly, allelic alterations associated with α1-antitrypsin deficiency have been linked to the development of AASV.[246, 248-254] Patients with the Z phenotype have more widespread organ involvement and higher mortality.[249,

[254, 255] It also appears that ANCA, themselves, may block the normal inhibition of PR3 by α1-antitrypsin, allowing PR3 to incite vascular injury.[256, 257]

T lymphocytes are certainly important participants in the granulomatous response of WG and CSS, and in the glomerular lesions of rapidly progressive GN.[162, 258-260] There is evidence of excessive Th1 lymphocyte activity in WG. T cells from these patients elaborate increased amounts of TNF-α and IFN-γ.[261, 262] Serum markers of T cell activation have been shown to correlate with disease activity in WG.[234, 258, 263, 264] Autoreactive T cell populations specific for PR3 and MPO have been identified in patients with AASV.[265-268] These cells may assist B lymphocytes with the production of ANCA, or participate in direct cell-mediated cytotoxicity.[269] The adoptive transfer of anti-MPO specific lymphocytes in MPO-knockout mice immunized with MPO has been shown to cause glomerulonephritis and systemic necrotizing vasculitis (including pulmonary capillaritis).[212] While T cell responses (exogenous and autoimmune) are normally closely linked to HLA molecule expression, no consistent HLA associations have yet been identified in AASV.[269]

The major effector cells in CSS are eosinophils, lymphocytes and endothelial cells.[234, 270] Derangements in CD95 mediated apoptosis of eosinophils and lymphocytes, and oligoclonal T cell expansion has been identified in CSS.[271] Eosinophil products like eosinophilic cationic protein and major basic protein are important contributors to tissue damage in CSS. These proteins are cytotoxic, can activate complement and coagulation cascades, trigger the release of proinflammatory cytokines and upregulate adhesion molecule expression.[15]

There is increasing evidence that dysfunctional co-stimulatory pathways may also play a role in the pathogenesis of vasculitis.[272] Cytotoxic T lymphocyte associated antigen-4 (CTLA-4) is expressed on activated T cells and downregulates inflammation after binding to the antigen presenting cell.[272-274] Animals that are deficient in CTLA-4 develop fatal lymphoproliferation and vasculitis.[275, 276] Certain CTLA-4 polymorphisms have been associated with WG, and could contribute to the development of vasculitis by allowing for uncontrolled T cell activation by antigen.[277]

Cell adhesion molecules play an essential role in the interaction between circulating leukocytes and vascular endothelium. They permit attachment of white blood cells, provide co-stimulatory activation signals, and direct the migration of inflammatory cells into tissues.[197, 278] Adhesion molecule expression is clearly elevated in patients with vasculitis.[278-283] Polymorphisms in CD18, a leukocyte adhesion molecule, have also been associated with MPO-ANCA positive vasculitis.[284, 285]

Treatment of AASV

There is no doubt that combination therapy with cytotoxic agents and corticosteroids markedly reduces mortality and helps reclaim organ function in patients with AASV.[286] Unfortunately, it does so at a considerable physiologic price. Patients survive longer, but suffer from high rates of disease and treatment-related morbidity.[286] Once almost uniformly fatal diseases, the ANCA-associated vasculitides have been transformed into chronic, often relapsing disorders that may require several years of therapy.[287-289] The focus of initial therapy, of course, is the rapid induction of disease remission. The intensity of treatment, however, should be tailored to the severity of the presentation. Once the disease is controlled, a less toxic maintenance regimen can be introduced.[33, 94, 288] Unfortunately, a substantial proportion of patients will relapse after immunosuppression is tapered or discontinued, regardless of what drug regimen is initially employed.[13, 34, 99, 290, 291] Even in WG, where relapse rates are highest, the traditional NIH regimen based on daily oral cyclophosphamide (2 mg/kg/day maintained for one year after disease remission) can no longer be recommended.[292] That aggressive treatment results in complete disease remission in 75% to 90% of patients, but as many as one half will still relapse, and major

side effects of therapy are seen in over 40%.[34, 40] Treatment-related deaths may be related to infection, hemorrhagic cystitis, bladder cancer or hematologic malignancy.[34, 293-297]

The presence of generalized vasculitis or serious organ dysfunction (e.g., diffuse alveolar hemorrhage, severe GN, CNS, cardiac or GI involvement) at presentation probably warrants 3-6 months of daily, oral cyclophosphamide (CYC) before switching to IV CYC, methotrexate (MTX) or azathioprine (AZA).[4, 33, 298, 299] Methotrexate (20-25 mg/week) has been shown to induce remission in about three quarters of WG patients who did not have life-threatening disease manifestations at the time of presentation.[300, 301] It is effective in patients with active GN as well, but should not be used if the serum creatinine level is above 2 mg/dl, or if other serious complications such as DAH or CNS involvement are present.[112, 302] Relapses appear to occur most often when patients are taking ≤ 15 mg/week.[303] Both MTX and azathioprine (AZA) seem capable of maintaining CYC-induced remission.[33, 304] Longer initial courses of oral CYC do not appear to reduce the risk of relapse when immunosuppressive drugs are finally withdrawn, but are associated with more toxicity.[291] The optimal duration of maintenance therapy, unfortunately, has not been established.[33]

The debate over the relative efficacy of pulse, intravenous CYC (0.5-0.75 gm/m^2 every month) continues. Compared to daily, oral administration, pulse CYC is generally better tolerated, and associated with significantly less cumulative drug exposure.[305, 306] One study, however, suggested that WG patients with widespread disease and high ANCA titers (≥1:64) do not respond well to intermittent dosing.[307] The relapse rate has also been reported to be higher in some WG treatment trials utilizing pulse CYC.[305, 307, 308] In other studies, favorable responses were seen when patients who failed to achieve remission or relapsed on pulse CYC were converted to a daily, oral regimen.[305, 309] Notwithstanding, Haubitz and colleagues prospectively evaluated pulse, intravenous CYC versus daily, oral CYC in 47 WG and MPA patients with renal involvement and did not find a significant difference in relapse rate, renal outcome or patient survival.[306] In fact, 100% of patients in the pulse CYC group achieved remission compared to 84% in the daily, oral CYC group. One of the studies showing a higher relapse rate with pulse CYC also showed equivalent efficacy in remission induction, and actually a lower mortality rate (33%) in the IV group compared to the daily, oral CYC group (44%).[305] One study showed a much higher relapse rate for pulse CYC,[308] but many of the patients included had previously failed daily, oral CYC therapy. In a meta-analysis of 11 non-randomized treatment trials in AASV, pulse CYC was actually less likely to fail to induce remission when compared to daily, oral CYC.[310] Patients receiving pulse CYC had a significantly lower risk of developing leukopenia and infection. Mortality, the risk of developing end stage renal disease, and relapse rate were not statistically different in the two groups, although there was a trend toward a higher relapse rate in patients treated with pulse CYC.[310] For patients with CSS who require cytotoxic therapy, and for most patients with MPA, pulse CYC is generally preferred unless immediately life-threatening disease is present.[311]

Corticosteroids are usually employed at an initial dose of 1 mg/kg/day along with cytotoxic therapy until significant clinical improvement is seen. For patients with advanced disease (e.g., DAH or severe GN), pulse methylprednisolone (250 mg IV every six hours) may be given for three days. Steroids alone may control upper airway disease and improve systemic symptoms, but they are not sufficient to prevent progression of pulmonary or renal disease.[34, 40, 87, 312-314] In most cases, prednisone can be tapered to 20-30 mg/day by two to three months, and it can often be discontinued by six to twelve months. Some authors recommend tapering glucocorticoids on an alternate day regimen to limit side effects (including infection risk).[1, 289, 292, 315]

While corticosteroids are the cornerstone of therapy for CSS, concomitant cytotoxic therapy is warranted in patients who present with cardiac involvement, significant mesenteric ischemia, CNS involvement or RPGN, and for others who respond poorly to corticosteroids alone, or relapse.[112] In patients that can be managed with corticosteroids as monotherapy, the

response is often brisk, and tapering can begin within one month.[11, 102] However, in Solans' series of 32 patients, only 40% could be managed with corticosteroids alone.[316]

Upper airway relapse can be significantly reduced by the addition of trimethoprim/sulfamethoxazole (TMP/SMX), but major organ system flares cannot.[24, 304, 317-319] Some authors have recommended an aggressive regimen of nasal irrigation, nasal steroids and antibiotics (TMP/SMX or other) for isolated upper airway flares, followed by oral steroids or MTX if that is ineffective.[85]

Intravenous immunoglobulin (IVIG) has shown benefit in some patients with AASV.[320-324] In the only randomized, placebo controlled study, a single course of IVIG resulted in decreased disease activity among persistently active (despite conventional therapy) AASV patients, but not beyond 3 months.[322] No patients, however, received repeated dosing of IVIG. An immunosuppressant drug-sparing effect was not identified, and the IVIG group experienced more adverse events.[322] The authors suggested that the use of IVIG was, therefore, not supported. However, when 26 patients with active systemic vasculitis were given open label treatment with IVIG, 13 patients entered full remission, and all patients experienced clinical improvement.[325] A number of these patients had disease refractory to steroids and cytotoxic agents, and others were previously untreated. After 12 months, clinical benefit was maintained in 18 of the patients. In another study, four of six new AASV patients with early disease entered full clinical remission lasting at least one year after a single course of IVIG while receiving no immunosuppressive treatment.[320] IVIG has also shown a marked clinical benefit in a handful of patients with CSS, and can be considered in patients refractory to, or intolerant of, the usual therapies.[326] The remission of systemic vasculitis may be associated with the generation of anti-idiotypic antibodies against ANCA.[327, 328] Stimulation of idiotypic regulation by IVIG may be the most important mechanism by which this therapy aids in the restoration of self-tolerance and clinical remission of the vasculitis.[329, 330] IVIG may cause reversible impairment of renal function in patients with glomerulonephritis.[331] It carries some risk of viral transmission and has a number of potential infusion-related side effects, but it is generally safe.[331] It is currently utilized mostly in individuals with fulminant or refractory disease, but further study may reveal a broader role for IVIG in the management of AASV.

The precise role of plasma exchange in the management of AASV is similarly ill-defined. Its use has largely been limited to patients with fulminant presentations as well.[17, 332] The purpose of plasma exchange is to remove pathogenic ANCA from the circulation. Other desirable effects may be linked to the removal of proinflammatory cytokines, complement and coagulation factors.[286] Plasma exchange has been reported to improve outcomes in patients with AASV and either DAH or dialysis-dependent renal failure.[17, 333-337] Two studies, however, failed to show additional benefit to steroid or combination steroid/cytotoxic therapy in other patients with MPA or CSS.[338, 339] It has been suggested that initiation of plasma exchange in patients with severe pulmonary-renal syndromes or rapidly progressive GN may be wise while awaiting the completion of the laboratory and histopathologic assessment.[17]

Although no data exist to confirm their benefit, a variety of adjunctive measures may prove to be useful in dealing with AASV patients. The association in MPO-ANCA patients between proteinuria and poor long-term renal outcome argues for an aggressive strategy of blood pressure control and angiotensin converting enzyme inhibitor use in these patients.[88] Prophylactic antibiotics may be useful to prevent opportunistic infection, and to reduce nasal carriage of staphylococcal organisms that have been linked to disease relapse in WG.[292, 340, 341] Local therapies like intranasal mupirocin (which has excellent anti-staphylococcal activity) or antibiotics with both direct anti-inflammatory, immunomodulating and antimicrobial effects (i.e., macrolides or tetracyclines) could prove useful.

For patients with refractory, life-threatening disease, immune ablation and stem cell rescue can be considered.[342] This allows for the deletion of autoreactive T cell clones, and is

being used with increasing frequency, in an experimental setting, for vasculitis and collagen vascular disease.[342]

Ultimately, targeted biological therapies should allow for control of these vasculitic illnesses, saving patients from the severe untoward effects associated with months or years of cytotoxic and glucocorticoid treatment.[24, 272, 343] For example, interferon-α has demonstrated efficacy in diseases characterized by excess Th2 responses and hypereosinophilia, and has been useful in patients with CSS.[343-347] Unfortunately, this drug has been associated with cardiac toxicity that could limit its use in this setting.[348] Monoclonal antibodies directed at T lymphocytes have shown promise, anecdotally, in the treatment of various vasculitides, including some otherwise refractory cases.[6, 349, 350] Rabbit anti-thymocyte globulin infusion managed to effect a partial or complete remission in four cases of WG refractory to conventional treatment.[351] Eternacept, an anti-tumor necrosis factor agent, has been associated with improvement in disease activity scores and few adverse events in a preliminary trial to assess safety in WG.[352] A randomized treatment trial in WG is underway. Interferon-γ is responsible for macrophage activation leading to increased production of reactive oxygen species and metalloproteinases, increased adhesion molecule expression and growth factor elaboration that promotes intimal hyperplasia.[272, 353-355] Blocking its effects could also prove useful in patients with AASV. Inhibition of adhesion molecule function may provide another important therapeutic option in patients with systemic vasculitis.[278] Treatment with an antibody to the integrin VLA-1 in a rat model of crescentic GN led to improved serum creatinine, improved renal survival, and decreased fibronectin and type IV collagen deposition.[356]

The Natural History of AASV

The natural history of AASV is variable. Some patients with AASV have several months of prodromal symptoms, while others present with fulminant, life-threatening disease manifestations with little forewarning.[87, 286, 332] Overall, relapses occur in 25-50% of patients.[13, 34, 99, 158, 291, 294, 296, 357] Patients with PR3-ANCA have a higher risk of relapse compared to those with MPO-ANCA.[358] Patients with sinus involvement and elevated serum creatinine levels are also more likely to relapse.[317, 359] CSS appears to have slightly higher remission rates (80-90%) and slightly lower relapse rates (25%) relative to other ANCA-associated systemic vasculitis patients.[11, 99, 102, 175, 294, 316] For the most part, relapses are not as severe as the initial presentation. When they do occur, relapses tend to affect the same organ systems that were involved at presentation.[360]

With combination cytotoxic and corticosteroid therapy, the five year mortality for WG and MPA has been reduced to around 20%.[4] In a follow-up study of 96 CSS patients, the survival at 6.5 years was 72%.[99] In Solans' analysis of 32 CSS patients, however, the long term survival was 90% at 5 years and beyond.[316] In this group, additional immunosuppressive agents were appropriately added to patients with severe neurological, cardiac or gastrointestinal involvement. Mortality in AASV is particularly high among elderly patients and those with renal disease (creatinine > 1.6 mg/dl, or proteinuria > 1 gm/day).[123, 286, 359, 361] Other factors identifying patients at increased risk for dying include diffuse alveolar hemorrhage, cardiomyopathy, gastrointestinal or central nervous system involvement.[58, 123] Mortality is higher in patients with c-ANCA, and in those who do not receive cyclophosphamide in their treatment regimen.[359]

It appears that much of the organ damage associated with AASV occurs early.[362] Part of this may be attributed to long average delays of 5-17 months from the onset of symptoms until diagnosis and initiation of treatment.[34, 37, 363] The most important determinant of outcome in AASV is the presence of renal disease, and the serum creatinine level at presentation seems to be the best predictor of renal outcome.[296, 359, 360] The presence of higher amounts of proteinuria at presentation is also indicative of a worse long-term renal prognosis.[154] Patients who do require renal replacement therapy at the time of presentation can recover sufficient function to have a

substantial dialysis-free interval.[86, 335, 364, 365] In a retrospective study of 246 new patients with ANCA-associated renal vasculitis, 56 patients presented with a creatinine clearance above 6 mg/dl, and 55% of these were able to achieve dialysis independence.[86] The long term renal prognosis, however, is poor for these individuals.[357, 366] The renal outcome of AASV patients after kidney transplantation, interestingly, is not different from other causes of end stage renal disease.[367] Relapses of vasculitis are, in fact, uncommon in this setting.[368]

In some cases, it is hard to distinguish a disease flare from an opportunistic infection or other drug-related untoward effect. When patients experience clinical deterioration after initial improvement on a stable immunosuppressive regimen, they must be presumed to have an infection or other treatment related side effect until proven otherwise.[112] In a study of infectious complications among 207 vasculitis patients receiving cyclophosphamide where leukopenia was specifically avoided, 10% were still found to develop serious infections, often within the first three months of therapy.[369] Glucocorticoid use further increases this risk.

Many patients will suffer from some type of permanent morbidity in the form of chronic renal insufficiency, visual or hearing impairment, chronic rhinosinusitis, long-term side effects of drug therapy, or, in the case of CSS, chronic steroid-dependent asthma.[2, 34, 270] Hoffman and colleagues found that 80% of WG patients reported long-term limitations with regard to activities of daily living, with one third being forced to accept total disability.[363]

Summary

The ANCA-associated vasculitides are a group of closely related systemic, small vessel inflammatory disorders with protean clinical manifestations. Wegener's granulomatosis is best known for necrotizing, granulomatous upper and lower respiratory tract disease, kidney involvement and c-ANCA (anti-PR3) positivity. Churg Strauss syndrome, another granulomatous vasculitis, is strongly associated with asthma and eosinophilia. Major organs involved in CSS include the lung, skin, heart and nervous system. It is usually associated with p-ANCA (anti-MPO) positivity. Microscopic polyangiitis is essentially a diagnosis of exclusion. It does not have specific clinical or histopathologic findings that distinguish it from other AASV. Glomerulonephritis is almost always seen in this patient group, and it is usually associated with MPO-ANCA. Skin, GI and lung involvement are fairly common, but without granulomas. MPA is the most common cause of the classic pulmonary-renal syndrome with glomerulonephritis and diffuse alveolar hemorrhage.

Heritable factors predisposing individuals to the development of AASV (or affecting disease phenotype) may include allelic variations in MPO and PR3 (the ANCA target antigens), Fc receptors on leukocytes, adhesion molecules, α-1 antitrypsin (or other anti-proteases), and HLA antigens. Defective clearance of apoptotic cells may augment the inflammatory process in AASV, and play an important role in the development of ANCA and autoreactive T cell clones. Disease expression likely depends on the complex interaction of several endogenous and exogenous factors. A certain genetic makeup may be required for the development of systemic vasculitis, but infection or other environmental factors may provide the inflammatory stimulus needed to prime leukocytes and trigger vascular inflammation in ANCA-positive patients.

Rapid recognition of these disorders is key, preferably prior to the onset of widespread organ damage. The probability of suffering permanent morbidity is high when patients present with multisystem disease, even if the initial treatment is successful. Rapid induction of disease remission is important, particularly when vital organs are at risk; but initial treatment should be customized to the severity of the presentation, and may include cytotoxics, corticosteroids, plasma exchange and IVIG. Once remission is achieved, less toxic maintenance regimens are employed to reduce the chance of relapse. Relapse is, nevertheless, a common occurrence, and the optimal duration of maintenance therapy is simply not known. Ultimately, targeted biological therapies are expected to assume a major role in the control of AASV.

References

1. Langford CA. 15. Vasculitis. *J Allergy Clin Immunol.* Feb 2003;111(2 Suppl):S602-612.
2. Gatenby PA. Vasculitis--diagnosis and treatment. *Aust N Z J Med.* Oct 1999;29(5):662-677.
3. Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med.* Nov 20 1997;337(21):1512-1523.
4. Savage CO, Harper L, Adu D. Primary systemic vasculitis. *Lancet.* Feb 22 1997;349(9051):553-558.
5. Hoffman GS. Classification of the systemic vasculitides: antineutrophil cytoplasmic antibodies, consensus and controversy. *Clin Exp Rheumatol.* Mar-Apr 1998;16(2):111-115.
6. Gross WL. Systemic necrotizing vasculitis. *Baillieres Clin Rheumatol.* May 1997;11(2):259-284.
7. D'Agati V. Antineutrophil cytoplasmic antibody and vasculitis: much more than a disease marker. *J Clin Invest.* Oct 2002;110(7):919-921.
8. DeRemee RA. Antineutrophil cytoplasmic autoantibody-associated diseases: a pulmonologist's perspective. *Am J Kidney Dis.* Aug 1991;18(2):180-183.
9. Franssen C, Gans R, Kallenberg C, Hageluken C, Hoorntje S. Disease spectrum of patients with antineutrophil cytoplasmic autoantibodies of defined specificity: distinct differences between patients with anti-proteinase 3 and anti-myeloperoxidase autoantibodies. *J Intern Med.* Sep 1998;244(3):209-216.
10. Mansi IA, Opran A, Rosner F. ANCA-associated small-vessel vasculitis. *Am Fam Physician.* Apr 15 2002;65(8):1615-1620.
11. Lhote F, Cohen P, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome. *Lupus.* 1998;7(4):238-258.
12. Guillevin L, Lhote F. Polyarteritis nodosa and microscopic polyangiitis. *Clin Exp Immunol.* Jul 1995;101 Suppl 1:22-23.
13. Guillevin L, Durand-Gasselin B, Cevallos R, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum.* Mar 1999;42(3):421-430.
14. Duna GF, Galperin C, Hoffman GS. Wegener's granulomatosis. *Rheum Dis Clin North Am.* Nov 1995;21(4):949-986.
15. Cottin V, Cordier JF. Churg-Strauss syndrome. *Allergy.* Jun 1999;54(6):535-551.
16. Conron M, Beynon HL. Churg-Strauss syndrome. *Thorax.* Oct 2000;55(10):870-877.
17. Falk RJ, Nachman PH, Hogan SL, Jennette JC. ANCA glomerulonephritis and vasculitis: a Chapel Hill perspective. *Semin Nephrol.* May 2000;20(3):233-243.
18. Frankel SK, Sullivan EJ, Brown KK. Vasculitis: Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, polyarteritis nodosa, and Takayasu arteritis. *Crit Care Clin.* Oct 2002;18(4):855-879.
19. Watts RA, Scott DG. Classification and epidemiology of the vasculitides. *Baillieres Clin Rheumatol.* May 1997;11(2):191-217.
20. Watts RA, Jolliffe VA, Carruthers DM, Lockwood M, Scott DG. Effect of classification on the incidence of polyarteritis nodosa and microscopic polyangiitis. *Arthritis Rheum.* Jul 1996;39(7):1208-1212.
21. Watts RA, Carruthers DM, Scott DG. Epidemiology of systemic vasculitis: changing incidence or definition? *Semin Arthritis Rheum.* Aug 1995;25(1):28-34.
22. Watts RA, Scott DG. Epidemiology of the vasculitides. *Curr Opin Rheumatol.* Jan 2003;15(1):11-16.
23. Watts RA, Scott DG, Lane SE. Epidemiology of Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome. *Cleve Clin J Med.* 2002;69 Suppl 2:SII84-86.
24. Langford CA, Hoffman GS. Rare diseases.3: Wegener's granulomatosis. *Thorax.* Jul 1999;54(7):629-637.
25. Martin RM, Wilton, L.V., Mann, R.D. Prevalence of Churg-Strauss syndrome, vasculitis, eosinophilia and associated conditions: retrospective analysis of 58 prescription-event monitoring cohort studies. *Pharmacoepidemiol Drug Saf.* 1999;8:179-189.
26. Kallenberg CG, Tervaert JW. What is new with anti-neutrophil cytoplasmic antibodies: diagnostic, pathogenetic and therapeutic implications. *Curr Opin Nephrol Hypertens.* May 1999;8(3):307-315.
27. Kallenberg CG, Brouwer E, Weening JJ, Tervaert JW. Anti-neutrophil cytoplasmic antibodies: current diagnostic and pathophysiological potential. *Kidney Int.* Jul 1994;46(1):1-15.
28. Lie JT. Histopathologic specificity of systemic vasculitis. *Rheum Dis Clin North Am.* Nov 1995;21(4):883-909.
29. Luqmani RA, Robinson H. Introduction to, and classification of, the systemic vasculitides. *Best Pract Res Clin Rheumatol.* Jun 2001;15(2):187-202.
30. Jennette JC, Thomas DB, Falk RJ. Microscopic polyangiitis (microscopic polyarteritis). *Semin Diagn Pathol.* Feb 2001;18(1):3-13.
31. Jennette JC, Wilkman AS, Falk RJ. Anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and vasculitis. *Am J Pathol.* Nov 1989;135(5):921-930.
32. Falk RJ, Jennette JC. ANCA small-vessel vasculitis. *J Am Soc Nephrol.* Feb 1997;8(2):314-322.
33. 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.* Jul 3 2003;349(1):36-44.

34. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med.* Mar 15 1992;116(6):488-498.
35. Falk RJ, Hogan S, Carey TS, Jennette JC. Clinical course of anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and systemic vasculitis. The Glomerular Disease Collaborative Network. *Ann Intern Med.* Nov 1 1990;113(9):656-663.
36. Noritake DT, Weiner SR, Bassett LW, Paulus HE, Weisbart R. Rheumatic manifestations of Wegener's granulomatosis. *J Rheumatol.* Oct 1987;14(5):949-951.
37. Anderson G, Coles ET, Crane M, et al. Wegener's granuloma. A series of 265 British cases seen between 1975 and 1985. A report by a sub-committee of the British Thoracic Society Research Committee. *Q J Med.* Jun 1992;83(302):427-438.
38. Specks U, DeRemee RA. Granulomatous vasculitis. Wegener's granulomatosis and Churg-Strauss syndrome. *Rheum Dis Clin North Am.* May 1990;16(2):377-397.
39. Murty GE. Wegener's granulomatosis: otorhinolaryngological manifestations. *Clin Otolaryngol.* Aug 1990;15(4):385-393.
40. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med.* Jan 1983;98(1):76-85.
41. DeRemee RA. Extrapulmonary manifestations of Wegener's granulomatosis and other respiratory vasculitides. *Semin Respir Med.* 1988;9:403-408.
42. McCaffrey TV, McDonald TJ, Facer GW, DeRemee RA. Otologic manifestations of Wegener's granulomatosis. *Otolaryngol Head Neck Surg.* Sep-Oct 1980;88(5):586-593.
43. Guyot JP, Baud C, Montandon P. Wegener's granulomatosis with otological disorders as primary symptoms. *ORL J Otorhinolaryngol Relat Spec.* 1990;52(5):327-334.
44. Robin JB, Schanzlin DJ, Meisler DM, deLuise VP, Clough JD. Ocular involvement in the respiratory vasculitides. *Surv Ophthalmol.* Sep-Oct 1985;30(2):127-140.
45. Haynes BF, Fishman ML, Fauci AS, Wolff SM. The ocular manifestations of Wegener's granulomatosis. Fifteen years experience and review of the literature. *Am J Med.* Jul 1977;63(1):131-141.
46. Charles SJ, Meyer PA, Watson PG. Diagnosis and management of systemic Wegener's granulomatosis presenting with anterior ocular inflammatory disease. *Br J Ophthalmol.* Apr 1991;75(4):201-207.
47. Bullen CL, Liesegang TJ, McDonald TJ, DeRemee RA. Ocular complications of Wegener's granulomatosis. *Ophthalmology.* Mar 1983;90(3):279-290.
48. Lie JT. Wegener's granulomatosis: histological documentation of common and uncommon manifestations in 216 patients. *Vasa.* Nov 1997;26(4):261-270.
49. Cordier JF, Valeyre D, Guillevin L, Loire R, Brechot JM. Pulmonary Wegener's granulomatosis. A clinical and imaging study of 77 cases. *Chest.* Apr 1990;97(4):906-912.
50. Seo JB, Im JG, Chung JW, et al. Pulmonary vasculitis: the spectrum of radiological findings. *Br J Radiol.* Nov 2000;73(875):1224-1231.
51. Papiris SA, Manoussakis MN, Drosos AA, Kontogiannis D, Constantopoulos SH, Moutsopoulos HM. Imaging of thoracic Wegener's granulomatosis: the computed tomographic appearance. *Am J Med.* Nov 1992;93(5):529-536.
52. Kuhlman JE, Hruban RH, Fishman EK. Wegener granulomatosis: CT features of parenchymal lung disease. *J Comput Assist Tomogr.* Nov-Dec 1991;15(6):948-952.
53. Weir IH, Muller NL, Chiles C, Godwin JD, Lee SH, Kullnig P. Wegener's granulomatosis: findings from computed tomography of the chest in 10 patients. *Can Assoc Radiol J.* Feb 1992;43(1):31-34.
54. Specks U. Diffuse alveolar hemorrhage syndromes. *Curr Opin Rheumatol.* Jan 2001;13(1):12-17.
55. Travis WD, Hoffman GS, Leavitt RY, Pass HI, Fauci AS. Surgical pathology of the lung in Wegener's granulomatosis. Review of 87 open lung biopsies from 67 patients. *Am J Surg Pathol.* Apr 1991;15(4):315-333.
56. Leatherman JW, Davies SF, Hoidal JR. Alveolar hemorrhage syndromes: diffuse microvascular lung hemorrhage in immune and idiopathic disorders. *Medicine (Baltimore).* Nov 1984;63(6):343-361.
57. Green RJ, Ruoss SJ, Kraft SA, Duncan SR, Berry GJ, Raffin TA. Pulmonary capillaritis and alveolar hemorrhage. Update on diagnosis and management. *Chest.* Nov 1996;110(5):1305-1316.
58. Schwarz MI, Brown KK. Small vessel vasculitis of the lung. *Thorax.* Jun 2000;55(6):502-510.
59. Myers JL, Katzenstein AL. Wegener's granulomatosis presenting with massive pulmonary hemorrhage and capillaritis. *Am J Surg Pathol.* Nov 1987;11(11):895-898.
60. Sanchez-Masiques J, Ettensohn DB. Alveolar hemorrhage in Wegener's granulomatosis. *Am J Med Sci.* Jun 1989;297(6):390-393.
61. Primack SL, Miller RR, Muller NL. Diffuse pulmonary hemorrhage: clinical, pathologic, and imaging features. *AJR Am J Roentgenol.* Feb 1995;164(2):295-300.
62. Albelda SM, Gefter WB, Epstein DM, Miller WT. Diffuse pulmonary hemorrhage: a review and classification. *Radiology.* Feb 1985;154(2):289-297.

63. De Lassence A, Fleury-Feith J, Escudier E, Beaune J, Bernaudin JF, Cordonnier C. Alveolar hemorrhage. Diagnostic criteria and results in 194 immunocompromised hosts. *Am J Respir Crit Care Med.* Jan 1995;151(1):157-163.

64. Kahn FW, Jones JM, England DM. Diagnosis of pulmonary hemorrhage in the immunocompromised host. *Am Rev Respir Dis.* Jul 1987;136(1):155-160.

65. Daum TE, Specks U, Colby TV, et al. Tracheobronchial involvement in Wegener's granulomatosis. *Am J Respir Crit Care Med.* Feb 1995;151(2 Pt 1):522-526.

66. Aberle DR, Gamsu G, Lynch D. Thoracic manifestations of Wegener granulomatosis: diagnosis and course. *Radiology.* Mar 1990;174(3 Pt 1):703-709.

67. Maskell GF, Lockwood CM, Flower CD. Computed tomography of the lung in Wegener's granulomatosis. *Clin Radiol.* Dec 1993;48(6):377-380.

68. Lebovics RS, Hoffman GS, Leavitt RY, et al. The management of subglottic stenosis in patients with Wegener's granulomatosis. *Laryngoscope.* Dec 1992;102(12 Pt 1):1341-1345.

69. Langford CA, Sneller MC, Hallahan CW, et al. Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis. *Arthritis Rheum.* Oct 1996;39(10):1754-1760.

70. De Oreo GA. Wegener's granulomatosis. *Arch Dermatol.* 1960;81:169.

71. Irvine AD, Bruce IN, Walsh M, Burrows D, Handley J. Dermatological presentation of disease associated with antineutrophil cytoplasmic antibodies: a report of two contrasting cases and a review of the literature. *Br J Dermatol.* May 1996;134(5):924-928.

72. Daoud MS, Gibson LE, DeRemee RA, Specks U, el-Azhary RA, Su WP. Cutaneous Wegener's granulomatosis: clinical, histopathologic, and immunopathologic features of thirty patients. *J Am Acad Dermatol.* Oct 1994;31(4):605-612.

73. Davis MD, Daoud MS, McEvoy MT, Su WP. Cutaneous manifestations of Churg-Strauss syndrome: a clinicopathologic correlation. *J Am Acad Dermatol.* Aug 1997;37(2 Pt 1):199-203.

74. Haworth SJ, Pusey CD. Severe intestinal involvement in Wegener's granulomatosis. *Gut.* Nov 1984;25(11):1296-1300.

75. Tupler RH, McCuskey WH. Wegener granulomatosis of the colon: CT and histologic correlation. *J Comput Assist Tomogr.* Mar-Apr 1991;15(2):314-316.

76. Uribe A, Goobar J, Rubio C. Colonic ulcerations in Wegener's granulomatosis. *J Rheumatol.* Sep 1991;18(9):1429-1430.

77. Geraghty J, Mackay IR, Smith DC. Intestinal perforation in Wegener's granulomatosis. *Gut.* Apr 1986;27(4):450-451.

78. Lie JT. Vasculitis and the gut: unwitting partners or strange bedfellows. *J Rheumatol.* May 1991;18(5):647-649.

79. Tokuda M, Kurata N, Daikuhara H, et al. Small intestinal perforation in Wegener's granulomatosis. *J Rheumatol.* Apr 1989;16(4):547-549.

80. Wilson RT, Dean PJ, Upshaw JD, Wruble LD. Endoscopic appearance of Wegener's granulomatosis involving the colon. *Gastrointest Endosc.* Oct 1987;33(5):388-389.

81. Moore PM, Cupps TR. Neurological complications of vasculitis. *Ann Neurol.* Aug 1983;14(2):155-167.

82. Moore PM, Calabrese LH. Neurologic manifestations of systemic vasculitides. *Semin Neurol.* Dec 1994;14(4):300-306.

83. Nishino H, Rubino FA, DeRemee RA, Swanson JW, Parisi JE. Neurological involvement in Wegener's granulomatosis: an analysis of 324 consecutive patients at the Mayo Clinic. *Ann Neurol.* Jan 1993;33(1):4-9.

84. Drachman DA. Neurological complications of Wegener's granulomatosis. *Arch Neurol.* 1963;8:145.

85. Langford CA. Wegener granulomatosis. *Am J Med Sci.* Jan 2001;321(1):76-82.

86. Booth AD, Almond MK, Burns A, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis.* Apr 2003;41(4):776-784.

87. Savage CO, Winearls CG, Evans DJ, Rees AJ, Lockwood CM. Microscopic polyarteritis: presentation, pathology and prognosis. *Q J Med.* Aug 1985;56(220):467-483.

88. Franssen CF, Stegeman CA, Kallenberg CG, et al. Antiproteinase 3- and antimyeloperoxidase-associated vasculitis. *Kidney Int.* Jun 2000;57(6):2195-2206.

89. Guillevin L, Lhote F, Gherardi R. Polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: clinical aspects, neurologic manifestations, and treatment. *Neurol Clin.* Nov 1997;15(4):865-886.

90. Niles JL, Bottinger EP, Saurina GR, et al. The syndrome of lung hemorrhage and nephritis is usually an ANCA-associated condition. *Arch Intern Med.* Feb 26 1996;156(4):440-445.

91. Shin MS, Young KR, Ho KJ. Wegener's granulomatosis upper respiratory tract and pulmonary radiographic manifestations in 30 cases with pathogenetic consideration. *Clin Imaging.* Mar-Apr 1998;22(2):99-104.

92. Lhote F, Cohen P, Genereau T, Gayraud M, Guillevin L. Microscopic polyangiitis: clinical aspects and treatment. *Ann Med Interne (Paris).* 1996;147(3):165-177.

93. Lauque D, Cadranel J, Lazor R, et al. Microscopic polyangiitis with alveolar hemorrhage. A study of 29 cases and review of the literature. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). *Medicine (Baltimore).* Jul 2000;79(4):222-233.

94. Guillevin L, Lhote F. Treatment of polyarteritis nodosa and microscopic polyangiitis. *Arthritis Rheum.* Dec 1998;41(12):2100-2105.

95. Serra A, Cameron JS, Turner DR, et al. Vasculitis affecting the kidney: presentation, histopathology and long-term outcome. *Q J Med.* Spring 1984;53(210):181-207.

96. D'Agati V, Chander P, Nash M, Mancilla-Jimenez R. Idiopathic microscopic polyarteritis nodosa: ultrastructural observations on the renal vascular and glomerular lesions. *Am J Kidney Dis.* Jan 1986;7(1):95-110.

97. Adu D, Howie AJ, Scott DG, Bacon PA, McGonigle RJ, Micheal J. Polyarteritis and the kidney. *Q J Med.* Mar 1987;62(239):221-237.

98. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine (Baltimore).* Mar 1984;63(2):65-81.

99. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore).* Jan 1999;78(1):26-37.

100. Eustace JA, Nadasdy T, Choi M. Disease of the month. The Churg Strauss Syndrome. *J Am Soc Nephrol.* Sep 1999;10(9):2048-2055.

101. Guillevin L, Guittard T, Bletry O, Godeau P, Rosenthal P. Systemic necrotizing angiitis with asthma: causes and precipitating factors in 43 cases. *Lung.* 1987;165(3):165-172.

102. Cohen P, Guillevin L, Baril L, Lhote F, Noel LH, Lesavre P. Persistence of antineutrophil cytoplasmic antibodies (ANCA) in asymptomatic patients with systemic polyarteritis nodosa or Churg-Strauss syndrome: follow-up of 53 patients. *Clin Exp Rheumatol.* Mar-Apr 1995;13(2):193-198.

103. Chumbley LC, Harrison EG, Jr., DeRemee RA. Allergic granulomatosis and angiitis (Churg-Strauss syndrome). Report and analysis of 30 cases. *Mayo Clin Proc.* Aug 1977;52(8):477-484.

104. Gross WL. Churg-Strauss syndrome: update on recent developments. *Curr Opin Rheumatol.* Jan 2002;14(1):11-14.

105. Degesys GE, Mintzer RA, Vrla RF. Allergic granulomatosis: Churg-Strauss syndrome. *AJR Am J Roentgenol.* Dec 1980;135(6):1281-1282.

106. Weisbrod GL. Pulmonary angiitis and granulomatosis: a review. *Can Assoc Radiol J.* Jun 1989;40(3):127-134.

107. Worthy SA, Muller NL, Hansell DM, Flower CD. Churg-Strauss syndrome: the spectrum of pulmonary CT findings in 17 patients. *AJR Am J Roentgenol.* Feb 1998;170(2):297-300.

108. Buschman DL, Waldron JA, Jr., King TE, Jr. Churg-Strauss pulmonary vasculitis. High-resolution computed tomography scanning and pathologic findings. *Am Rev Respir Dis.* Aug 1990;142(2):458-461.

109. Staples CA. Pulmonary angiitis and granulomatosis. *Radiol Clin North Am.* Sep 1991;29(5):973-982.

110. Erzurum SC, Underwood GA, Hamilos DL, Waldron JA. Pleural effusion in Churg-Strauss syndrome. *Chest.* Jun 1989;95(6):1357-1359.

111. Churg A. Recent advances in the diagnosis of Churg-Strauss syndrome. *Mod Pathol.* Dec 2001;14(12):1284-1293.

112. Stone JH, Calabrese LH, Hoffman GS, Pusey CD, Hunder GG, Hellmann DB. Vasculitis. A collection of pearls and myths. *Rheum Dis Clin North Am.* Nov 2001;27(4):677-728, v.

113. Schwartz RA, Churg J. Churg-Strauss syndrome. *Br J Dermatol.* Sep 1992;127(3):199-204.

114. Vogel PS, Nemer J, Sau P, Hnatiuk O. Churg-Strauss syndrome. *J Am Acad Dermatol.* Nov 1992;27(5 Pt 2):821-824.

115. Lhote F, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome. Clinical aspects and treatment. *Rheum Dis Clin North Am.* Nov 1995;21(4):911-947.

116. Fraioli P, Barberis M, Rizzato G. Gastrointestinal presentation of Churg Strauss syndrome. *Sarcoidosis.* Mar 1994;11(1):42-45.

117. Guillevin L, Lhote F, Gallais V, et al. Gastrointestinal tract involvement in polyarteritis nodosa and Churg-Strauss syndrome. *Ann Med Interne (Paris).* 1995;146(4):260-267.

118. Kurita M, Niwa Y, Hamada E, et al. Churg-Strauss syndrome (allergic granulomatous angiitis) with multiple perforating ulcers of the small intestine, multiple ulcers of the colon, and mononeuritis multiplex. *J Gastroenterol.* Apr 1994;29(2):208-213.

119. Sharma MC, Safaya R, Sidhu BS. Perforation of small intestine caused by Churg-Strauss syndrome. *J Clin Gastroenterol.* Oct 1996;23(3):232-235.

120. Sehgal M, Swanson JW, DeRemee RA, Colby TV. Neurologic manifestations of Churg-Strauss syndrome. *Mayo Clin Proc.* Apr 1995;70(4):337-341.

121. Ramakrishna G, Connolly HM, Tazelaar HD, Mullany CJ, Midthun DE. Churg-Strauss syndrome complicated by eosinophilic endomyocarditis. *Mayo Clin Proc.* Jun 2000;75(6):631-635.

122. Chang Y, Kargas SA, Goates JJ, Horoupian DS. Intraventricular and subarachnoid hemorrhage resulting from necrotizing vasculitis of the choroid plexus in a patient with Churg-Strauss syndrome. *Clin Neuropathol.* Mar-Apr 1993;12(2):84-87.

123. Guillevin L, Lhote F, Gayraud M, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore).* Jan 1996;75(1):17-28.

124. Renaldini E, Spandrio S, Cerudelli B, Affatato A, Balestrieri GP. Cardiac involvement in Churg-Strauss syndrome: a follow-up of three cases. *Eur Heart J.* Dec 1993;14(12):1712-1716.

125. Hunsaker JC, 3rd, O'Connor WN, Lie JT. Spontaneous coronary arterial dissection and isolated eosinophilic coronary arteritis: sudden cardiac death in a patient with a limited variant of Churg-Strauss syndrome. *Mayo Clin Proc.* Aug 1992;67(8):761-766.

126. Hellemans S, Dens J, Knockaert D. Coronary involvement in the Churg-Strauss syndrome. *Heart.* Jun 1997;77(6):576-578.

127. Lie JT, Bayardo RJ. Isolated eosinophilic coronary arteritis and eosinophilic myocarditis. A limited form of Churg-Strauss syndrome. *Arch Pathol Lab Med.* Feb 1989;113(2):199-201.

128. Gaskin G, Clutterbuck EJ, Pusey CD. Renal disease in the Churg-Strauss syndrome. Diagnosis, management and outcome. *Contrib Nephrol.* 1991;94:58-65.

129. Clutterbuck EJ, Evans DJ, Pusey CD. Renal involvement in Churg-Strauss syndrome. *Nephrol Dial Transplant.* 1990;5(3):161-167.

130. Gross WL, Schmitt WH, Csernok E. ANCA and associated diseases: immunodiagnostic and pathogenetic aspects. *Clin Exp Immunol.* Jan 1993;91(1):1-12.

131. Falk RJ, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. *N Engl J Med.* Jun 23 1988;318(25):1651-1657.

132. Savige J, Gillis D, Benson E, et al. International Consensus Statement on Testing and Reporting of Antineutrophil Cytoplasmic Antibodies (ANCA). *Am J Clin Pathol.* Apr 1999;111(4):507-513.

133. Gross WL. Antineutrophil cytoplasmic autoantibody testing in vasculitides. *Rheum Dis Clin North Am.* Nov 1995;21(4):987-1011.

134. Davenport A. "False positive" perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibody results leading to misdiagnosis of Wegener's granulomatosis and/or microscopic polyarteritis. *Clin Nephrol.* Mar 1992;37(3):124-130.

135. Davenport A, Lock RJ, Wallington TB. Clinical relevance of testing for antineutrophil cytoplasm antibodies (ANCA) with a standard indirect immunofluorescence ANCA test in patients with upper or lower respiratory tract symptoms. *Thorax.* Mar 1994;49(3):213-217.

136. Gal AA, Velasquez A. Antineutrophil cytoplasmic autoantibody in the absence of Wegener's granulomatosis or microscopic polyangiitis: implications for the surgical pathologist. *Mod Pathol.* Mar 2002;15(3):197-204.

137. Lim LC, Taylor JG, 3rd, Schmitz JL, et al. Diagnostic usefulness of antineutrophil cytoplasmic autoantibody serology. Comparative evaluation of commercial indirect fluorescent antibody kits and enzyme immunoassay kits. *Am J Clin Pathol.* Mar 1999;111(3):363-369.

138. Merkel PA, Polisson RP, Chang Y, Skates SJ, Niles JL. Prevalence of antineutrophil cytoplasmic antibodies in a large inception cohort of patients with connective tissue disease. *Ann Intern Med.* Jun 1 1997;126(11):866-873.

139. Rao JK, Weinberger M, Oddone EZ, Allen NB, Landsman P, Feussner JR. The role of antineutrophil cytoplasmic antibody (c-ANCA) testing in the diagnosis of Wegener granulomatosis. A literature review and meta-analysis. *Ann Intern Med.* Dec 15 1995;123(12):925-932.

140. Galperin C, Hoffman GS. Antineutrophil cytoplasmic antibodies in Wegener's granulomatosis and other diseases: clinical issues. *Cleve Clin J Med.* Nov-Dec 1994;61(6):416-427.

141. Nolle B, Specks U, Ludemann J, Rohrbach MS, DeRemee RA, Gross WL. Anticytoplasmic autoantibodies: their immunodiagnostic value in Wegener granulomatosis. *Ann Intern Med.* Jul 1 1989;111(1):28-40.

142. Tervaert JW, van der Woude FJ, Fauci AS, et al. Association between active Wegener's granulomatosis and anticytoplasmic antibodies. *Arch Intern Med.* Nov 1989;149(11):2461-2465.

143. Tervaert JW, Goldschmeding R, Elema JD, von dem Borne AE, Kallenberg CG. Antimyeloperoxidase antibodies in the Churg-Strauss syndrome. *Thorax.* Jan 1991;46(1):70-71.

144. Hagen EC, Daha MR, Hermans J, et al. Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. *Kidney Int.* Mar 1998;53(3):743-753.

145. Jennings JG, Chang L, Savige JA. Anti-proteinase 3 antibodies, their characterization and disease associations. *Clin Exp Immunol.* Feb 1994;95(2):251-256.

146. Segelmark M, Baslund B, Wieslander J. Some patients with anti-myeloperoxidase autoantibodies have a C-ANCA pattern. *Clin Exp Immunol.* Jun 1994;96(3):458-465.

147. Egner W, Chapel HM. Titration of antibodies against neutrophil cytoplasmic antigens is useful in monitoring disease activity in systemic vasculitides. *Clin Exp Immunol.* Nov 1990;82(2):244-249.

148. Tervaert JW, Huitema MG, Hene RJ, et al. Prevention of relapses in Wegener's granulomatosis by treatment based on antineutrophil cytoplasmic antibody titre. *Lancet.* Sep 22 1990;336(8717):709-711.

149. Kerr GS, Fleisher TA, Hallahan CW, Leavitt RY, Fauci AS, Hoffman GS. Limited prognostic value of changes in antineutrophil cytoplasmic antibody titer in patients with Wegener's granulomatosis. *Arthritis Rheum.* Mar 1993;36(3):365-371.

150. Gaskin G, Savage CO, Ryan JJ, et al. Anti-neutrophil cytoplasmic antibodies and disease activity during long-term follow-up of 70 patients with systemic vasculitis. *Nephrol Dial Transplant.* 1991;6(10):689-694.

151. Tervaert JW, Stegeman CA, Kallenberg CG. Serial ANCA testing is useful in monitoring disease activity of patients with ANCA-associated vasculitides. *Sarcoidosis Vasc Diffuse Lung Dis.* Oct 1996;13(3):241-245.

152. Stegeman CA. Anti-neutrophil cytoplasmic antibody (ANCA) levels directed against proteinase-3 and myeloperoxidase are helpful in predicting disease relapse in ANCA-associated small-vessel vasculitis. *Nephrol Dial Transplant.* Dec 2002;17(12):2077-2080.

153. Pettersson E, Heigl Z. Antineutrophil cytoplasmic antibody (cANCA and pANCA) titers in relation to disease activity in patients with necrotizing vasculitis: a longitudinal study. *Clin Nephrol.* May 1992;37(5):219-228.

154. Franssen CF, Stegeman CA, Oost-Kort WW, et al. Determinants of renal outcome in anti-myeloperoxidase-associated necrotizing crescentic glomerulonephritis. *J Am Soc Nephrol.* Oct 1998;9(10):1915-1923.

155. Specks U. ANCA subsets: influence on disease phenotype. *Cleve Clin J Med.* 2002;69 Suppl 2:SII56-59.

156. Geffriaud-Ricouard C, Noel LH, Chauveau D, Houhou S, Grunfeld JP, Lesavre P. Clinical spectrum associated with ANCA of defined antigen specificities in 98 selected patients. *Clin Nephrol.* Mar 1993;39(3):125-136.

157. Franssen CF, Gans RO, Arends B, et al. Differences between anti-myeloperoxidase- and anti-proteinase 3-associated renal disease. *Kidney Int.* Jan 1995;47(1):193-199.

158. Niles JL. A renal biopsy is essential for the management of ANCA-positive patients with glomerulonephritis: the contra-view. *Sarcoidosis Vasc Diffuse Lung Dis.* Oct 1996;13(3):232-234.

159. Devaney KO, Travis WD, Hoffman G, Leavitt R, Lebovics R, Fauci AS. Interpretation of head and neck biopsies in Wegener's granulomatosis. A pathologic study of 126 biopsies in 70 patients. *Am J Surg Pathol.* Jun 1990;14(6):555-564.

160. Travis WD. Pathology of pulmonary granulomatous vasculitis. *Sarcoidosis Vasc Diffuse Lung Dis.* Mar 1996;13(1):14-27.

161. Travis WD, Colby TV, Lombard C, Carpenter HA. A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. *Am J Surg Pathol.* Dec 1990;14(12):1112-1125.

162. Harper L, Savage CO. Pathogenesis of ANCA-associated systemic vasculitis. *J Pathol.* Feb 2000;190(3):349-359.

163. Colby TV. Diffuse pulmonary hemorrhage in Wegener's granulomatosis. *Semin Respir Med.* 1989;10:136.

164. Yoshimura N, Matsubara O, Tamura A, Kasuga T, Mark EJ. Wegener's granulomatosis. Associated with diffuse pulmonary hemorrhage. *Acta Pathol Jpn.* Sep 1992;42(9):657-661.

165. Weiss MA, Crissman JD. Renal biopsy findings in Wegener's granulomatosis: segmental necrotizing glomerulonephritis with glomerular thrombosis. *Hum Pathol.* Oct 1984;15(10):943-956.

166. Schwarz MI, Zamora MR, Hodges TN, Chan ED, Bowler RP, Tuder RM. Isolated pulmonary capillaritis and diffuse alveolar hemorrhage in rheumatoid arthritis and mixed connective tissue disease. *Chest.* Jun 1998;113(6):1609-1615.

167. Cohen S. Diffuse pulmonary hemorrhage: evolutionary 'flaw' or consequence of evolutionary progress? *Am J Med Sci.* Mar 2002;323(3):130-139.

168. Zamora MR, Warner ML, Tuder R, Schwarz MI. Diffuse alveolar hemorrhage and systemic lupus erythematosus. Clinical presentation, histology, survival, and outcome. *Medicine (Baltimore).* May 1997;76(3):192-202.

169. Jennette JC, Falk RJ. The pathology of vasculitis involving the kidney. *Am J Kidney Dis.* Jul 1994;24(1):130-141.

170. Aoyama T, Shimizu T, Matsuo T, et al. MPO-ANCA-positive slowly progressive glomerulonephritis with focal tuft necrosis and crescents. *Intern Med.* Jun 2002;41(6):458-462.

171. Nakabayashi K. Slowly progressive, not rapidly progressive, MPO-ANCA positive glomerulonephritis and its characteristics. *Intern Med.* Jun 2002;41(6):418-419.

172. Churg J, Strauss, L. Allergic granulomatosis, allergic angiitis and periarteritis nodosa. *Am J Pathol.* 1951;27:27-301.

173. Hattori N, Ichimura M, Nagamatsu M, et al. Clinicopathological features of Churg-Strauss syndrome-associated neuropathy. *Brain.* Mar 1999;122 (Pt 3):427-439.

174. Reid AJ, Harrison BD, Watts RA, Watkin SW, McCann BG, Scott DG. Churg-Strauss syndrome in a district hospital. *Qjm.* Mar 1998;91(3):219-229.

175. Abu-Shakra M, Smythe H, Lewtas J, Badley E, Weber D, Keystone E. Outcome of polyarteritis nodosa and Churg-Strauss syndrome. An analysis of twenty-five patients. *Arthritis Rheum.* Dec 1994;37(12):1798-1803.

176. Clutterbuck EJ, Pusey CD. Severe alveolar haemorrhage in Churg-Strauss syndrome. *Eur J Respir Dis.* Sep 1987;71(3):158-163.

177. Akikusa B, Sato T, Ogawa M, Ueda S, Kondo Y. Necrotizing alveolar capillaritis in autopsy cases of microscopic polyangiitis. Incidence, histopathogenesis, and relationship with systemic vasculitis. *Arch Pathol Lab Med.* Feb 1997;121(2):144-149.

178. Lai RS, Lin SL, Lai NS, Lee PC. Churg-Strauss syndrome presenting with pulmonary capillaritis and diffuse alveolar hemorrhage. *Scand J Rheumatol.* 1998;27(3):230-232.

179. Schnabel A, Reuter M, Csernok E, Richter C, Gross WL. Subclinical alveolar bleeding in pulmonary vasculitides: correlation with indices of disease activity. *Eur Respir J.* Jul 1999;14(1):118-124.

180. Falk RJ, Jennette JC. ANCA are pathogenic--oh yes they are! *J Am Soc Nephrol.* Jul 2002;13(7):1977-1979.

181. Kallenberg CG, Rarok A, Stegeman CA, Limburg PC. New insights into the pathogenesis of antineutrophil cytoplasmic autoantibody-associated vasculitis. *Autoimmun Rev.* Feb 2002;1(1-2):61-66.

182. Preston GA, Yang JJ, Xiao H, Falk RJ. Understanding the pathogenesis of ANCA: where are we today? *Cleve Clin J Med.* 2002;69 Suppl 2:SII51-54.

183. Csernok E, Muller A, Gross WL. Immunopathology of ANCA-associated vasculitis. *Intern Med.* Oct 1999;38(10):759-765.

184. Gross WL, Csernok E. Immunodiagnostic and pathophysiologic aspects of antineutrophil cytoplasmic antibodies in vasculitis. *Curr Opin Rheumatol.* Jan 1995;7(1):11-19.

185. Ewert BH, Jennette JC, Falk RJ. The pathogenic role of antineutrophil cytoplasmic autoantibodies. *Am J Kidney Dis.* Aug 1991;18(2):188-195.

186. Noronha IL, Kruger C, Andrassy K, Ritz E, Waldherr R. In situ production of TNF-alpha, IL-1 beta and IL-2R in ANCA-positive glomerulonephritis. *Kidney Int.* Mar 1993;43(3):682-692.

187. Grimminger F, Hattar K, Papavassilis C, et al. Neutrophil activation by anti-proteinase 3 antibodies in Wegener's granulomatosis: role of exogenous arachidonic acid and leukotriene B4 generation. *J Exp Med.* Oct 1 1996;184(4):1567-1572.

188. Kallenberg CG, Heeringa P. Pathogenesis of vasculitis. *Lupus.* 1998;7(4):280-284.

189. Brooks CJ, King WJ, Radford DJ, Adu D, McGrath M, Savage CO. IL-1 beta production by human polymorphonuclear leucocytes stimulated by anti-neutrophil cytoplasmic autoantibodies: relevance to systemic vasculitis. *Clin Exp Immunol.* Nov 1996;106(2):273-279.

190. Casselman BL, Kilgore KS, Miller BF, Warren JS. Antibodies to neutrophil cytoplasmic antigens induce monocyte chemoattractant protein-1 secretion from human monocytes. *J Lab Clin Med.* Nov 1995;126(5):495-502.

191. Ralston DR, Marsh CB, Lowe MP, Wewers MD. Antineutrophil cytoplasmic antibodies induce monocyte IL-8 release. Role of surface proteinase-3, alpha1-antitrypsin, and Fcgamma receptors. *J Clin Invest.* Sep 15 1997;100(6):1416-1424.

192. Muller Kobold AC, Mesander G, Stegeman CA, Kallenberg CG, Tervaert JW. Are circulating neutrophils intravascularly activated in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides? *Clin Exp Immunol.* Dec 1998;114(3):491-499.

193. Keogan MT, Rifkin I, Ronda N, Lockwood CM, Brown DL. Anti-neutrophil cytoplasm antibodies (ANCA) increase neutrophil adhesion to cultured human endothelium. *Adv Exp Med Biol.* 1993;336:115-119.

194. Mayet WJ, Schwarting A, Orth T, Duchmann R, Meyer zum Buschenfelde KH. Antibodies to proteinase 3 mediate expression of vascular cell adhesion molecule-1 (VCAM-1). *Clin Exp Immunol.* Feb 1996;103(2):259-267.

195. Johnson PA, Alexander HD, McMillan SA, Maxwell AP. Up-regulation of the endothelial cell adhesion molecule intercellular adhesion molecule-1 (ICAM-1) by autoantibodies in autoimmune vasculitis. *Clin Exp Immunol.* May 1997;108(2):234-242.

196. Johnson PA, Alexander HD, McMillan SA, Maxwell AP. Up-regulation of the granulocyte adhesion molecule Mac-1 by autoantibodies in autoimmune vasculitis. *Clin Exp Immunol.* Mar 1997;107(3):513-519.

197. Kevil CG, Bullard DC. Roles of leukocyte/endothelial cell adhesion molecules in the pathogenesis of vasculitis. *Am J Med.* Jun 1999;106(6):677-687.

198. Charles LA, Caldas ML, Falk RJ, Terrell RS, Jennette JC. Antibodies against granule proteins activate neutrophils in vitro. *J Leukoc Biol.* Dec 1991;50(6):539-546.

199. Falk RJ, Terrell RS, Charles LA, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. *Proc Natl Acad Sci U S A.* Jun 1990;87(11):4115-4119.

200. Ewert BH, Becker ME, Jennette JC, Falk RJ. Antimyeloperoxidase antibodies induce neutrophil adherence to cultured human endothelial cells. *Ren Fail.* Mar 1995;17(2):125-133.

201. Mayet WJ, Csernok E, Szymkowiak C, Gross WL, Meyer zum Buschenfelde KH. Human endothelial cells express proteinase 3, the target antigen of anticytoplasmic antibodies in Wegener's granulomatosis. *Blood.* Aug 15 1993;82(4):1221-1229.

202. Vargunam M, Adu D, Taylor CM, et al. Endothelium myeloperoxidase-antimyeloperoxidase interaction in vasculitis. *Nephrol Dial Transplant.* 1992;7(11):1077-1081.

203. Savage CO, Gaskin G, Pusey CD, Pearson JD. Anti-neutrophil cytoplasm antibodies can recognize vascular endothelial cell-bound anti-neutrophil cytoplasm antibody-associated autoantigens. *Exp Nephrol.* May-Jun 1993;1(3):190-195.

204. Savage CO, Pottinger BE, Gaskin G, Pusey CD, Pearson JD. Autoantibodies developing to myeloperoxidase and proteinase 3 in systemic vasculitis stimulate neutrophil cytotoxicity toward cultured endothelial cells. *Am J Pathol.* Aug 1992;141(2):335-342.

205. Savage CO. Interactions between leukocytes, the vascular endothelium and autoantibodies in the development of systemic vasculitis. *Ann Med Interne (Paris).* 1993;144(5):353-356.

206. Mayet WJ, Schwarting A, Meyer zum Buschenfelde KH. Cytotoxic effects of antibodies to proteinase 3 (C-ANCA) on human endothelial cells. *Clin Exp Immunol.* Sep 1994;97(3):458-465.

207. Hoffman GS, Specks U. Antineutrophil cytoplasmic antibodies. *Arthritis Rheum.* Sep 1998;41(9):1521-1537.

208. Sibelius U, Hattar K, Schenkel A, et al. Wegener's granulomatosis: anti-proteinase 3 antibodies are potent inductors of human endothelial cell signaling and leakage response. *J Exp Med.* Feb 16 1998;187(4):497-503.

209. Cockwell P, Brooks CJ, Adu D, Savage CO. Interleukin-8: A pathogenetic role in antineutrophil cytoplasmic autoantibody-associated glomerulonephritis. *Kidney Int.* Mar 1999;55(3):852-863.

210. Kobayashi K, Shibata T, Sugisaki T. Aggravation of rat nephrotoxic serum nephritis by anti-myeloperoxidase antibodies. *Kidney Int.* Feb 1995;47(2):454-463.

211. Heeringa P, Brouwer E, Klok PA, et al. Autoantibodies to myeloperoxidase aggravate mild anti-glomerular-basement-membrane-mediated glomerular injury in the rat. *Am J Pathol.* Nov 1996;149(5):1695-1706.

212. Xiao H, Heeringa P, Hu P, et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J Clin Invest.* Oct 2002;110(7):955-963.

213. Smyth CL, Smith, J., Cook, H.T., Haskard, D.O., Pusey, C.C. Anti-myeloperoxidase associated pauci-immune focal segmental glomerulonephritis in rats [Abstract]. *Cleve Clin J Med.* 2002;69(suppl 2):156.

214. Gilligan HM, Bredy B, Brady HR, et al. Antineutrophil cytoplasmic autoantibodies interact with primary granule constituents on the surface of apoptotic neutrophils in the absence of neutrophil priming. *J Exp Med.* Dec 1 1996;184(6):2231-2241.

215. Esnault VL. Apoptosis: the central actor in the three hits that trigger anti-neutrophil cytoplasmic antibody-related systemic vasculitis. *Nephrol Dial Transplant.* Oct 2002;17(10):1725-1728.

216. Stuart L, Hughes J. Apoptosis and autoimmunity. *Nephrol Dial Transplant.* May 2002;17(5):697-700.

217. Savill J. Recognition and phagocytosis of cells undergoing apoptosis. *Br Med Bull.* 1997;53(3):491-508.

218. Rosen A, Casciola-Rosen L. Autoantigens as substrates for apoptotic proteases: implications for the pathogenesis of systemic autoimmune disease. *Cell Death Differ.* Jan 1999;6(1):6-12.

219. Jacobson MD, Weil M, Raff MC. Programmed cell death in animal development. *Cell.* Feb 7 1997;88(3):347-354.

220. Haslett C. Granulocyte apoptosis and its role in the resolution and control of lung inflammation. *Am J Respir Crit Care Med.* Nov 1999;160(5 Pt 2):S5-11.

221. Albert ML, Sauter B, Bhardwaj N. Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLs. *Nature.* Mar 5 1998;392(6671):86-89.

222. Patry YC, Trewick DC, Gregoire M, et al. Rats injected with syngenic rat apoptotic neutrophils develop antineutrophil cytoplasmic antibodies. *J Am Soc Nephrol.* Aug 2001;12(8):1764-1768.

223. Harper L, Ren Y, Savill J, Adu D, Savage CO. Antineutrophil cytoplasmic antibodies induce reactive oxygen-dependent dysregulation of primed neutrophil apoptosis and clearance by macrophages. *Am J Pathol.* Jul 2000;157(1):211-220.

224. Mulder AH, Heeringa P, Brouwer E, Limburg PC, Kallenberg CG. Activation of granulocytes by anti-neutrophil cytoplasmic antibodies (ANCA): a Fc gamma RII-dependent process. *Clin Exp Immunol.* Nov 1994;98(2):270-278.

225. Porges AJ, Redecha PB, Kimberly WT, Csernok E, Gross WL, Kimberly RP. Anti-neutrophil cytoplasmic antibodies engage and activate human neutrophils via Fc gamma RIIa. *J Immunol.* Aug 1 1994;153(3):1271-1280.

226. Kocher M, Siegel ME, Edberg JC, Kimberly RP. Cross-linking of Fc gamma receptor IIa and Fc gamma receptor IIIb induces different proadhesive phenotypes on human neutrophils. *J Immunol.* Oct 15 1997;159(8):3940-3948.

227. Kocher M, Edberg JC, Fleit HB, Kimberly RP. Antineutrophil cytoplasmic antibodies preferentially engage Fc gammaRIIIb on human neutrophils. *J Immunol.* Dec 15 1998;161(12):6909-6914.

228. Dijstelbloem HM, Scheepers RH, Oost WW, et al. Fcgamma receptor polymorphisms in Wegener's granulomatosis: risk factors for disease relapse. *Arthritis Rheum.* Sep 1999;42(9):1823-1827.

229. Savage CO, Pottinger BE, Gaskin G, Lockwood CM, Pusey CD, Pearson JD. Vascular damage in Wegener's granulomatosis and microscopic polyarteritis: presence of anti-endothelial cell antibodies and their relation to anti-neutrophil cytoplasm antibodies. *Clin Exp Immunol.* Jul 1991;85(1):14-19.

230. Varagunam M, Nwosu AC, Adu D, et al. Little evidence for anti-endothelial-cell antibodies in microscopic polyarteritis and Wegener's granulomatosis. *Adv Exp Med Biol.* 1993;336:419-422.

231. Chan TM, Frampton G, Jayne DR, Perry GJ, Lockwood CM, Cameron JS. Clinical significance of anti-endothelial cell antibodies in systemic vasculitis: a longitudinal study comparing anti-endothelial cell antibodies and anti-neutrophil cytoplasm antibodies. *Am J Kidney Dis.* Sep 1993;22(3):387-392.

232. del Papa N, Meroni PL, Barcellini W, et al. Antibodies to endothelial cells in primary vasculitides mediate in vitro endothelial cytotoxicity in the presence of normal peripheral blood mononuclear cells. *Clin Immunol Immunopathol.* Jun 1992;63(3):267-274.

233. Del Papa N, Guidali L, Sironi M, et al. Anti-endothelial cell IgG antibodies from patients with Wegener's granulomatosis bind to human endothelial cells in vitro and induce adhesion molecule expression and cytokine secretion. *Arthritis Rheum.* May 1996;39(5):758-766.

234. Schmitt WH, Csernok E, Kobayashi S, Klinkenborg A, Reinhold-Keller E, Gross WL. Churg-Strauss syndrome: serum markers of lymphocyte activation and endothelial damage. *Arthritis Rheum.* Mar 1998;41(3):445-452.

235. Preston GA, Zarella CS, Pendergraft WF, 3rd, et al. Novel effects of neutrophil-derived proteinase 3 and elastase on the vascular endothelium involve in vivo cleavage of NF-kappaB and proapoptotic changes in JNK, ERK, and p38 MAPK signaling pathways. *J Am Soc Nephrol.* Dec 2002;13(12):2840-2849.

236. van der Geld YM, Limburg PC, Kallenberg CG. Proteinase 3, Wegener's autoantigen: from gene to antigen. *J Leukoc Biol.* Feb 2001;69(2):177-190.

237. Taekema-Roelvink ME, van Kooten C, Verburgh CA, Daha MR. Role of proteinase 3 in activation of endothelium. *Springer Semin Immunopathol.* 2001;23(3):299-314.

238. Taekema-Roelvink ME, Kooten C, Kooij SV, Heemskerk E, Daha MR. Proteinase 3 enhances endothelial monocyte chemoattractant protein-1 production and induces increased adhesion of neutrophils to endothelial cells by upregulating intercellular cell adhesion molecule-1. *J Am Soc Nephrol.* May 2001;12(5):932-940.

239. Berger SP, Seelen MA, Hiemstra PS, et al. Proteinase 3, the major autoantigen of Wegener's granulomatosis, enhances IL-8 production by endothelial cells in vitro. *J Am Soc Nephrol.* May 1996;7(5):694-701.

240. Taekema-Roelvink ME, van Kooten C, Janssens MC, Heemskerk E, Daha MR. Effect of anti-neutrophil cytoplasmic antibodies on proteinase 3-induced apoptosis of human endothelial cells. *Scand J Immunol.* Jul 1998;48(1):37-43.

241. Yang JJ, Kettritz R, Falk RJ, Jennette JC, Gaido ML. Apoptosis of endothelial cells induced by the neutrophil serine proteases proteinase 3 and elastase. *Am J Pathol.* Nov 1996;149(5):1617-1626.

242. Brockmann H, Schwarting A, Kriegsmann J, et al. Proteinase-3 as the major autoantigen of c-ANCA is strongly expressed in lung tissue of patients with Wegener's granulomatosis. *Arthritis Res.* 2002;4(3):220-225.

243. Witko-Sarsat V, Lesavre P, Lopez S, et al. A large subset of neutrophils expressing membrane proteinase 3 is a risk factor for vasculitis and rheumatoid arthritis. *J Am Soc Nephrol.* Jun 1999;10(6):1224-1233.

244. Rarok AA, Stegeman CA, Limburg PC, Kallenberg CG. Neutrophil membrane expression of proteinase 3 (PR3) is related to relapse in PR3-ANCA-associated vasculitis. *J Am Soc Nephrol.* Sep 2002;13(9):2232-2238.

245. Gencik M, Meller S, Borgmann S, Fricke H. Proteinase 3 gene polymorphisms and Wegener's granulomatosis. *Kidney Int.* Dec 2000;58(6):2473-2477.

246. Esnault VL, Testa A, Audrain M, et al. Alpha 1-antitrypsin genetic polymorphism in ANCA-positive systemic vasculitis. *Kidney Int.* Jun 1993;43(6):1329-1332.

247. Segelmark M, Persson B, Hellmark T, Wieslander J. Binding and inhibition of myeloperoxidase (MPO): a major function of ceruloplasmin? *Clin Exp Immunol.* Apr 1997;108(1):167-174.

248. Magro CM, Morrison C, Pope-Harman A, Rothrauff SK, Ross P, Jr. Direct and indirect immunofluorescence as a diagnostic adjunct in the interpretation of nonneoplastic medical lung disease. *Am J Clin Pathol.* Feb 2003;119(2):279-289.

249. Elzouki AN, Segelmark M, Wieslander J, Eriksson S. Strong link between the alpha 1-antitrypsin PiZ allele and Wegener's granulomatosis. *J Intern Med.* Nov 1994;236(5):543-548.

250. Esnault VL, Audrain MA, Sesboue R. Alpha-1-antitrypsin phenotyping in ANCA-associated diseases: one of several arguments for protease/antiprotease imbalance in systemic vasculitis. *Exp Clin Immunogenet.* 1997;14(3):206-213.

251. Callea F, Gregorini G, Sinico A, et al. alpha 1-Antitrypsin (AAT) deficiency and ANCA-positive systemic vasculitis: genetic and clinical implications. *Eur J Clin Invest.* Aug 1997;27(8):696-702.

252. Baslund B, Szpirt W, Eriksson S, et al. Complexes between proteinase 3, alpha 1-antitrypsin and proteinase 3 anti-neutrophil cytoplasm autoantibodies: a comparison between alpha 1-antitrypsin PiZ allele carriers and non-carriers with Wegener's granulomatosis. *Eur J Clin Invest.* Sep 1996;26(9):786-792.

253. Savige JA, Chang L, Cook L, Burdon J, Daskalakis M, Doery J. Alpha 1-antitrypsin deficiency and anti-proteinase 3 antibodies in anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis. *Clin Exp Immunol.* May 1995;100(2):194-197.

254. Segelmark M, Elzouki AN, Wieslander J, Eriksson S. The PiZ gene of alpha 1-antitrypsin as a determinant of outcome in PR3-ANCA-positive vasculitis. *Kidney Int.* Sep 1995;48(3):844-850.

255. Mazodier P, Elzouki AN, Segelmark M, Eriksson S. Systemic necrotizing vasculitides in severe alpha1-antitrypsin deficiency. *Qjm.* Aug 1996;89(8):599-611.

256. Dolman KM, Stegeman CA, van de Wiel BA, et al. Relevance of classic anti-neutrophil cytoplasmic autoantibody (C-ANCA)-mediated inhibition of proteinase 3-alpha 1-antitrypsin complexation to disease activity in Wegener's granulomatosis. *Clin Exp Immunol.* Sep 1993;93(3):405-410.

257. Esnault VL. ANCA-positive vasculitis and alpha 1-antitrypsin deficiency: could free ANCA antigens released by neutrophils mediate vasculitic lesions? *Nephrol Dial Transplant.* Feb 1997;12(2):249-251.

258. Schlesier M, Kaspar T, Gutfleisch J, Wolff-Vorbeck G, Peter HH. Activated CD4+ and CD8+ T-cell subsets in Wegener's granulomatosis. *Rheumatol Int.* 1995;14(5):213-219.

259. Muller GA, Muller CA, Markovic-Lipkovski J, Kilper RB, Risler T. Renal, major histocompatibility complex antigens and cellular components in rapidly progressive glomerulonephritis identified by monoclonal antibodies. *Nephron.* 1988;49(2):132-139.

260. Sneller MC. Granuloma formation, implications for the pathogenesis of vasculitis. *Cleve Clin J Med.* 2002;69 Suppl 2:SII40-43.

261. 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.* Apr 1999;42(4):742-750.

262. Ludviksson BR, Sneller MC, Chua KS, et al. Active Wegener's granulomatosis is associated with HLA-DR+ CD4+ T cells exhibiting an unbalanced Th1-type T cell cytokine pattern: reversal with IL-10. *J Immunol.* Apr 1 1998;160(7):3602-3609.

263. Schmitt WH, Heesen C, Csernok E, Rautmann A, Gross WL. Elevated serum levels of soluble interleukin-2 receptor in patients with Wegener's granulomatosis. Association with disease activity. *Arthritis Rheum.* Sep 1992;35(9):1088-1096.

264. Stegeman CA, Tervaert JW, Huitema MG, Kallenberg CG. Serum markers of T cell activation in relapses of Wegener's granulomatosis. *Clin Exp Immunol.* Mar 1993;91(3):415-420.

265. King WJ, Brooks CJ, Holder R, Hughes P, Adu D, Savage CO. T lymphocyte responses to anti-neutrophil cytoplasmic autoantibody (ANCA) antigens are present in patients with ANCA-associated systemic vasculitis and persist during disease remission. *Clin Exp Immunol.* Jun 1998;112(3):539-546.

266. Griffith ME, Coulthart A, Pusey CD. T cell responses to myeloperoxidase (MPO) and proteinase 3 (PR3) in patients with systemic vasculitis. *Clin Exp Immunol.* Feb 1996;103(2):253-258.

267. Brouwer E, Stegeman CA, Huitema MG, Limburg PC, Kallenberg CG. T cell reactivity to proteinase 3 and myeloperoxidase in patients with Wegener's granulomatosis (WG). *Clin Exp Immunol.* Dec 1994;98(3):448-453.

268. Ballieux BE, van der Burg SH, Hagen EC, van der Woude FJ, Melief CJ, Daha MR. Cell-mediated autoimmunity in patients with Wegener's granulomatosis (WG). *Clin Exp Immunol.* May 1995;100(2):186-193.

269. Griffith ME, Pusey CD. HLA genes in ANCA-associated vasculitides. *Exp Clin Immunogenet.* 1997;14(3):196-205.

270. Noth I, Strek ME, Leff AR. Churg-Strauss syndrome. *Lancet.* Feb 15 2003;361(9357):587-594.

271. Muschen M, Warskulat U, Perniok A, et al. Involvement of soluble CD95 in Churg-Strauss syndrome. *Am J Pathol.* Sep 1999;155(3):915-925.

272. Levine SM, Stone JH. New approaches to treatment in systemic vasculitis: biological therapies. *Best Pract Res Clin Rheumatol.* Jun 2001;15(2):315-333.

273. Allison JP, Krummel MF. The Yin and Yang of T cell costimulation. *Science.* Nov 10 1995;270(5238):932-933.

274. Krummel MF, Allison JP. CTLA-4 engagement inhibits IL-2 accumulation and cell cycle progression upon activation of resting T cells. *J Exp Med.* Jun 1 1996;183(6):2533-2540.

275. Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA, Sharpe AH. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. *Immunity.* Nov 1995;3(5):541-547.

276. Waterhouse P, Penninger JM, Timms E, et al. Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4. *Science.* Nov 10 1995;270(5238):985-988.

277. Huang D, Giscombe R, Zhou Y, Lefvert AK. Polymorphisms in CTLA-4 but not tumor necrosis factor-alpha or interleukin 1beta genes are associated with Wegener's granulomatosis. *J Rheumatol.* Feb 2000;27(2):397-401.

278. Tervaert JW, Kallenberg CG. Cell adhesion molecules in vasculitis. *Curr Opin Rheumatol.* Jan 1997;9(1):16-25.

279. Bradley JR, Lockwood CM, Thiru S. Endothelial cell activation in patients with systemic vasculitis. *Qjm.* Dec 1994;87(12):741-745.

280. Gutfleisch J, Baumert E, Wolff-Vorbeck G, Schlesier M, Strutz HJ, Peter HH. Increased expression of CD25 and adhesion molecules on peripheral blood lymphocytes of patients with Wegener's granulomatosis (WG) and ANCA positive vasculitides. *Adv Exp Med Biol.* 1993;336:397-404.

281. Mrowka C, Sieberth HG. Circulating adhesion molecules ICAM-1, VCAM-1 and E-selectin in systemic vasculitis: marked differences between Wegener's granulomatosis and systemic lupus erythematosus. *Clin Investig.* Oct 1994;72(10):762-768.

282. Pall AA, Howie AJ, Adu D, et al. Glomerular vascular cell adhesion molecule-1 expression in renal vasculitis. *J Clin Pathol.* Mar 1996;49(3):238-242.

283. Sais G, Vidaller A, Jucgla A, Condom E, Peyri J. Adhesion molecule expression and endothelial cell activation in cutaneous leukocytoclastic vasculitis. An immunohistologic and clinical study in 42 patients. *Arch Dermatol.* Apr 1997;133(4):443-450.

284. Gencik M, Meller S, Borgmann S, et al. The association of CD18 alleles with anti-myeloperoxidase subtypes of ANCA-associated systemic vasculitides. *Clin Immunol.* Jan 2000;94(1):9-12.

285. Meller S, Jagiello P, Borgmann S, Fricke H, Epplen JT, Gencik M. Novel SNPs in the CD18 gene validate the association with MPO-ANCA+ vasculitis. *Genes Immun.* Aug 2001;2(5):269-272.

286. Jayne DR. Conventional treatment and outcome of Wegener's granulomatosis and microscopic polyangiitis. *Cleve Clin J Med.* 2002;69 Suppl 2:SII110-115.

287. Carruthers D, Bacon P. Activity, damage and outcome in systemic vasculitis. *Best Pract Res Clin Rheumatol.* Jun 2001;15(2):225-238.

288. Langford CA. Treatment of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: where do we stand? *Arthritis Rheum.* Mar 2001;44(3):508-512.

289. Langford CA. Management of systemic vasculitis. *Best Pract Res Clin Rheumatol.* Jun 2001;15(2):281-297.

290. Gordon M, Luqmani RA, Adu D, et al. Necrotizing vasculitis--relapse despite cytotoxic therapy. *Adv Exp Med Biol.* 1993;336:477-481.

291. Gordon M, Luqmani RA, Adu D, et al. Relapses in patients with a systemic vasculitis. *Q J Med.* Dec 1993;86(12):779-789.

292. Hoffman GS. Treatment of Wegener's granulomatosis: time to change the standard of care? *Arthritis Rheum.* Dec 1997;40(12):2099-2104.

293. Stillwell TJ, Benson RC, Jr., DeRemee RA, McDonald TJ, Weiland LH. Cyclophosphamide-induced bladder toxicity in Wegener's granulomatosis. *Arthritis Rheum.* Apr 1988;31(4):465-470.

294. Gayraud M, Guillevin L, le Toumelin P, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum.* Mar 2001;44(3):666-675.

295. Talar-Williams C, Hijazi YM, Walther MM, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med.* Mar 1 1996;124(5):477-484.

296. Westman KW, Bygren PG, Olsson H, Ranstam J, Wieslander J. Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. *J Am Soc Nephrol.* May 1998;9(5):842-852.

297. Stillwell TJ, Benson RC, Jr. Cyclophosphamide-induced hemorrhagic cystitis. A review of 100 patients. *Cancer.* Feb 1 1988;61(3):451-457.

298. Jayne DR, Rasmussen N. Treatment of antineutrophil cytoplasm autoantibody-associated systemic vasculitis: initiatives of the European Community Systemic Vasculitis Clinical Trials Study Group. *Mayo Clin Proc.* Aug 1997;72(8):737-747.

299. de Groot K, Gross WL. Wegener's granulomatosis: disease course, assessment of activity and extent and treatment. *Lupus.* 1998;7(4):285-291.

300. Stone JH, Tun W, Hellman DB. Treatment of non-life threatening Wegener's granulomatosis with methotrexate and daily prednisone as the initial therapy of choice. *J Rheumatol.* May 1999;26(5):1134-1139.

301. Hoffman GS, Leavitt RY, Kerr GS, Fauci AS. The treatment of Wegener's granulomatosis with glucocorticoids and methotrexate. *Arthritis Rheum.* Nov 1992;35(11):1322-1329.

302. Langford CA, Talar-Williams C, Sneller MC. Use of methotrexate and glucocorticoids in the treatment of Wegener's granulomatosis. Long-term renal outcome in patients with glomerulonephritis. *Arthritis Rheum.* Aug 2000;43(8):1836-1840.

303. Langford CA, Sneller MC, Hoffman GS. Methotrexate use in systemic vasculitis. *Rheum Dis Clin North Am.* Nov 1997;23(4):841-853.

304. de Groot K, Reinhold-Keller E, Tatsis E, et al. Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis. Methotrexate versus trimethoprim/sulfamethoxazole. *Arthritis Rheum.* Dec 1996;39(12):2052-2061.

305. Guillevin L, Cordier JF, Lhote F, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum.* Dec 1997;40(12):2187-2198.

306. Haubitz M, Schellong S, Gobel U, et al. Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. *Arthritis Rheum.* Oct 1998;41(10):1835-1844.

307. Reinhold-Keller E, Kekow J, Schnabel A, Schwarz-Eywill M, Schmitt WH, Gross WL. Effectiveness of cyclophosphamide pulse treatment in Wegener's granulomatosis. *Adv Exp Med Biol.* 1993;336:483-486.

308. Hoffman GS, Leavitt RY, Fleisher TA, Minor JR, Fauci AS. Treatment of Wegener's granulomatosis with intermittent high-dose intravenous cyclophosphamide. *Am J Med.* Oct 1990;89(4):403-410.

309. Genereau T, Lortholary O, Leclerq P, et al. Treatment of systemic vasculitis with cyclophosphamide and steroids: daily oral low-dose cyclophosphamide administration after failure of a pulse intravenous high-dose regimen in four patients. *Br J Rheumatol.* Oct 1994;33(10):959-962.

310. de Groot K, Adu D, Savage CO. The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. *Nephrol Dial Transplant.* Oct 2001;16(10):2018-2027.

311. Gayraud M, Guillevin L, Cohen P, et al. Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. French Cooperative Study Group for Vasculitides. *Br J Rheumatol.* Dec 1997;36(12):1290-1297.

312. Hoffman GS. Wegener's granulomatosis. *Curr Opin Rheumatol.* Jan 1993;5(1):11-17.

313. Hollander D, Manning RT. The use of alkylating agents in the treatment of Wegener's granulomatosis. *Ann Intern Med.* Aug 1967;67(2):393-398.

314. Rodgers H, Guthrie JA, Brownjohn AM, Turney JH. Microscopic polyarteritis: clinical features and treatment. *Postgrad Med J.* Aug 1989;65(766):515-518.

315. Langford CA. Chronic immunosuppressive therapy for systemic vasculitis. *Curr Opin Rheumatol.* Jan 1997;9(1):41-47.

316. Solans R, Bosch JA, Perez-Bocanegra C, et al. Churg-Strauss syndrome: outcome and long-term follow-up of 32 patients. *Rheumatology (Oxford).* Jul 2001;40(7):763-771.

317. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. *N Engl J Med.* Jul 4 1996;335(1):16-20.

318. Reinhold-Keller E, De Groot K, Rudert H, Nolle B, Heller M, Gross WL. Response to trimethoprim/sulfamethoxazole in Wegener's granulomatosis depends on the phase of disease. *Qjm.* Jan 1996;89(1):15-23.

319. DeRemee RA. The treatment of Wegener's granulomatosis with trimethoprim/sulfamethoxazole: illusion or vision? *Arthritis Rheum.* Aug 1988;31(8):1068-1074.

320. Jayne DR, Lockwood CM. Intravenous immunoglobulin as sole therapy for systemic vasculitis. *Br J Rheumatol.* Nov 1996;35(11):1150-1153.

321. Jayne DRW. Intravenous immunoglobulins in the therapy of systemic vasculitis. *Transfus Sci.* 1992;13:317-324.

322. Jayne DR, Chapel H, Adu D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *Qjm.* Jul 2000;93(7):433-439.

323. Richter C, Schnabel A, Csernok E, Reinhold-Keller E, Gross WL. Treatment of Wegener's granulomatosis with intravenous immunoglobulin. *Adv Exp Med Biol.* 1993;336:487-489.

324. Tuso P, Moudgil A, Hay J, et al. Treatment of antineutrophil cytoplasmic autoantibody-positive systemic vasculitis and glomerulonephritis with pooled intravenous gammaglobulin. *Am J Kidney Dis.* Nov 1992;20(5):504-508.

325. Jayne DR, Lockwood CM. Pooled intravenous immunoglobulin in the management of systemic vasculitis. *Adv Exp Med Biol.* 1993;336:469-472.

326. Levy Y, George J, Fabbrizzi F, Rotman P, Paz Y, Shoenfeld Y. Marked improvement of Churg-Strauss vasculitis with intravenous gammaglobulins. *South Med J.* Apr 1999;92(4):412-414.

327. Rossi F, Jayne DR, Lockwood CM, Kazatchkine MD. Anti-idiotypes against anti-neutrophil cytoplasmic antigen autoantibodies in normal human polyspecific IgG for therapeutic use and in the remission sera of patients with systemic vasculitis. *Clin Exp Immunol.* Feb 1991;83(2):298-303.

328. Pall AA, Varagunam M, Adu D, et al. Anti-idiotypic activity against anti-myeloperoxidase antibodies in pooled human immunoglobulin. *Clin Exp Immunol.* Feb 1994;95(2):257-262.

329. Jayne DR, Esnault VL, Lockwood CM. Anti-idiotype antibodies to anti-myeloperoxidase autoantibodies in patients with systemic vasculitis. *J Autoimmun.* Apr 1993;6(2):221-226.

330. Jayne DR, Esnault VL, Lockwood CM. ANCA anti-idiotype antibodies and the treatment of systemic vasculitis with intravenous immunoglobulin. *J Autoimmun.* Apr 1993;6(2):207-219.

331. Schifferli JA. Adverse effects of intravenous immunoglobulins. *Transfus Sci.* 1992;13:331-338.

332. Burns A. Pulmonary vasculitis. *Thorax.* Mar 1998;53(3):220-227.

333. Pusey CD, Rees AJ, Evans DJ, Peters DK, Lockwood CM. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. *Kidney Int.* Oct 1991;40(4):757-763.

334. Frasca GM, Zoumparidis NG, Borgnino LC, Neri L, Vangelista A, Bonomini V. Plasma exchange treatment in rapidly progressive glomerulonephritis associated with anti-neutrophil cytoplasmic autoantibodies. *Int J Artif Organs.* Mar 1992;15(3):181-184.

335. Frasca GM, Zoumparidis NG, Borgnino LC, Neri L, Vangelista A, Bonomini V. Combined treatment in Wegener's granulomatosis with crescentic glomerulonephritis--clinical course and long-term outcome. *Int J Artif Organs.* Jan 1993;16(1):11-19.

336. Gianviti A, Trompeter RS, Barratt TM, Lythgoe MF, Dillon MJ. Retrospective study of plasma exchange in patients with idiopathic rapidly progressive glomerulonephritis and vasculitis. *Arch Dis Child.* Sep 1996;75(3):186-190.

337. Lhote F, Guillevin, L. Indications of plasma exchanges in the treatment of polyarteritis nodosa and other systemic vasculitides. *Transfus Sci.* 1996;17:211-213.

338. Guillevin L, Fain O, Lhote F, et al. Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome. A prospective, randomized trial in 78 patients. *Arthritis Rheum.* Feb 1992;35(2):208-215.

339. Guillevin L, Cevallos R, Durand-Gasselin B, Lhote F, Jarrousse B, Callard P. Treatment of glomerulonephritis in microscopic polyangiitis and Churg-Strauss syndrome. Indications of plasma

exchanges, Meta-analysis of 2 randomized studies on 140 patients, 32 with glomerulonephritis. *Ann Med Interne (Paris).* 1997;148(3):198-204.

340. Ognibene FP, Shelhamer JH, Hoffman GS, et al. Pneumocystis carinii pneumonia: a major complication of immunosuppressive therapy in patients with Wegener's granulomatosis. *Am J Respir Crit Care Med.* Mar 1995;151(3 Pt 1):795-799.

341. Godeau B, Mainardi JL, Roudot-Thoraval F, et al. Factors associated with Pneumocystis carinii pneumonia in Wegener's granulomatosis. *Ann Rheum Dis.* Dec 1995;54(12):991-994.

342. Bacon PA, Carruthers D. New therapeutic aspects: haemopoietic stem cell transplantation. *Best Pract Res Clin Rheumatol.* Jun 2001;15(2):299-313.

343. Booth AD, Firth JD, Jayne DR. Immunotherapy for autoimmune and inflammatory renal diseases. *Expert Opin Biol Ther.* Jun 2003;3(3):487-500.

344. Tatsis E, Schnabel A, Gross WL. Interferon-alpha treatment of four patients with the Churg-Strauss syndrome. *Ann Intern Med.* Sep 1 1998;129(5):370-374.

345. Butterfield JH, Gleich GJ. Interferon-alpha treatment of six patients with the idiopathic hypereosinophilic syndrome. *Ann Intern Med.* Nov 1 1994;121(9):648-653.

346. Gutterman JU. Cytokine therapeutics: lessons from interferon alpha. *Proc Natl Acad Sci U S A.* Feb 15 1994;91(4):1198-1205.

347. Metzler C. Long-term treatment of Churg-Strauss syndrome with interferon-alpha. *Arthritis Rheum.* 2000;43:S369.

348. Sartori M, Andorno S, La Terra G, et al. Assessment of interferon cardiotoxicity with quantitative radionuclide angiocardiography. *Eur J Clin Invest.* Jan 1995;25(1):68-70.

349. Lockwood CM, Thiru S, Isaacs JD, Hale G, Waldmann H. Long-term remission of intractable systemic vasculitis with monoclonal antibody therapy. *Lancet.* Jun 26 1993;341(8861):1620-1622.

350. Mathieson PW, Cobbold SP, Hale G, et al. Monoclonal-antibody therapy in systemic vasculitis. *N Engl J Med.* Jul 26 1990;323(4):250-254.

351. Hagen EC, de Keizer RJ, Andrassy K, et al. Compassionate treatment of Wegener's granulomatosis with rabbit anti-thymocyte globulin. *Clin Nephrol.* Jun 1995;43(6):351-359.

352. Stone JH, Uhlfelder ML, Hellmann DB, Crook S, Bedocs NM, Hoffman GS. Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety. *Arthritis Rheum.* May 2001;44(5):1149-1154.

353. Rittner HL, Kaiser M, Brack A, Szweda LI, Goronzy JJ, Weyand CM. Tissue-destructive macrophages in giant cell arteritis. *Circ Res.* May 14 1999;84(9):1050-1058.

354. Weyand CM, Goronzy JJ. Multisystem interactions in the pathogenesis of vasculitis. *Curr Opin Rheumatol.* Jan 1997;9(1):3-11.

355. Kaiser M, Weyand CM, Bjornsson J, Goronzy JJ. Platelet-derived growth factor, intimal hyperplasia, and ischemic complications in giant cell arteritis. *Arthritis Rheum.* Apr 1998;41(4):623-633.

356. Cook HT, Khan SB, Allen A, et al. Treatment with an antibody to VLA-1 integrin reduces glomerular and tubulointerstitial scarring in a rat model of crescentic glomerulonephritis. *Am J Pathol.* Oct 2002;161(4):1265-1272.

357. Nachman PH, Hogan SL, Jennette JC, Falk RJ. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol.* Jan 1996;7(1):33-39.

358. De'Oliviera J, Gaskin G, Dash A, Rees AJ, Pusey CD. Relationship between disease activity and anti-neutrophil cytoplasmic antibody concentration in long-term management of systemic vasculitis. *Am J Kidney Dis.* Mar 1995;25(3):380-389.

359. Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ. Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol.* Jan 1996;7(1):23-32.

360. Savige J, Davies D, Falk RJ, Jennette JC, Wiik A. Antineutrophil cytoplasmic antibodies and associated diseases: a review of the clinical and laboratory features. *Kidney Int.* Mar 2000;57(3):846-862.

361. Krafcik SS, Covin RB, Lynch JP, 3rd, Sitrin RG. Wegener's granulomatosis in the elderly. *Chest.* Feb 1996;109(2):430-437.

362. Exley AR, Carruthers DM, Luqmani RA, et al. Damage occurs early in systemic vasculitis and is an index of outcome. *Qjm.* Jun 1997;90(6):391-399.

363. Hoffman GS, Drucker Y, Cotch MF, Locker GA, Easley K, Kwoh K. Wegener's granulomatosis: patient-reported effects of disease on health, function, and income. *Arthritis Rheum.* Dec 1998;41(12):2257-2262.

364. Mekhail TM, Hoffman GS. Longterm outcome of Wegener's granulomatosis in patients with renal disease requiring dialysis. *J Rheumatol.* May 2000;27(5):1237-1240.

365. ten Berge IJ, Wilmink JM, Meyer CJ, et al. Clinical and immunological follow-up of patients with severe renal disease in Wegener's granulomatosis. *Am J Nephrol.* 1985;5(1):21-29.

366. Bindi P, Mougenot B, Mentre F, et al. Necrotizing crescentic glomerulonephritis without significant immune deposits: a clinical and serological study. *Q J Med.* Jan 1993;86(1):55-68.

367. Kliem V, Haubitz M, Ehlerding G, et al. Outcome of kidney transplantation in patients with systemic autoimmune diseases. *Transplant Proc.* Feb-Mar 1997;29(1-2):957-958.

368. Rostaing L, Modesto A, Oksman F, Cisterne JM, Le Mao G, Durand D. Outcome of patients with antineutrophil cytoplasmic autoantibody-associated vasculitis following cadaveric kidney transplantation. *Am J Kidney Dis.* Jan 1997;29(1):96-102.

369. Bradley JD, Brandt KD, Katz BP. Infectious complications of cyclophosphamide treatment for vasculitis. *Arthritis Rheum.* Jan 1989;32(1):45-53.