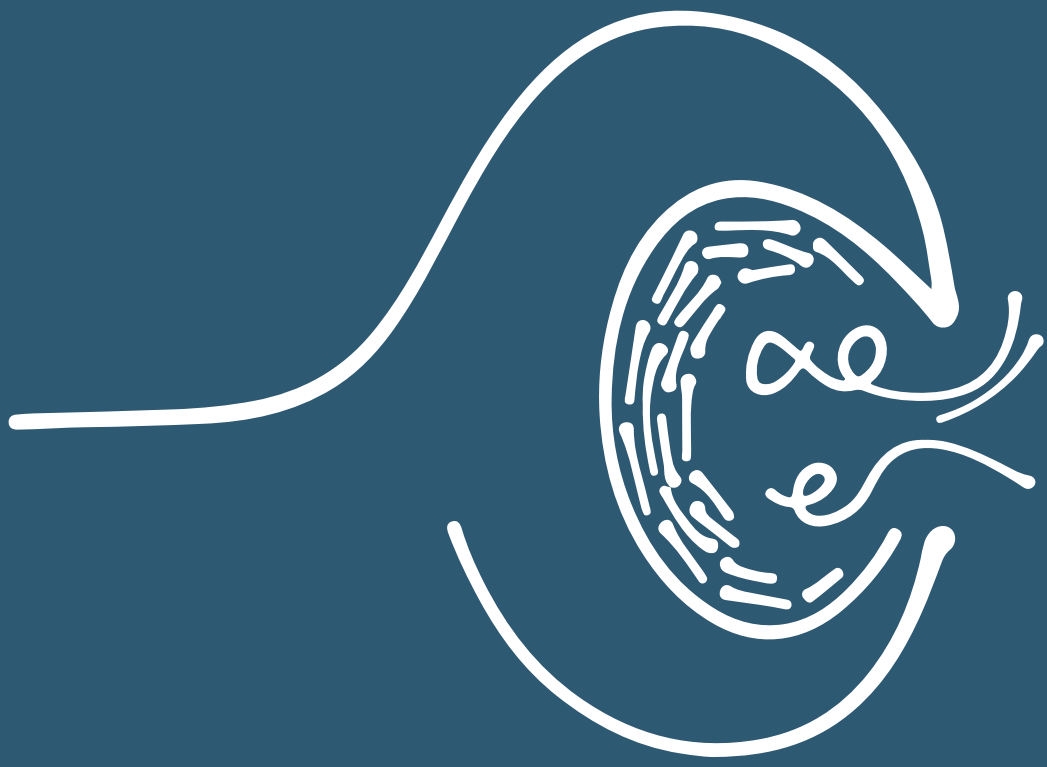
ANCA-associated vasculitis: On clinical management and renal outcome

Goceroglu, A.

6



DIAGNOSIS AND MANAGEMENT OF ANCA-ASSOCIATED VASCULITIS

Annelies E. Berden[1], Arda Göçeroğlu[1], David R.W. Jayne[2], Raashid Luqmani[3], Niels Rasmussen[4], Jan A. Bruijn[1] and Ingeborg M. Bajema[1]

British Medical Journal 2012; 344: e26

[1] Department of Pathology, Leiden University Medical Centre, the Netherlands; [2] Renal Unit, Addenbrooke's Hospital, Cambridge, UK; [3] Department of Rheumatology, University of Oxford, Oxford, UK; [4] Department of Autoimmune Serology, Statens Seruminstitut, Copenhagen, Denmark

SUMMARY POINTS

Consider antineutrophil cytoplasmic antibody (ANCA) associated vasculitis when inflammatory disease cannot be ascribed to any other disease and inflammation progresses despite antibiotics.

Avoid diagnostic delay to prevent end organ damage, particularly renal disease.

Test for ANCA in patients with chronic destructive upper airway disease, pulmonary nodules, renal and pulmonary inflammatory disease, rapidly progressive glomerulonephritis, skin vasculitis with systemic illness, mononeuritis multiplex, subglottic stenosis of the trachea, and retro-orbital mass.

Patients should be managed by a specialist in vasculitides.

Remission is usually induced with high dose glucocorticoids and cyclophosphamide and followed by remission maintenance treatment.

Adverse responses to treatment are common, as are relapses, so long term follow-up is needed.

Vasculitides associated with antineutrophil cytoplasmic antibodies (ANCA) are systemic autoimmune diseases of unknown cause that affect small to medium sized blood vessels. They include granulomatosis with polyangiitis (formerly Wegener's granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome). This review mainly focuses on granulomatosis with polyangiitis and microscopic polyangiitis. Although they are relatively rare, they must be diagnosed and treated early because untreated disease may rapidly develop into multiple organ failure and death. With modern treatment, these diseases are no longer fatal but chronic. Early diagnosis and treatment may prevent progression to end organ damage and lengthen healthier life. A recent large survey of patients with ANCA associated vasculitis found a lag of three to 12 months between disease onset and diagnosis, suggesting that diagnostic delay is a problem.[1] We review the diagnosis and management of ANCA associated vasculitides for the generalist reader, drawing on the findings of observational studies, randomised controlled trials, and meta-analyses.

SOURCES AND SELECTION CRITERIA

We searched PubMed (original search performed in August 2011, updated in December 2011) for relevant articles on epidemiology, diagnosis, and management of antineutrophil cytoplasmic antibody (ANCA) associated vasculitis. Where possible, we sought data from prospective randomised clinical trials and meta-analyses. We also screened personal archives for relevant papers and consulted experts in otolaryngology (NR), nephrology (DJ), and rheumatology (RL). All relevant keyword variations were used. All searches contained the keywords "ANCA" or "vasculitis", or both. We limited results to articles written in English.

WHO GETS IT?

The overall annual incidence of ANCA associated vasculitis in Europe and Northern America is approximately 20 per million (with point prevalence of 130/million for granulomatosis with polyangiitis and 47.9/million for microscopic polyangiitis in the United Kingdom in 2008).[2,3] Disease onset usually occurs at 65-74 years, although it can occur at any age.[3] Prevalence is generally higher in men, but women more often develop disease at a younger age.[1] The overall prevalence of ANCA associated vasculitis is highest in Caucasians.[1,4] The incidence of granulomatosis with polyangiitis is higher in northern Europe, whereas that of microscopic polyangiitis is higher in southern Europe and Japan.[2,5]

HOW DO PATIENTS PRESENT?

Patients typically present with prodromal "flu-like" symptoms of several weeks' or months' duration,[6,7] such as fever, polymyalgia, polyarthralgia, headache, malaise, anorexia, and unintended weight loss. These non-specific symptoms overlap with symptoms of non-vasculitic processes such as post-viral syndrome, infections, or malignancy. Consider vasculitis as a differential diagnosis in patients with general symptoms and signs of inflammatory disease. Some patients may initially present with focal vasculitic disease such as rash, cutaneous vasculitis, bloody-purulent rhinitis, scleritis, or arthritis. In such patients, careful examination of other organ systems may show other disease manifestations.

Figure 1 shows the many ways in which vasculitis can manifest. Patients may report different symptoms over time. Symptoms of the different ANCA associated vasculitides overlap, but some symptoms are more common in certain diseases. For example, ear, nose, and throat problems—such as hearing loss, otalgia, (bloody nasal) rhinorrhoea, otorrhoea, sinusitis, nasal crusting, and recurrent otitis media—occur in about 90% of patients with granulomatosis with polyangiitis and in 35% of those with microscopic polyangiitis.[6,7] Large observational studies have shown that the airways and lung parenchyma are commonly affected, as are the kidneys, although this may not be apparent until renal failure occurs.[6,8,9] Urinalysis may therefore identify renal involvement early on in the disease. About 50% of patients have cutaneous manifestations of disease such as urticarial rash or tender skin nodules. The eyes and nervous system are also commonly affected.[6,8,9] A careful physical examination is needed to determine the full extent of disease.

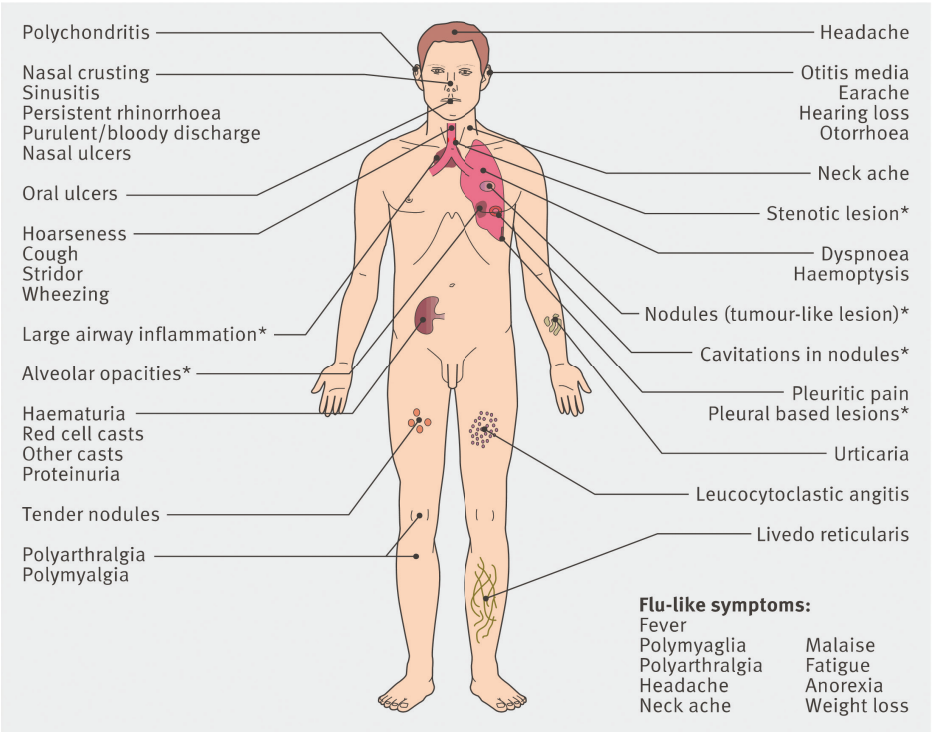


Figure 1 | Clinical manifestations of antineutrophil cytoplasmic antibody associated vasculitis. Alveolar haemorrhage is an important cause of mortality. Renal involvement manifests with early detectable haematuria, red cell and other casts, and proteinuria. It is an important cause of morbidity and mortality. The most common skin lesion is leucocytoclastic angiitis, which mostly causes purpura on the lower extremities, sometimes accompanied by focal necrosis and ulcerations. Skin lesions can appear on parts of the body not shown here. Eye disease presents as a painful or painless red eye. Mononeuritis multiplex is seen in 20% of patients.
*These lesions can be seen on chest radiography and computed tomography.

HOW CAN IT BE DIAGNOSED?

Investigations that can be undertaken in primary care

Blood tests requested in primary care may show leucocytosis, thrombocytosis, raised erythrocyte sedimentation rate and C reactive protein values, normochromic-normocytic anaemia, and a raised serum creatinine.[6] Patients with symptoms and signs of vasculitis and abnormalities on these blood tests require urinalysis, including urinary sedimentation, to look for haematuria and proteinuria. An increased serum creatinine indicates that renal damage has already occurred. Chest radiography in patients with pulmonary symptoms such as dyspnoea, cough, or haemoptysis may show infiltrates, nodules, or cavitations in the lung parenchyma.

An ANCA assay can be requested in primary care. The test is indicated in a patient with unexplained illness that has lasted more than a few weeks (box 1) and is associated with a raised erythrocyte sedimentation rate or C reactive protein, particularly if more than one organ system is affected. Four large international randomised controlled trials found that the test is positive in 90-95% of patients with active generalised granulomatosis with polyangiitis or microscopic polyangiitis before treatment.[10-13] Two types of assay are generally used: indirect immunofluorescence (IIF) and the enzyme linked immunosorbent assay (ELISA). Table 1 outlines the properties of these tests. An international multicentre observational study found that IIF is more sensitive but that ELISA is more specific.[14] The current international standard approach is to use IIF as a screening test and ELISA to confirm positive results.[15] ANCA assays should be performed only in experienced laboratories. Testing is not standardised, so sensitivity and specificity vary between laboratories and reference values are unavailable. Although the ANCA test is positive in most patients with untreated disease, a negative result does not exclude the diagnosis of ANCA associated vasculitis because 5-10% of patients do not develop ANCA. Neither does a negative ANCA test exclude the presence of other non-ANCA associated small and medium vessel vasculitic syndromes. Such patients may require more systematic investigation to ascertain the extent of their disease. Although the ANCA test is widely used as a routine screening tool for vasculitis in secondary care, it provides poor sensitivity and specificity in this setting.[16,17] When there is a clearer indication and likelihood of vasculitis the yield from testing is higher. If there is a high index of suspicion on the basis of clinical findings but the ANCA test is negative, an ANCA assay can be repeated a few weeks after the original test, but if patients have disease manifestations in multiple sites immediate referral is indicated.

Box 1 | Targeted testing for antineutrophil cytoplasmic antibodies

Test when patients have one or more of the following sets of symptoms:

- General: Persistent flu-like condition with headache, myalgias, arthralgias, and weight loss
- Ear, nose, and throat: Hearing loss that slowly develops over days to weeks without a preceding cold, but with "chronic flu"; slowly developing nasal stenosis with midfacial pain and increasing bloody purulent secretion with crust formation that does not respond to antibiotics (granulomatosis with polyangiitis)
- Eyes: Unexplained conjunctivitis combined with general symptoms, uveitis, unilateral proptosis, and paresis of the ocular motor nerves (granulomatosis with polyangiitis)
- Lungs: Slowly developing cough and shortness of breath possibly with bloody-purulent sputum, bilateral infiltrates on radiography that do not respond to antibiotics, non-tuberculous cavitating lesions (granulomatosis with polyangiitis), alveolar haemorrhage (microscopic polyangiitis)
- Skin: Bursts of small cutaneous vasculitis elements, pyoderma gangraenosum, and oedema
- Kidneys: Haematuria, proteinuria, hypertension, decreasing renal function (granulomatosis with polyangiitis and microscopic polyangiitis)

Table 1 | Properties of ANCA tests and their clinical importance

	PR3-ANCA	MPO-ANCA
Test methods	Finely granular staining of the cytoplasm (c-ANCA) is seen on IIF; PR3 is the antigen in direct, capture, anchor, and luminex ELISAs	Perinuclear staining of the neutrophils (p-ANCA) is seen on IIF; MPO is used as the antigen in direct, capture, and luminex ELISAs
Diagnostic potential	Almost all patients in northern Europe with untreated acute granulomatosis with polyangiitis will be positive	Most patients in northern Europe with untreated acute microscopic polyangiitis and some with granulomatosis with polyangiitis will be positive
Relation to disease activity	Immunomodulatory treatment reduces positivity for PR3-ANCA, but positivity increases when treatment is tapered off; reappearance of PR3-ANCA in non-treated patients may reflect disease activity	Immunomodulatory treatment also reduces positivity for MPO-ANCA and it increases when treatment is tapered off, but fluctuations often occur that are not related to disease activity

ANCA=antineutrophil cytoplasmic autoantibodies; ELISA=enzyme linked immunosorbent assay; IIF=indirect immunofluorescence; MPO=myeloperoxidase; PR3=proteinase 3.

Refer any patient with a positive ANCA test result to a specialist in vasculitis, usually a rheumatologist or a nephrologist, or possibly a chest physician or ear, nose, and throat surgeon, depending on clinical presentation (box 2). Referral to specialists without experience with vasculitis may delay diagnosis. Many conditions can be associated

with a positive ANCA test result, including inflammatory bowel disease, chronic infections (such as tuberculosis), and autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis, and ANCA can be induced by several drugs. This highlights the need for judicious testing. The clinical setting in which the test is performed is crucial for interpreting the results. We recommend ANCA testing routinely in the following circumstances: acute or chronic destructive upper airway disease; evidence of renal inflammatory disease as indicated by an active urine sediment or laboratory parameters indicative of rapidly progressive glomerulonephritis; evidence of pulmonary inflammatory disease as indicated by a variety of clinical symptoms or radiographic abnormalities; skin vasculitis associated with systemic illness; and mononeuritis multiplex. ANCA testing is also indicated in subglottic stenosis of the trachea manifesting as slowly progressive dyspnoea and retro-orbital mass manifesting as protrusion of the eye bulb and diplopia, although these conditions may be difficult to recognise without specialist tests.

Box 2 | Specialist otolaryngological management of patients with granulomatosis with polyangiitis

These patients most often have problems in the nose and sinuses. Initially midfacial pain, nasal stenosis, bloody-purulent rhinorrhoea, crust formations that may grow into large "casts" of the entire nasal cavities, and hearing loss are important problems, but these symptoms often disappear on treatment. However, sometimes symptoms do not resolve or slowly reappear as treatment is tapered. Most patients with nasal symptoms have a chronic nasal infection with *S aureus*. Daily nasal lavage with saline is helpful but not curative. Long term antibiotics can be effective, but the infection often reappears when they are tapered. As chronic infection may be difficult to differentiate from smouldering disease, patients may need to be seen by ear, nose, and throat surgeons with experience in vasculitis.

Some patients eventually develop destructive midface lesions, such as the saddle nose deformity, and in these cases plastic surgery can be performed when the disease is inactive and patients are on low dose immunomodulatory treatment.

Investigations performed in specialist care

Computed tomography scanning will provide additional information on the location and nature of lesions identified on chest radiography. A diagnosis of ANCA associated vasculitis is confirmed by specific abnormalities found on tissue biopsies obtained from sites of active disease, such as vasculitis, giant cells, "geographical necrosis," and granulomas. In granulomatosis with polyangiitis, biopsies from the respiratory tract—mainly nose and sinuses—often do not show more than one of the histopathological

hallmarks.[18] In such cases, the doctor has to treat the patient on the basis of typical clinical findings or a positive ANCA test (or both). Multiple biopsies from active lesions, if possible taken from different organs at different times, increase the chance of establishing a histological diagnosis. When the kidneys are affected, renal biopsies have a higher diagnostic yield, generally showing variable amounts of focal necrotising glomerulonephritis. In international randomised unblinded controlled trials that investigated more than 95 renal biopsies, a histopathological diagnosis of ANCA associated glomerulonephritis could be established in 80-98% of biopsies.[11,13,19]

HOW CAN A SPECIALIST IN VASCULITIS BE FOUND?

Not all hospitals will have an expert on vasculitis, but many regional centres have local or national experts or groups of experts. It is not always easy to contact such experts; local patient organisations, under the umbrella of Vasculitis UK or the Vaculitis Foundation are a useful resource because they have regular contact with regional experts in their area. In the UK, experts are often linked to societies or organisations because they run educational or research meetings and are usually engaged in active research programmes. International organisations such as the Vasculitis Foundation in the United States and the European Vasculitis Society (EUVAS) can help with inquiries to locate an expert.

WHAT IS THE NATURAL COURSE OF DISEASE IF LEFT UNTREATED?

A key natural history study of 56 patients in 1958 found that average patient survival was about five months; 82% of patients did not survive the first year after diagnosis and more than 90% of patients died within two years. The main cause of death was “uraemia” as a result of rapidly progressive renal failure, and the second most common cause was respiratory failure.[20]

HOW IS ANCA ASSOCIATED VASCULITIS CURRENTLY TREATED?

Standard treatment consists of inducing remission with high dose glucocorticoids and high dose oral or intravenous pulse cyclophosphamide for three to six months, and maintaining remission with azathioprine or methotrexate while glucocorticoids are slowly reduced and withdrawn.[21]

Trials with intravenous pulse cyclophosphamide as induction therapy have used a minimum six month course. Courses of intravenous pulse cyclophosphamide of less than six months may still be appropriate when rapid disease control is obtained.

Treatment requires specialist supervision; it aims to control disease activity to prevent further damage to organs and to prevent the recurrence of vasculitis. Managing treatment toxicity is an important part of patient care, and the general practitioner may be confronted with this problem (box 3).

According to a large randomised unblinded trial, 75% of patients treated with daily oral cyclophosphamide and prednisolone achieve remission by three months. By that time, prednisolone is usually reduced to 10-15 mg/day,[12] and cyclophosphamide is withdrawn because of the risk of cumulative toxicity and replaced with an alternative immunosuppressant. Patients who do not respond initially to treatment continue with induction treatment for longer and may be considered for second line treatment.[22]

The optimum duration of maintenance treatment is not known and practice differs widely between centres. Alternative maintenance immunosuppressive agents, such as mycophenolate mofetil, might be indicated in individual patients.

Although methotrexate has been used as induction therapy in place of the potentially more toxic cyclophosphamide for limited or non-severe disease, an unblinded randomised controlled trial of 100 patients found that it was associated with higher relapse rates, so its use remains controversial.[10]

In the longer term, regular visits to the specialist are needed (every three months at least) to check on disease activity and treatment side effects, and to manage the consequences of irreversible tissue damage, such as renal failure.

Box 3 | Side effects of commonly used immunosuppressive agents

Cyclophosphamide*: Leucopenia or neutropenia, infections (usually respiratory and urinary tract), infertility, cancer (especially bladder cancer and leukaemia), haemorrhagic cystitis, alopecia, and amenorrhea.

Glucocorticoids: Osteoporosis, candida infection (oral and vaginal), other infections, weight gain, hyperglycaemia or diabetes, hypertension, Cushingoid appearance, skin atrophy, and cataract.

Azathioprine: Nausea, leucopenia or neutropenia, infection, hypersensitivity, cancer, alopecia, cholestasis, and thrombocytopenia.

Methotrexate: Nausea, oral ulcers, liver dysfunction, infection, hypertension, leucopenia.

Mycophenolate mofetil: Infection, leucopenia, gastrointestinal tract manifestations, anaemia, thrombocytopenia.

Rituximab: Infections (encephalitis is particularly dangerous), cancer, anaemia, neutropenia, thrombocytopenia, hypogammaglobulinaemia.

*Cyclophosphamide can be given in two ways: daily oral cyclophosphamide and pulse cyclophosphamide. In the CYCLOPS trial the group that received pulse cyclophosphamide had significantly less leucopenia than the daily oral group. During pulse administration, the patient can be given prehydration and 2-mercaptoethanesulfonate sodium to protect the bladder against the toxicity of cyclophosphamide.[11]

With modern treatment ANCA associated vasculitis has changed from being an imminently life-threatening condition to a chronic condition prone to relapse throughout life. A large observational study of 107 patients found that about 50% of treated patients experience one or more relapses by five years.[23]

Long term follow-up studies have clearly shown that reducing exposure to cyclophosphamide is associated with a higher risk of late relapse, so a balance is needed between reduced exposure to cyclophosphamide and the increased risk of relapse.[24]

Prospectively collected data from 524 patients showed that important risks of treatment with cyclophosphamide include infection, infertility, and incident cancer.[25] Long term treatment with corticosteroids also has many side effects. These adverse effects drive the search for more efficacious and safer treatment modalities.

NEWER THERAPEUTIC AGENTS UNDER STUDY

Two recent prospective randomised controlled trials found that the B cell depleting agent rituximab effectively induced remission in patients with ANCA associated vasculitis, and that its safety profile was comparable with that of standard treatment.[26,27] Further investigation of the efficacy and safety of rituximab is needed, although it was recently approved by the Food and Drug Administration in the US for use in combination with glucocorticoids to treat patients with granulomatosis with polyangiitis and microscopic polyangiitis.

Plasma exchange has been investigated as an adjunct to standard treatment for patients with severe renal disease. In 2007, a large international randomised controlled trial of 137 patients favoured plasma exchange over methylprednisolone as adjunctive treatment with regard to recovery of renal function,[13] but a recent meta-analysis concluded that more data are needed to establish the long term benefit of this treatment.[28]

Plasma exchange is generally safe. A large study of 7538 exchanges in 887 patients showed side effects and technical incidents in 16.8% of all exchanges. This included a transfusion reaction in 6.9%, insufficient flow rate in 5%, hypotension in 2.9%, electrocardiographic alterations in 1.8%, hypocalcaemia in 1.4%, collapse in 0.9%, and pulmonary distress in 0.5%. Plasma exchange was discontinued in only 4% of cases.[29]

WHAT IS THE LONG TERM OUTLOOK FOR PATIENTS WITH ANCA ASSOCIATED VASCULITIS?

With modern treatment the disease has changed from being universally fatal to being a chronic relapsing and remitting disease. Several organs are often affected; renal involvement is common, and glomerulonephritis results in end stage renal failure and a need for renal replacement in 20-40% of patients according to observational studies (within a median follow-up of 3.1 to ≥5 years).[30-33]

The risk of death for patients treated with current treatments is still 2.6 times higher than that of age matched background controls.[34] The increased risk of death is greatest in the first year after diagnosis, when infections and active vasculitis account for most early deaths. Older patients with severe renal impairment have a particularly high risk of dying in the first few months after presentation; this reflects the severity of their disease as well as their increased susceptibility to the toxicity of current treatments.[34] Mortality in patients who survive the first year after diagnosis is still 1.3 times higher than that of age matched population controls. Death after the first year is mainly caused by infections, cardiovascular disease, and cancer.[34]

Patients are at lifelong increased risk of infections and often need treatment with antibiotics. In a population based case-control study, many patients reported fatigue, which affected employment and overall quality of life, as a major problem.[35] The socioeconomic impact of the disease, however, has proved difficult to assess.[36]

WHAT SHOULD GENERALISTS BE AWARE OF WITH REGARD TO TREATMENT?

Patients may turn to their general practitioner for support and information. The first few weeks of treatment can be difficult because patients usually still have symptoms associated with vasculitis. Frequent hospital visits and blood tests are needed to monitor disease activity and response to treatment.

Before each treatment with high dose cyclophosphamide, platelet and white cell counts, particularly the neutrophil count, must be above the lower limit of normal and liver function must be stable. Creatinine concentrations are needed to make dose adjustments. For daily oral cyclophosphamide, azathioprine, or mycophenolate mofetil, and for weekly methotrexate, routine monitoring of blood counts, liver function, and renal function are important to avoid drug toxicity. It is usually more convenient for patients to attend the primary care practice for these routine blood tests, but this requires good communication between primary care and secondary care. Guidelines

on how treatment should be changed in response to unexpected results should be agreed on before treatment.

Patients are susceptible to infections particularly during induction treatment (most usually respiratory or urinary tract infections), and early intervention with antibiotics is necessary for confirmed infections. In case of pulse cyclophosphamide, which is routinely followed by antiemetics and oral antifungal treatment, the most vulnerable time for patients is seven to 10 days after each pulse. The drug suppresses the bone marrow, causing neutropenia and increased risk of infection. Patients are advised not to visit or be visited by anyone with an upper or lower respiratory tract infection during this time. Patients on pulse cyclophosphamide may become profoundly tired in the two to three days after administration but will gradually improve. However, be aware of potential drug interactions. For example, patients with granulomatosis with polyangiitis may be treated with high doses of methotrexate and could develop severe neutropenia if treated for a urinary tract infection with standard dose co-trimoxazole; prophylactic use of low dose co-trimoxazole (960 mg three times a week) is therefore suggested as standard concomitant treatment with methotrexate.

Remember to consider consequences of damage caused by the disease, such as chronic kidney disease, and the effects of treatment, such as osteoporosis and impaired glycaemic control caused by chronic exposure to glucocorticoids. Patients are also at increased risk of cancer and premature and accelerated atherosclerosis, which predisposes them to early cardiovascular disease, including strokes.[37-41] It is important to control and treat all well known cardiovascular risk factors. Three observational studies found an increased incidence of venous thromboembolic events, which did not seem to be attributable to classic prothrombic risk factors.[42-44] Proton pomp inhibitors are prescribed to prevent mucosal damage of the stomach as a result of high doses of glucocorticoids. Patients taking immunosuppressive drugs usually require prophylaxis with co-trimoxazole because of an increased risk of acquiring *Pneumocystis jiroveci* pneumonia (box 4).

Box 4 | Important points for generalists

Regularly follow up the patient and be aware of some specific problems and prophylactic strategies*

Specific problems and prophylactic strategies

- Osteoporosis: Use of bisphosphonates
- Cardiovascular disease: Use of statins and smoking cessation
- Hyperglycaemia or diabetes: Regular glycaemic control
- Hypertension: Regular blood pressure control
- Gastric mucosal damage: Use of a proton pump inhibitor
- Oral ulcers: Use of folic acid or folinic acid
- *Pneumocystis jiroveci* pneumonia: Prophylactic co-trimoxazole
- Fatigue: Informal support or formal counselling

*The specialist will supervise this, but generalists need to be aware. If one of these problems occurs, the patient must be seen immediately by the doctor in charge at the vasculitis clinic. Rapid referral to specialist care is also needed if patients become ill with no obvious cause, especially if they report unusual symptoms.

Because relapse can occur after many years in remission, patients often remain on indefinite follow-up. Disease flares are common and patients must be encouraged to seek urgent medical attention if they experience a flare—that is, recurrence, deterioration, or new onset of symptoms and signs attributable to active vasculitis (box 5). If patients have a flare or experience serious complications of treatment they may require hospital admission. If early symptoms are missed or ignored, a serious episode of vasculitis with renal or respiratory failure may ensue. Patients are usually educated to look out for early symptoms of relapse so that this kind of avoidable disaster can be prevented.

Box 5 | Characteristics of a flare

Flare: Recurrence, deterioration, or new onset of symptoms and signs attributable to active vasculitis.

Major flare: Recurrence, deterioration, or new onset of at least one item on the Birmingham vasculitis activity score (see supplementary material),[45-47] indicating a threat to vital organ function as a result of active vasculitis. Examples include:

- 30% increase of creatinine or 25% decrease of glomerular filtration rate within three months
- Evidence of severe pulmonary haemorrhage or granulomata
- Threatened vision (including orbital granuloma and retinal vasculitis)
- Sensorineural deafness
- New multifocal neurological lesions or mononeuritis multiplex
- Gastrointestinal haemorrhage or perforation

Minor flare: Recurrence, deterioration, or new onset of at least three other items on the Birmingham vasculitis activity score related to non-vital organs attributable to active vasculitis. Examples include:

- Epistaxis, nasal crusting, lesions on nasal endoscopy
- Conductive deafness
- Deafness
- Rash
- Myalgia, arthralgia, arthritis
- (Epi)scleritis
- Pulmonary symptoms not characteristic of a major relapse

WHAT CAUSES VASCULITIS?

Although the precise causes are unknown, ANCA associated vasculitis probably results from an interplay between genetic and environmental factors. Several associations have been made with genes that encode proteins involved in immunity, which are also often associated with other autoimmune diseases.[48] However, family members or twins of patients with granulomatosis with polyangiitis are rarely reported to have disease manifestations, which goes against a strong genetic predisposition.[1] A recent study using Swedish nationwide registers did show some increased familial occurrence of granulomatosis with polyangiitis, which might denote genetic susceptibility to the disease, but exposure to similar environmental factors might also induce familial clustering.[49]

Among the environmental factors that have been implicated are occupational exposure to silica (such as farming, construction work), antithyroid and antihypertensive drugs (propylthiouracil and hydralazine), and several microbial agents, particularly *Staphylococcus aureus*.[50] Chronic nasal carriage of this agent has been associated with a higher incidence of relapse in granulomatosis with polyangiitis,[51] and a multicentre randomised double blind controlled trial showed that prophylactic treatment with co-trimoxazole reduces the incidence of relapses in granulomatosis with polyangiitis.[52]

All these factors may play a role in the development of ANCA, which are generally considered a pathogenic factor. The most direct clinical evidence for their pathogenicity is the development of pulmonary renal syndrome in a neonate shortly after being born to a mother with myeloperoxidase (MPO)-ANCA positive microscopic polyangiitis, probably because of transplacental transmission of maternal MPO-ANCA.[53,54] No other such cases have been reported, however, and a full term healthy normal child was recently born to a mother with microscopic polyangiitis, despite transplacental transfer of MPO-ANCA.[55] The development of a mouse model in which injection of MPO-ANCA induced glomerulonephritis and vasculitis similar to that seen in human disease provides strong in vivo evidence for the pathogenicity of these antibodies.[56] However, to date, an equally good model has not been developed for proteinase 3 (PR3)-ANCA.

A key role for neutrophils in the acute injury to the blood vessel wall is firmly established in ANCA associated vasculitis. Priming of circulating neutrophils by cytokines, possibly during infection, is thought to underlie local accumulation of neutrophils in the disease. Neutrophil priming causes PR3 and MPO to be expressed on the neutrophil cell membrane, where it becomes accessible to ANCA. Neutrophils activated by ANCA degranulate, produce reactive oxygen species, and release proteolytic enzymes that damage blood vessel walls.[57,58] Apart from ANCA and neutrophils, abnormalities in cellular immunity are probably important,[59] and in recent years an important role for the alternative pathway of complement has also been proposed. Because human ANCA associated glomerulonephritis is pauci-immune, with virtually no deposition of complement in the renal tissue, it had been assumed that complement played no role in this disease. However, recent studies support a role for the alternative pathway of complement in experimental models and in human pauci-immune MPO-ANCA associated vasculitis.[60,61]

Questions for future research

What is the optimum duration of maintenance treatment? This question may be answered by the findings of the REMAIN trial (AVERT project BIOMED-2: BMH-CT93-1078, trial registration number REMAIN 08.022006; www.vasculitis.org) conducted by EUVAS, which is investigating benefits of prolonged maintenance treatment.

With increasing insights into the pathogenesis of the disease and the detection of new biomarkers, might new targeted treatments replace existing standard treatments?

How might we develop patient tailored treatments for patients on the basis of clinical signs and symptoms in combination with genetic information? CCX168, an antagonist of complement factor C5a, is currently a candidate for clinical development.

What are the benefits of plasma exchange? A EUVAS/Vasculitis Clinical Research Consortium (VCRC) trial (PEXIVAS), which is designed to confirm and further explore the benefit of adjuvant plasma exchange, is currently under way.

A question that is important to patients is "How can fatigue associated with vasculitis and its treatment be managed?"

What causes the development of antineutrophil cytoplasmic antibodies (ANCA) and how do we prevent ANCA-associated vasculitis?

More basic research studies are needed to answer these questions.

DISCLOSURES

DJ has received a grant and consulting fee/honorarium from Roche; RL does consultancy of Chemocentryx and Nordic, reports for solicitors on individual cases (expert testimony), is in discussion with Nordic for administrative support to oversee data collection for a Nordic funded study in vasculitis (grants/grants pending), gets paid for lectures including service on speakers bureaus for UCB, receives royalties from EPS research for software that he originally designed to manage use of biologic therapy within NICE guidelines, and receives travel, accommodation and registration fees to attend the annual American College of Rheumatology and European League Against Rheumatism meetings, NR gets paid for lectures including service on speakers bureaus for Phadia and EuroDiagnostica, IB does consultancy of Roche on lupus nephritis; no other relationships or activities that could appear to have influenced the submitted work.

A patient's perspective

Nine years ago I visited my general practitioner with pain in my right knee. He tested twice for rheumatoid arthritis but the results were negative. I was then referred to the rheumatologist at the university clinic. A few months later most of my joints were affected and it seemed that I would be condemned to a wheelchair. The rheumatologist diagnosed rheumatoid arthritis and treated me accordingly. One month later my condition had worsened—I was vomiting two or three times a day, my eyes were reddish, and I had nasal crusting. My rheumatologist had seen a patient with these symptoms once before and she tested me for various factors including antineutrophil cytoplasmic antibody. The next day I was seen by her and a nephrologist. The new diagnosis was Wegener's granulomatosis. This news was a blessing in disguise. I would probably walk again, but I had lost 50% of my renal function. My treatment consisted of heavy immunosuppression including corticosteroids. Over the nine years that followed I had two cataract operations, a prosthetic knee implant, many erythropoietin injections, and a kidney transplant (a gift from my wife); I also experienced Guillain-Barré syndrome, cerebral haemorrhage, and constant bronchitis. Now I am fine. At the age of 69, I now have enough energy to enjoy life.

Henk van Wilpe, *Utrecht*

Additional educational resources

Resources for clinicians

Europe European Vaculitis Society (www.vasculitis.org/) and US Vasculitis Clinical Research Consortium (http://rarediseasesnetwork.epi.usf.edu/vcrc/)—Research collaboratives that focus on vasculitis.

Johns Hopkins Vasculitis Center (www.hopkinsvasculitis.org/)—Provides detailed information on vasculitis.

Fries JF, Hunder GG, Bloch DA, Michel BA, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. *Arthritis Rheum* 1990;33:1135-6

Resources for patients

Vasculitis Foundation (www.vasculitisfoundation.org)—US website providing relevant information for doctors and patients.

Vasculitis Foundation Canada (www.vasculitis.ca)—Canadian website providing information and support for patients.

The Dutch Vaculitis Patient Foundation (www.vasculitis.nl)—Dutch website providing useful information for medical professionals and patients.

Vasculitis UK (www.vasculitis-uk.org.uk/news.html)—Provides information on vasculitis and on local support groups.

REFERENCES

1 Abdou NI, Kullman GJ, Hoffman GS, et al. Wegener's granulomatosis: survey of 701 patients in North America. Changes in outcome in the 1990s. *J Rheumatol,* 2002;29: 309-316.

2 Watts RA, Scott DG, Jayne DR, et al. Renal vasculitis in Japan and the UK—are there differences in epidemiology and clinical phenotype? *Nephrol Dial Transplant,* 2008;23: 3928-3931.

3 Watts RA, Lane SE, Bentham G, Scott DG. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum,* 2000;43: 414-419.

4 Mahr A, Guillevin L, Poissonnet M, Ayme S. Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. *Arthritis Rheum,* 2004;51: 92-99.

5 Watts RA, Lane SE, Scott DG, et al. Epidemiology of vasculitis in Europe. *Ann Rheum Dis,* 2001;60: 1156-1157.

6 Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med,* 1992;116: 488-498.

7 Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med,* 1997;337: 1512-1523.

8 Reinhold-Keller E, Beuge N, Latza U, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. *Arthritis Rheum,* 2000;43: 1021-1032.

9 Stone JH. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial. *Arthritis Rheum,* 2003;48: 2299-2309.

10 De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum,* 2005;52: 2461-2469.

11 De Groot K, Harper L, Jayne DR, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med,* 2009;150: 670-680.

12 Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med,* 2003;349: 36-44.

13 Jayne DR, Gaskin G, Rasmussen N, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol,* 2007;18: 2180-2188.

14 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,* 1998;53: 743-753.

15 Savige J, Gillis D, Benson E, et al. International consensus statement on testing and reporting of antineutrophil cytoplasmic antibodies (ANCA). *Am J Clin Pathol,* 1999;111: 507-513.

16 Arnold DF, Timms A, Luqmani R, Misbah SA. Does a gating policy for ANCA overlook patients with ANCA associated vasculitis? An audit of 263 patients. *J Clin Pathol,* 2010;63: 678-680.

17 McLaren JS, Stimson RH, McRorie ER, Coia JE, Luqmani RA. The diagnostic value of anti-neutrophil cytoplasmic antibody testing in a routine clinical setting. *QJM*, 2001;94: 615-621.
18 Rasmussen N, Petersen J, Jensen H, Andersen V. Histopathological findings in biopsies from patients with Wegener's granulomatosis. *APMIS Suppl*, 1990;19: 15-16.
19 Hauer HA, Bajema IM, van Houwelingen HC, et al. Determinants of outcome in ANCA-associated glomerulonephritis: a prospective clinico-histopathological analysis of 96 patients. *Kidney Int*, 2002;62: 1732-1742.
20 Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *BMJ*, 1958;2: 265-270.
21 Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med*, 2008;359: 2790-2803.
22 Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis*, 2009;68: 310-317.
23 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*, 1996;7: 23-32.
24 Harper L, Morgan MD, Walsh M, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis*, 2012;71: 955-960.
25 Little MA, Nightingale P, Verburgh CA, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis*, 2010;69: 1036-1043.
26 Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*, 2010;363: 211-220.
27 Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*, 2010;363: 221-232.
28 Walsh M, Catapano F, Szpirt W, et al. Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis. *Am J Kidney Dis*, 2011;57: 566-574.
29 Bussel A, Jais JP. Side effects and mortality associated with plasma exchange: a three year experience with a regional register. *Life Support Syst*, 1987;5: 353-358.
30 Booth AD, Almond MK, Burns A, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis*, 2003;41: 776-784.
31 Koldingsnes W, Nossent H. Predictors of survival and organ damage in Wegener's granulomatosis. *Rheumatol (Oxford)*, 2002;41: 572-581.
32 Little MA, Nazar L, Farrington K. Outcome in glomerulonephritis due to systemic small vessel vasculitis: effect of functional status and non-vasculitic co-morbidity. *Nephrol Dial Transplant*, 2004;19: 356-364.
33 Slot MC, Tervaert JW, Franssen CF, Stegeman CA. Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. *Kidney Int*, 2003;63: 670-677.
34 Flossmann O, Berden A, De Groot K, et al. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis*, 2011;70: 488-494.
35 Basu N, Jones GT, Fluck N, et al. Fatigue: a principal contributor to impaired quality of life in ANCA-associated vasculitis. *Rheumatol (Oxford)*, 2010;49: 1383-1390.

36 Cotch MF. The socioeconomic impact of vasculitis. *Curr Opin Rheumatol,* 2000;12: 20-23.
37 De Leeuw K, Sanders JS, Stegeman C, Smit A, Kallenberg CG, Bijl M. Accelerated atherosclerosis in patients with Wegener's granulomatosis. *Ann Rheum Dis,* 2005;64: 753-759.
38 Faurschou M, Mellemkjaer L, Sorensen IJ, Svalgaard TB, Dreyer L, Baslund B. Increased morbidity from ischemic heart disease in patients with Wegener's granulomatosis. *Arthritis Rheum,* 2009;60: 1187-1192.
39 Heijl C, Harper L, Flossmann O, et al. Incidence of malignancy in patients treated for antineutrophil cytoplasm antibody-associated vasculitis: follow-up data from European Vasculitis Study Group clinical trials. *Ann Rheum Dis,* 2011;70: 1415-1421.
40 Morgan MD, Turnbull J, Selamet U, et al. Increased incidence of cardiovascular events in patients with antineutrophil cytoplasmic antibody-associated vasculitides: a matched-pair cohort study. *Arthritis Rheum,* 2009;60: 3493-3500.
41 Suppiah R, Judge A, Batra R, et al. A model to predict cardiovascular events in patients with newly diagnosed Wegener's granulomatosis and microscopic polyangiitis. *Arthritis Care Res (Hoboken),* 2011;63: 588-596.
42 Merkel PA, Lo GH, Holbrook JT, et al. Brief communication: high incidence of venous thrombotic events among patients with Wegener granulomatosis: the Wegener's Clinical Occurrence of Thrombosis (WeCLOT) study. *Ann Intern Med,* 2005;142: 620-626.
43 Stassen PM, Derks RP, Kallenberg CG, Stegeman CA. Venous thromboembolism in ANCA-associated vasculitis—incidence and risk factors. *Rheumatol (Oxford),* 2008;47: 530-534.
44 Weidner S, Hafezi-Rachti S, Rupprecht HD. Thromboembolic events as a complication of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum,* 2006;55: 146-149.
45 Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham vasculitis activity score (version 3). *Ann Rheum Dis,* 2009;68: 1827-1832.
46 Luqmani RA, Bacon PA, Moots RJ, et al. Birmingham vasculitis activity score (BVAS) in systemic necrotizing vasculitis. *QJM,* 1994;87: 671-678.
47 Luqmani RA, Exley AR, Kitas GD, Bacon PA. Disease assessment and management of the vasculitides. *Baillieres Clin Rheumatol,* 1997;11: 423-446.
48 Willcocks LC, Lyons PA, Rees AJ, Smith KG. The contribution of genetic variation and infection to the pathogenesis of ANCA-associated systemic vasculitis. *Arthritis Res Ther,* 2010;12: 202.
49 Knight A, Sandin S, Askling J. Risks and relative risks of Wegener's granulomatosis among close relatives of patients with the disease. *Arthritis Rheum,* 2008;58: 302-307.
50 De Lind van Wijngaarden RA, van Rijn L, Hagen EC, et al. Hypotheses on the etiology of antineutrophil cytoplasmic autoantibody associated vasculitis: the cause is hidden, but the result is known. *Clin J Am Soc Nephrol,* 2008;3: 237-252.
51 Stegeman CA, Tervaert JW, Sluiter WJ, Manson WL, de Jong PE, Kallenberg CG. Association of chronic nasal carriage of Staphylococcus aureus and higher relapse rates in Wegener granulomatosis. *Ann Intern Med,* 1994;120: 12-17.

52 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*, 1996;335: 16-20.

53 Bansal PJ, Tobin MC. Neonatal microscopic polyangiitis secondary to transfer of maternal myeloperoxidase-antineutrophil cytoplasmic antibody resulting in neonatal pulmonary hemorrhage and renal involvement. *Ann Allergy Asthma Immunol*, 2004;93: 398-401.

54 Schlieben DJ, Korbet SM, Kimura RE, Schwartz MM, Lewis EJ. Pulmonary-renal syndrome in a newborn with placental transmission of ANCAs. *Am J Kidney Dis*, 2005;45: 758-761.

55 Silva F, Specks U, Sethi S, Irazabal MV, Fervenza FC. Successful pregnancy and delivery of a healthy newborn despite transplacental transfer of antimyeloperoxidase antibodies from a mother with microscopic polyangiitis. *Am J Kidney Dis*, 2009;54: 542-545.

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

57 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*, 1990;87: 4115-4119.

58 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,* 1994;153: 1271-1280.

59 Berden AE, Kallenberg CG, Savage CO, et al. Cellular immunity in Wegener's granulomatosis: characterizing T lymphocytes. *Arthritis Rheum,* 2009;60: 1578-1587.

60 Xiao H, Schreiber A, Heeringa P, Falk RJ, Jennette JC. Alternative complement pathway in the pathogenesis of disease mediated by anti-neutrophil cytoplasmic autoantibodies. *Am J Pathol,* 2007;170: 52-64.

61 Xing GQ, Chen M, Liu G, et al. Complement activation is involved in renal damage in human antineutrophil cytoplasmic autoantibody associated pauci-immune vasculitis. *J Clin Immunol,* 2009;29: 282-291.

SUPPLEMENTARY MATERIAL

Diagnosis and management of ANCA-associated vasculitis

Birmingham Vasculitis Activity Score (version 3)

Patient ID: **Date of birth:** **Total score:**

Assessor: **Date of assessment:**

Tick an item **only** if attributable to active vasculitis. If there are no abnormalities in a section, please tick 'None' for that organ-system.			If **all** abnormalities are due to persistent disease (active vasculitis which is not new/worse in the prior 4 weeks), tick the **PERSISTENT** box at the bottom right corner		
Is this the patient's first assessment?			**Yes** ○	**No** ○	
	None	Active disease		None	Active disease
1. General	○		**6. Cardiovascular**	○	
Myalgia		○	Loss of pulses		○
Arthralgia / arthritis		○	Valvular heart disease		○
Fever ≥38° C		○	Pericarditis		○
Weight loss ≥2 kg		○	**◊ Ischaemic cardiac pain**		○
2. Cutaneous	○		**◊ Cardiomyopathy**		○
Infarct		○	**◊ Congestive cardiac failure**		○
Purpura		○	**7. Abdominal**	○	
Ulcer		○	Peritonitis		○
◊ Gangrene		○	Bloody diarrhoea		○
Other skin vasculitis		○	**◊ Ischaemic abdominal pain**		○
3. Mucous membranes / eyes	○		**8. Renal**	○	
Mouth ulcers		○	Hypertension		○
Genital ulcers		○	Proteinuria >1+		○
Adnexal inflammation		○	**◊Haematuria ≥10 RBCs/hpf**		○
Significant proptosis		○	Creatinine 125-249µ/L(1.41-2.82mg/dl)*		○
Scleritis / Episcleritis		○	Creatinine 250-499 µ/L(2.83-5.64mg/dl)*		○
Conjunctivitis / Blepharitis / Keratitis		○	**◊Creatinine ≥500 µ/L (≥5.66mg/dl)***		○
Blurred vision		○	**◊Rise in serum creatinine >30% or fall in creatinine clearance >25%**		○
Sudden visual loss		○			
Uveitis		○	***Can only be scored on the first assessment**		
◊Retinal changes (vasculitis / thrombosis / exudate / haemorrhage)		○	**9. Nervous system**	○	
			Headache		○
			Meningitis		○
4. ENT	○		Organic confusion		○
Bloody nasal discharge / crusts / ulcers / granulomata		○	Seizures (not hypertensive)		○
			◊Cerebrovascular accident		○
Paranasal sinus involvement		○	**◊Spinal cord lesion**		○
Subglottic stenosis		○	**◊Cranial nerve palsy**		○
Conductive hearing loss		○	Sensory peripheral neuropathy		○
◊Sensorineural hearing loss		○	**◊Mononeuritis multiplex**		○

5. Chest	○		
Wheeze	○	**10. Other**	○
Nodules or cavities	○	a.	○
Pleural effusion / pleurisy	○	b.	○
Infiltrate	○	c.	○
Endobronchial involvement	○	d.	○
◊ **Massive haemoptysis / alveolar haemorrhage**	○	**PERSISTENT DISEASE ONLY:**	
◊ **Respiratory failure**	○	(Tick here if **all** the abnormalities are due to persistent disease)	☐

◊ Major items highlighted
References: 45-47