

## Guidelines



# BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis

C. Lapraik<sup>1</sup>, R. Watts<sup>2,3</sup>, P. Bacon<sup>4</sup>, D. Carruthers<sup>5</sup>, K. Chakravarty<sup>6</sup>, D. D'Cruz<sup>7</sup>, L. Guillevin<sup>8</sup>, L. Harper<sup>9</sup>, D. Jayne<sup>10</sup>, R. Luqmani<sup>11</sup>, J. Mooney<sup>12</sup>, D. Scott<sup>1,2</sup> on behalf of the BSR and BHPR Standards, Guidelines and Audit Working Group

**KEY WORDS:** Vasculitis, Guideline, Management, Cyclophosphamide.

## Section 1: Scope and purpose

### 1.1 Background to disease

The primary systemic vasculitides (PSV) are heterogeneous, multi-system disorders characterized by inflammation and necrosis of small and medium blood vessels. Their aetiology is unknown. Three distinct clinico-pathological syndromes, often associated with anti-neutrophil cytoplasmic antibodies (ANCA) [sometimes called ANCA associated vasculitis (AAV)], have been identified and collectively comprise the most common subgroup: Wegener's granulomatosis (WG), Churg–Strauss syndrome (CSS) and microscopic polyangiitis (MPA). Other forms of systemic vasculitis (listed in Table 1) are usually ANCA negative, and are defined by their clinico-pathological features.

There are no validated diagnostic criteria for primary systemic vasculitis. However, the American College of Rheumatology (ACR) devised classification criteria for different vasculitides including WG, CSS and polyarteritis nodosa (PAN) but not MPA, and the Chapel Hill consensus conference (CHCC) recommended definitions for WG, CSS, PAN and MPA [1–4]. The CHCC definitions were not intended for classification or diagnosis but provide a useful description of disease and include some features that have been used for classification purposes.

<sup>1</sup>Department of Rheumatology, Norfolk and Norwich University Hospital, Norwich, <sup>2</sup>School of Medicine Health Policy and Practice, University of East Anglia, Norwich, <sup>3</sup>Department of Rheumatology, Ipswich Hospital NHS Trust, Ipswich, <sup>4</sup>Department of Rheumatology, University of Birmingham, <sup>5</sup>Department of Rheumatology, City Hospital Birmingham, <sup>6</sup>Department of Rheumatology, Harrold Wood Hospital, London, <sup>7</sup>Department of Rheumatology, St Thomas's Hospital, London, <sup>8</sup>Department of Internal Medicine, University of Paris-Nord, Paris, <sup>9</sup>Department of Nephrology, Queen Elizabeth Hospital, Birmingham, <sup>10</sup>Department of Nephrology, Addenbrooke's Hospital, Cambridge, <sup>11</sup>Department of Rheumatology, Nuffield Orthopaedic Centre and University of Oxford, Oxford and <sup>12</sup>School of Nursing and Midwifery, University of East Anglia, Norwich.

Submitted 3 November 2006; revised version accepted 24 April 2007.

Correspondence to: Dr Richard Watts, Consultant Rheumatologist, Ipswich Hospital NHS Trust, Heath Road, Ipswich IP4 5PD, UK. E-mail: Richard.watts@ipswichhospital.nhs.uk

Lanham *et al.* [5] reviewed CSS in 1984 and provided a slightly different and mainly clinical orientated set of classification criteria when compared with the ACR for CSS.

The ACR also provided classification criteria for giant cell arteritis, Takayasu's arteritis, classical polyarteritis nodosa and Henoch–Schönlein purpura. The treatment for these conditions is outside the scope of this review which concentrates on the ANCA associated vasculitides. However, there are patients with primary and secondary vasculitis that are treated with cyclophosphamide, and these guidelines can be used for such conditions although the references to clinical studies for these conditions have not been included in this document.

The classification of systemic vasculitis seen in Table 1 is the most widely accepted classification system [6].

There are several measures of disease activity, severity and damage such as the Birmingham Vasculitis Activity Score (BVAS), Vasculitis Damage Index (VDI), the damage extent index (DEI) and the five factor score. BVAS and VDI are validated clinical tools that are most widely used as measures of disease severity, activity and damage [7, 8]. It should be noted that these do not incorporate ANCA as part of the assessment of disease activity.

The use of cyclophosphamide and other immunosuppressive agents has transformed the prognosis of many of the systemic vasculitides. The natural history of untreated WG and MPA is of a rapidly progressive, usually fatal disease. Walton observed a mean survival of 5 months, with 82% of patients dying within 1 yr and more than 90% dying within 2 yrs in patients with WG [9]. The introduction of cyclophosphamide combined with prednisolone resulted in a significant improvement in mortality of WG with a 5-yr survival rate of 82%, although there remains considerable morbidity associated with both disease and treatment [10, 11]. The prognosis is worse for elderly patients, those with renal disease (especially high creatinine at presentation), pulmonary involvement, high ESR and those with a high disease activity and damage scores [12–17].

**Diagnosis.** In the early phases of the disease, the symptoms can be non-specific and a high index of suspicion is required to

TABLE 1. Classification of systemic vasculitis

Dominant vessel	Primary	Secondary
Large arteries	Giant cell arteritis Takayasu's arteritis	Aortitis associated with RA, infection (e.g. syphilis, TB)
Medium arteries	Classical PAN Kawasaki disease	Hepatitis B associated PAN
Small vessels and medium arteries	Wegener's granulomatosis <sup>a</sup> Churg–Strauss syndrome <sup>a</sup> Microscopic polyangiitis <sup>a</sup>	Vasculitis secondary to rheumatoid arthritis, systemic lupus erythematosus, Sjögrens syndrome, drugs, infection (e.g. HIV)
Small vessels	Henoch–Schönlein purpura Cryoglobulinaemia cutaneous leucocytoclastic angiitis	Drugs, hepatitis C-associated infection

<sup>a</sup>Diseases most commonly associated with ANCA and a significant risk of renal involvement, and most responsive to immunosuppression with cyclophosphamide.

achieve an early diagnosis. Symptoms that should prompt consideration of a diagnosis of vasculitis are unexplained systemic disturbance, arthritis or arthralgia, polymyalgia, episcleritis, neuropathy, microscopic haematuria, pulmonary infiltrates or nodules and maturity onset asthma.

Once major organ involvement occurs the diagnosis usually becomes clear. Unfortunately, the presence of more advanced disease at diagnosis limits the potential benefit of therapy. Detailed clinical and laboratory assessments are very important to provide a full picture of the disease and assist in identifying the specific type of vasculitis in the majority of cases. Laboratory and imaging studies are essential in helping to confirm a clinical diagnosis but are of limited value in the absence of clinical signs when considering a diagnosis of systemic vasculitis and its differential diagnosis [18].

**Differential diagnosis.** Vasculitic syndromes are considered in the differential diagnosis of patients with multi system illness or pyrexia of unknown origin. However, there are a number of specific conditions that can mimic vasculitis, including infections, non-infectious inflammatory diseases, malignancy, drugs and factitious illnesses. Disorders such as atrial myxoma, cholesterol emboli and catastrophic anti-phospholipid syndrome may also mimic vasculitic disorders. Vasculitis occurs commonly in the context of other autoimmune connective tissue diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [19, 20].

**Investigations.** Investigations are aimed at confirming the diagnosis, excluding secondary causes of vasculitis, assessing organ involvement and disease severity. Acute phase reactants such as CRP and ESR are typically elevated in the acute phases of most vasculitides. Urinalysis should be performed as soon as a diagnosis of vasculitis is suspected because renal involvement in particular may progress silently. Full blood count (FBC) should be measured, looking particularly for eosinophilia. It is essential to investigate critical organ function including renal, cardiac and pulmonary assessments, with appropriate organ-specific tests (creatinine clearance, echo-cardiography, pulmonary function tests, etc).

Autoantibodies including ANCA are useful in the appropriate clinical setting. It is important to recognize that a negative ANCA does not exclude vasculitis and a positive ANCA does not necessarily prove vasculitis [18]. ANCA specificity is also important, with the presence of PR3 ANCA being strongly suggestive of a diagnosis of WG [21]. MPO ANCA is less specific,

but also is most frequently associated with MPA and CSS. Thirty percentage of cases with CSS or localized WG may be ANCA negative.

Other useful tests include ANA (to exclude SLE, although it can be difficult to interpret the presence of pANCA in the presence of ANA), rheumatoid factor, complement levels (may be raised as part of an acute phase response but lowered in immune complex mediated essential mixed cryoglobulinaemia, bacterial infections and SLE), cardiolipin antibodies and lupus anticoagulant for anti-phospholipid syndrome and cryoglobulins. Cryoglobulinaemia may occur in isolation or in association with other connective tissue diseases. In essential mixed cryoglobulinaemia associated with small vessel vasculitis, the cryoglobulins may be associated with internal organ damage and may require aggressive therapy.

Infection should be excluded by blood culture and appropriate serology (including parvovirus, Hepatitis B, Hepatitis C and HIV) because the treatment for PSV involves intense immunosuppression. A tissue diagnosis should be obtained wherever possible. The choice of biopsy site is dependant on the clinical features, but skin and renal are often helpful for diagnosis. It is important to recognize that very early in the disease process, the classical histological features of vasculitis may be absent. For example, in one series of patients with WG with classical disease only 50% had classical granuloma on histology. Upper airway biopsy frequently shows changes compatible with the diagnosis but rarely classical granulomatous vasculitis. The treatment should not be delayed solely to get a biopsy if there are strong clinical grounds to make a diagnosis of vasculitis.

Imaging investigations including angiography should be carefully considered in appropriate cases. The role of MRA/MRI and PET are particularly valuable in assessing large vessel vasculitis such as giant cell arteritis, but they have limited availability. Coeliac axis angiography should be considered in situations where PAN is strongly suspected, such as patients with severe abdominal pain, frank haematuria and HBV infection.

### 1.2 Need for guideline

The primary systemic vasculitides are more common than was previously realized with an incidence of 20/million and peak age of onset 60–70 yrs [22]. Treatment has evolved over the last 20–30 yrs and a number of new treatments are now available. Therefore, it seems appropriate to review the current treatments and to highlight where there is an evidence base for treatment protocols and where treatment is based on individual preference.

### 1.3 Objective of guideline

The aim of this document is to provide guidelines for the management of adults with primary systemic vasculitis/ANCA associated vasculitis, especially the induction and maintenance of remission. The guidelines concentrate particularly on the indications for using cyclophosphamide and the different therapeutic regimens available.

### 1.4 Target audience

The target audience includes rheumatologists, general physicians and specialists who may come across vasculitis in the course of their work. We are also aiming guidance towards specialist registrars in training, nurse practitioners dealing with vasculitis and the information will also be of value to primary care physicians to increase their understanding of these unusual conditions.

It is important, however, to recognize that these diseases are relatively rare and it is recommended that a referral to a consultant with a specialist interest in vasculitis is made in most cases. Centres without consultants with a specialist interest in vasculitis should contact expert centres and be in close liaison for detailed advice.

### 1.5 The areas the guideline does not cover

The guidelines do not cover the management of other systemic vasculitides, for example giant cell arteritis, Takayasu's arteritis, cutaneous vasculitis, classical PAN, cryoglobulinaemic vasculitis, Henoch-Schönlein purpura.

## Section 2: Stakeholder involvement

### 2.1 Names and roles of members of multidisciplinary team

#### Coordination team

Chair. Professor David GI Scott, Consultant Rheumatologist, Norfolk and Norwich University Hospital; Honorary Professor, University of East Anglia School of Medicine, Health Policy and Practice.

Members. Dr Richard Watts, Consultant Rheumatologist, Ipswich Hospital, Senior Lecturer University of East Anglia School of Medicine, Health Policy and Practice.

Dr Chloe Lapraik, Rheumatology Research Fellow, Norfolk and Norwich University Hospital.

*Working group members/advisors.* Professor Paul Bacon, Emeritus Professor, Birmingham.

Dr David Carruthers, Consultant Rheumatologist, City Hospital Birmingham.

Professor Kuntal Chakravarty, Consultant Rheumatologist, Harrold Wood Hospital.

Dr David D'Cruz, Consultant Rheumatologist, St Thomas's Hospital.

Professor Loic Guillevin, Professor of Medicine, Hospital Avicenne, University of Paris-Nord.

Dr Lorraine Harper, Senior Lecturer in Nephrology, Birmingham.

Dr David Jayne, Consultant Nephrologist, Addenbrooke's Hospital, Cambridge.

Dr Raashid Luqmani, Consultant Rheumatologist, Nuffield Orthopaedic Centre, Oxford.

*Allied health care professional representative.* Mrs. Janice Mooney, Nurse Lecturer, School of Nursing and Midwifery, University of East Anglia.

### 2.2 Names and affiliations of users on the working party

The draft guidelines were reviewed by Mrs Judy Bilner (patient).

### 2.3 Involvement and affiliations of other people or organizations including user representative organization and pharmaceutical companies in the development of the guideline

The Stuart Strange Trust is a registered charity that offers support to family friends and sufferers of vasculitis. The guidelines have been reviewed by Paul Pegg, the general secretary for the Trust, who has given his approval and support on behalf of the Stuart Strange Trust.

## Section 3: Rigour of development

### 3.1 Statement of scope of literature search and strategy employed

The general search strategy was to look for all evidence synthesis in the Cochrane library and Medline (Ovid). The MEDLINE database was also searched for randomized controlled trials and non-randomized trials. The reference lists of identified papers and previous reviews were also searched.

### 3.2 Statement of extent of Cochrane, Nice, RCP, SIGN guidelines

To date, no Cochrane reviews have been published and there are few formal meta-analyses. There are no NICE, RCP, SIGN guidelines for the treatment of primary systemic vasculitis.

### 3.3 Statement of any limits of search

The search was conducted in November 2005. No time or language limits were placed on the search.

### 3.4 Statement of when guideline will be updated

The guideline will be updated every 3 yrs following publication.

## Section 4: The guideline itself

There are no clear cut diagnostic criteria for systemic vasculitis. It is common to apply classification criteria as surrogates for diagnosis, but we recognize the limitations of this approach. For the purpose of these guidelines, we have proposed the following statements to allow us to identify patients who have a diagnosis of vasculitis for the purpose of eligibility for treatment.

### 4.1 Eligibility criteria

Eligibility for treatment depends on the assumption that a definite diagnosis of vasculitis has already been made. The following criteria must be fulfilled prior to a diagnosis of vasculitis:

- A. Symptoms and signs characteristic of systemic vasculitis.
- B. At least one of the following:
  1. Histological evidence of vasculitis and/or granuloma formation,
  2. Positive serology for ANCA (either cANCA/PR3 or pANCA/MPO),
  3. Specific indirect evidence of vasculitis (from angiography, MRI, CT imaging, neurophysiology<sup>†</sup>).

<sup>†</sup>Neurophysiology must show mononeuritis multiplex or mononeuropathy

- C. No other diagnosis to account for symptoms or signs.

### 4.2 Exclusion criteria

For a diagnosis of primary systemic vasculitis, it is important to consider other causes of systemic illness as outlined below, which must be excluded as far as possible:

1. Malignancy,
2. Systemic infection—especially bacterial endocarditis,
3. Drugs—known to be associated with vasculitis (e.g. propylthiouracil, allopurinol, hydralazine and cocaine),
4. Secondary forms of vasculitis associated with primary connective tissue disease such as rheumatoid arthritis or systemic lupus erythematosus.
5. Other vasculitides including Behçet's disease, Takayasu's arteritis, giant cell arteritis, Kawasaki's disease, Cryoglobulinaemia, Henoch Schönlein Purpura (must have a biopsy demonstrating IgA deposits).
6. Vasculitis mimics, for example anti-phospholipid syndrome, cholesterol embolism, calciphylaxis and atrial myxoma.

### 4.3 Remission induction treatment

Treatment for vasculitis requires induction of remission followed by maintenance. Treatment regimens for each phase of disease are different and are outlined subsequently. The categorization used here follows that adopted by the European Vasculitis Study Group (EUVAS) for clinical trials.

TABLE 2. Categorization of disease severity [23]

Clinical subgroup	Constitutional symptoms	Typical ANCA status	Threatened vital organ function	Serum creatinine ( $\mu\text{mol/l}$ )	Treatment induction
Localized/early systemic	Yes	Positive or Negative	No	<150	Methotrexate or Cyclophosphamide
Generalized	Yes	Positive	Yes	<500	Cyclophosphamide
Severe	Yes	Positive	Yes	>500	Cyclophosphamide/Plasma exchange/Methyl prednisolone

TABLE 3. Pulsed cyclophosphamide reductions for renal function and age [25]

Age (years)	Creatinine 150–300 $\mu\text{mol/l}$	Creatinine 300–500 $\mu\text{mol/l}$
<60	15 mg/kg/pulse	12.5 mg/kg/pulse
>60 and <70	12.5 mg/kg/pulse	10 mg/kg/pulse
>70	10 mg/kg/pulse	7.5 mg/kg/pulse

Treatment is tailored according to severity and extent of disease. The level of immunosuppression should reflect the severity of vasculitis. Table 2 shows categorization of disease severity. Limited WG as used in the US literature most closely overlaps with the early systemic/localized group.

**4.3a Recommendation for patients with generalized disease/threatened organ involvement.** Initial treatment of patients with primary systemic vasculitis with generalized/threatened vital organ loss should include cyclophosphamide. Cyclophosphamide may be given orally or intravenously (daily oral 2 mg/kg or IV pulses at 2- or 3- week intervals at a dose of 15 mg/kg) (Table 3) (A).

Cyclophosphamide dose should be tapered to maintain total white cell count above  $4 \times 10^9/l$  and neutrophils  $>2.0 \times 10^9$  to reduce risk of infection (B). Cyclophosphamide dosage should be reduced for age (B) and renal function (C).

Current clinical practice with these protocols for remission induction are associated with an expected remission rate of ~80% at 3 months and 90% at 6 months [24].

#### Dose reductions

**Dose reductions for continuous low dose oral cyclophosphamide:** For oral administration, if age >60 years the dose of cyclophosphamide should be reduced by 25%. If the age is >75 years the dose should be reduced by 50% to avoid neutropenia [25] (B).

Reductions for pulsed cyclophosphamide, see Table 3.

#### Remission induction

**Continuous low dose oral cyclophosphamide regimen:** Continuous low dose cyclophosphamide 2 mg/kg/day should be given for 3 months. The maximum dosage of continuous low dose oral cyclophosphamide is 200 mg/day. If remission is not achieved by 3 months, continue 2 mg/kg/day, until remission is achieved then reduce cyclophosphamide to 1.5 mg/kg/day. The total duration of treatment with cyclophosphamide should not usually exceed 6 months [24].

Current clinical practice considers a transfer to maintenance therapy at 3 months or within 3 and 6 months if remission is delayed (A).

**Continuous low dose oral cyclophosphamide monitoring:** Check full blood count (FBC), weekly for the first month, 2 weekly for the second and third month and then monthly thereafter. If white blood cells (WCC)  $<4 \times 10^9/l$ , neutrophil count  $<2 \times 10^9$  stop oral cyclophosphamide temporarily and restart with a dose reduced by at least 25 mg when WCC have recovered, thereafter monitor weekly for 4 weeks. If severe (WCC  $<1 \times 10^9/l$ , neutrophil count  $<0.5 \times 10^9/l$ ) or prolonged leucopenia/neutropenia (WCC  $<4 \times 10^9/l$ , neutrophil count

$<2 \times 10^9/l$  for >2 weeks) then stop oral cyclophosphamide and restart cyclophosphamide at 50 mg/day when WCC and neutrophils counts have recovered, increasing to target dose weekly, WBC permitting. For falling WBC ( $<6 \times 10^9/l$  and a fall of  $>2 \times 10^9/l$  over previous count), reduce dose by 25%. Renal function should be measured alongside FBC monitoring and adjustments to cyclophosphamide dose should be made accordingly (C).

**Pulsed cyclophosphamide regimen:** The standard dose is 15 mg/kg, reduced for age and renal function (Table 3). The maximum IV cyclophosphamide dose is 1500 mg. Dissolve cyclophosphamide in water for injection and then dilute in 500 ml of saline 0.9% or dextrose 5% and administer as IV drip over 1 h, or longer if necessary. Patient should receive 11 pre-hydration with normal saline, and advised to have 3l/day oral fluid intake for 3 days.

The first three pulses are usually given at intervals of 2 weeks and thereafter at 3-week intervals. Current clinical practice considers possible transfer to maintenance therapy between 3–6 months and aims for a maximum duration of cyclophosphamide therapy of 6 months, where successful remission has been achieved (A).

**Pulsed cyclophosphamide monitoring:** Check the FBC on the day of the pulse or previous day. If WBC prior to the pulse  $<4 \times 10^9/l$ , neutrophil count  $<2 \times 10^9/l$  then postpone pulse until WBC  $>4 \times 10^9/l$  and neutrophil count  $>2 \times 10^9/l$ , while checking the FBC weekly. Reduce the dose of pulse by 25%. With any further episodes of leucopenia/neutropenia make equivalent dose reduction. After the first pulse of cyclophosphamide check FBC between days 10 and the day of the next pulse. If the leucocyte nadir is  $<3 \times 10^9/l$ , neutrophil nadir  $<1.5 \times 10^9/l$  even if the WBC just previous to the next pulse is  $4 \times 10^9/l$  and neutrophil count  $2 \times 10^9/l$  then reduce the dose of the next pulse by:

- Leucocyte nadir  $1-2 \times 10^9/l$  or neutrophil nadir  $0.5-1.0 \times 10^9/l$  reduce cyclophosphamide pulse by 40% of previous dose.
- Leucocyte nadir  $2-3 \times 10^9/l$  or neutrophil nadir  $1-1.5 \times 10^9/l$  reduce cyclophosphamide pulse by 20% of previous dose [25] (B).

Thereafter check the FBC on the day of the pulse or previous day unless there is an adjustment made to the dose of cyclophosphamide administered or interval period between infusions, in these cases the FBC should be additionally checked at day 10. Renal function should be measured on the day of each infusion or previous day and adjustments be made to cyclophosphamide dose as per Table 3 (C).

**Steroids:** Steroids are usually given as daily oral prednisolone as described in Table 4. The recommended regimen is based on that used in the published randomized trial of maintenance therapy for vasculitis (CYCAZAREM) by Jayne and colleagues [24] (A).

A recent survey of clinical practice was carried out by the EUVAS group. EUVAS members from 30 centres completed questionnaires on the management of two patients with newly

TABLE 4. Oral prednisolone regimen [24, 26] (B)

Time from entry (weeks)	Prednisolone dosage mg/kg/day	Prednisolone dosage mg/day for 60 kg
0	1	60
1	0.75	45
2	0.5	30
3	0.4	25
4	0.4	25
6	0.33	20
8	0.25	15
	Prednisolone dosage (mg/day)	
12	15	15
16	12.5	12.5
6 months	10	10
During months 12–15	7.5	7.5
During months 15–18	5	5

diagnosed primary systemic vasculitis. In all cases, prednisolone was tapered to  $\leq 15$  mg/day by 3 months, and only 13% continued steroids long-term in generalised disease (C).

Intravenous steroids are sometimes given just prior to the pulsed cyclophosphamide especially for the first two doses. For example, methylprednisolone 500 mg prior to the first pulse and 250 mg prior to the second pulse. This method of steroid treatment has anti-emetic properties [27] and is also immunosuppressive (A). A lower dose of oral steroids maybe considered if pulse methylprednisolone is used (C). Intravenous steroid (methyl prednisolone 500–3000 mg) is often used for severe vasculitis, in particular, rapidly progressive glomerulonephritis (B).

**Rationale:** Combination therapy with cyclophosphamide and prednisolone is effective in inducing remission, however, traditional regimes maintaining cyclophosphamide for 1 year following remission are associated with high treatment related morbidity. Recent evidence suggests that both oral and pulsed cyclophosphamide for 3–6 months with substitution of azathioprine on remission did not increase the rate of relapse or damage associated with vasculitis allowing safe reduction in exposure to cyclophosphamide [24]. Pulsed cyclophosphamide compared with continuous low dose oral cyclophosphamide may be associated with reduced morbidity related to infection and leucopenia, but is equally effective at inducing remission. The recently completed European trial of pulse vs continuous low dose oral cyclophosphamide has shown no difference in remission and no increased risk of relapse in the IV-treated patients. Continuous low dose oral cyclophosphamide was associated with a high total cyclophosphamide dosage and a significant increase in infection risk. The cumulative dose of cyclophosphamide is lower for the IV pulse regimen compared with the continuous oral regimen when administered for the same period of time (e.g. induction therapy 3–6 months) [25]. Infection is a common cause of early death in patients with primary systemic vasculitis. Risk factors for infection include advanced age, impaired renal function and leucopenia.

The recommended steroid taper is the regimen used in CYCAZAREM as that supports the cyclophosphamide/azathioprine regimen. More rapid steroid tapering of relapse [28] (B).

**4.3b Recommendation for patients with localized/early systemic disease (without threatened vital organ involvement).** Initial treatment of primary systemic vasculitis with localized/early systemic disease (without threatened vital organ disease or damage) may include methotrexate (15 mg/week escalating to a maximum of 20–25 mg/week by week 12) with oral steroids (regimen as per Table 2). This is the dosing schedule for methotrexate and oral steroids used in NORAM [29]. This avoids

cyclophosphamide exposure but this may be at the expense of a higher relapse rate (A).

Localized disease may have severe local consequences (especially retro-orbital disease) and such patients should receive cyclophosphamide (C).

**Rationale:** The long-term use of cyclophosphamide is limited due to associated toxicity. In patients with early systemic disease methotrexate with oral steroids is as effective at inducing remission as cyclophosphamide with oral steroids, allowing avoidance of cyclophosphamide in early systemic disease [30]. However, methotrexate therapy may be associated with more relapses at 18 months and increased risk of progression to more widespread disease than cyclophosphamide (A/B). Methotrexate is renally excreted and should be used with increased caution in those with serum creatinine  $>150 \mu\text{mol/l}$  due to increased toxicity (C).

Longer follow-up of patients treated with methotrexate may be required where there is evidence of systemic disease, albeit mild, as these patients have a higher relapse rate following withdrawal of therapy, and also there is a higher incidence of renal disease in those that relapse.

**Methotrexate monitoring:** Regular folic acid supplements are thought to reduce toxicity. Pre-treatment assessment should include; full blood count (FBC), renal function, liver function tests (LFTs) and chest X-ray. Thereafter FBC should be monitored fortnightly until 6 weeks after last dose increase and provided it is stable monthly thereafter. LFTs should be checked with each blood test. Renal function should be monitored 6–12 monthly or more frequently if required [31]. Further details of methotrexate monitoring as described in the British Society for Rheumatology guidelines [31].

**4.3c Recommendation severe/life threatening disease.** Patients with primary systemic vasculitis presenting with severe renal failure (creatinine  $\geq 500 \mu\text{mol/l}$ ) should be treated with cyclophosphamide and steroids (as per regimen in Table 4) with adjuvant plasma exchange ( $7 \times 4\text{l}$  exchanges over 2 weeks) (A) [32]. Treatment with plasma exchange should be considered in those with other life-threatening manifestations of disease such as pulmonary haemorrhage (C).

**Rationale:** Patients presenting with advanced renal failure have much poorer outcomes. The addition of plasma exchange to standard treatment regimes improves renal survival but does not affect immediate mortality as shown by a recently published randomized controlled trial [32]. The combination of methyl prednisolone and plasma exchange has not been evaluated but it is widely used (C).

**Patients intolerant of cyclophosphamide:** For cases where patients are intolerant of cyclophosphamide, alternative treatments such as methotrexate, azathioprine, leflunomide or mycophenolate mofetil may be used. However, there is little evidence except for methotrexate in their use as induction therapy.

#### 4.4 Maintenance of remission

**1. Recommendation.** In patients with primary systemic vasculitis who have achieved successful remission (usually between 3–6 months), cyclophosphamide should be withdrawn and substituted with either azathioprine (Table 5) or methotrexate (see above) in combination with oral steroids [24, 30] (A).

The CYCLOPS regimen used cyclophosphamide for a minimum of 6 months. It advised further treatment with cyclophosphamide for 3 months once remission had been achieved up to a total of 12 months treatment. In contrast, the CYCAZAREM study randomized patients to azathioprine or further

Table 5. Azathioprine and oral steroids regimen for maintenance of remission [24]

Time from entry	Prednisolone mg/day CYCAZAREM	Prednisolone mg/day WGET	Azathioprine mg/kg/day
3 months	15	15	2
4 months	12.5	8	2
6 months	10	0	2
12 months	10	0	1.5
15 months	7.5	0	1.5

cyclophosphamide at between 3 and 6 months. Current clinical practice considers possible transfer to maintenance therapy as early as 3 months for oral cyclophosphamide and between 3 and 6 months for intravenous cyclophosphamide and aims for a maximum duration of cyclophosphamide therapy of 6 months, where successful remission has been achieved (C).

**Azathioprine monitoring:** Pre-treatment assessment should include FBC, renal function, LFTs. Thereafter FBC should be checked weekly for 6 weeks and then at 2 and 4 weeks after each dose increase and thereafter monthly. LFTs should be checked monthly until the dose of azathioprine is stable [31]. Further details on azathioprine monitoring as per the British Society for Rheumatology Guidelines [31].

Methotrexate should be started at a dosage of 0.3 mg/kg, not to exceed 15 mg once a week. If the treatment is well tolerated after 1–2 weeks, the methotrexate dose may be increased by 2.5 mg each week up to a dosage of 20–25 mg/week and maintained at that level. If remission is sustained for 2 yrs, the methotrexate may be tapered by 2.5 mg each month until discontinuation [30] (B). Methotrexate is equivalent to azathioprine for the prevention of relapse [33] (A).

**Rationale:** Azathioprine or methotrexate may be substituted for cyclophosphamide after successful remission of disease. Both azathioprine and methotrexate have been shown to be effective in the maintenance of disease remission although there is stronger evidence for the use of azathioprine. Mycophenolate or leflunomide may be used as alternatives for intolerance or lack of efficacy of azathioprine or methotrexate [34] (B).

**Recommendation:** Patients with primary systemic vasculitis should continue maintenance therapy for at least 24 months following successful disease remission (B). Patients with WG or who remain ANCA positive should continue immunosuppression for up to 5 yrs (C).

Even in patients successfully treated at 24 months or 5 yrs, careful follow-up is recommended because of the risks of relapse. Clinical experience shows that many patients remain on immunosuppression beyond these time periods.

Hogan and colleagues studied predictors of relapse in 258 patients with primary systemic vasculitis who had attained remission with standard therapies. Among these 258 patients it was found that those with anti-PR3 antibodies were 1.87 times more likely to relapse than patients who were anti-MPO seropositive. Lung and upper respiratory tract involvement were each associated with an ~1.7-fold increase in risk of relapse whereas diseases involving other organs did not have a statistically significant impact. Black ethnicity was associated with a trend towards a higher risk for relapse, but was not statistically significant [35].

Slot *et al.* [36] recently analysed ANCA status in an observational study at the time of switching from cyclophosphamide to azathioprine in ANCA-associated vasculitis and observed that a positive PR3 ANCA at this time was associated with an increased risk of relapse.

**Rationale:** Withdrawal of therapy at 12 months results in unacceptably high relapse rates in patients with primary systemic

vasculitis, even when therapy is continued for 18 months relapse rates remain at 14.5% [29] (A). Patients with WG and those who remain ANCA positive are more likely to relapse furthermore the presence of lung and upper respiratory involvement and specific ethnic groups should prompt careful consideration for prolonged therapy [35] (B).

**Potential alternative therapies:** Cases that require the use of alternative therapies should be supervised by specialists and involve close liaison with specialist centres. The use of etanercept has been studied in a placebo-controlled RCT, and found to not be effective at maintenance of remission in WG and to not enhance the effects of standard therapy in induction of remission (A). Infliximab has been used as an additional agent for refractory disease and as a component of induction regimens, permitting steroid sparing. There is no current role for infliximab in induction therapy but it may be considered for refractory disease [37, 38] (B).

High dose intravenous immunoglobulin (IVIg) led to partial disease control for refractory vasculitis in a placebo controlled trial [39]. Two small uncontrolled trial of IVIg alone for initial therapy of vasculitis have also indicated some efficacy [40, 41]. IVIg may be considered as an alternative therapy in patients with refractory disease or in patients for whom conventional therapy is contra-indicated, for example, in the presence of infection, in the severely ill patient or in pregnancy (B). T-cell depletion with anti-thymocyte globulin and pan-lymphocyte depletion with CAMPATH 1H (alemtuzumab, anti-CD52) have led to sustained remissions in refractory disease [42, 43].

Their use is associated with a high risk of severe infection and should only be considered for refractory patients by centres with experience in their use (B).

B-cell depletion with rituximab has led to sustained remissions in refractory vasculitis [44]. Its use permits the withdrawal of immunosuppressive drugs and reduction or withdrawal of corticosteroids without appearing to increase the risk of infection. Rituximab may be considered for the treatment of refractory vasculitis or the treatment of vasculitis when conventional agents are contra-indicated (B). There is insufficient current evidence to recommend the routine use of rituximab in induction or maintenance regimens.

**Relapsing disease:** Relapses have been classified as minor or major, according to the absence or presence of threatened vital organ function. Minor relapse is treated with an increase in prednisolone dose to 30 mg/day then gradual taper and optimisation of the concurrent immunosuppressive dose. Major relapse is treated with cyclophosphamide as in remission induction and an increase in prednisolone to 30 mg/day, intravenous methyl prednisolone or plasma exchange may be considered (C).

Studies have shown that the nasal carriage of *Staphylococcus aureus* is associated with an increased risk of relapse in patients with WG although the causal relation and mechanisms remain speculative [45]. Cyclical nasal application of mupirocin should be considered in patients with WG.

There is also evidence for the use of trimethoprim/sulfamethoxazole in maintaining disease remission. The mechanism by which trimethoprim/sulfamethoxazole reduces relapse of WG is unclear. One theory is that trimethoprim/sulfamethoxazole eliminates *S. aureus* from the nasal passage and subsequently reduces relapses secondary to *S. aureus* carriage. A prospective randomized, placebo-controlled study of the efficacy of trimethoprim/sulfamethoxazole showed that treatment with trimethoprim/sulfamethoxazole reduced the incidence of respiratory tract relapse in patients with WG in remission. The study duration was 2 yrs, and the difference in relapse frequency was largest in the first 6 months [46].

**Refractory disease:** Disease refractory to full dose cyclophosphamide and prednisolone is rare. More commonly, optimal doses are not tolerated or a prolonged relapsing disease course with high cumulative exposure to cyclophosphamide and prednisolone are the indications for alternative agents. For relapses on azathioprine or methotrexate a switch to mycophenolate mofetil or leflunomide may be considered (B). The potential roles of infliximab, IVIg, antithymocyte globulin, CAMPATH-1H and rituximab have been outlined earlier. In the management of refractory vasculitis it is important to identify drives for vasculitis, such as, intercurrent infection or malignancy, or non-compliance. A novel immunosuppressive, deoxyspergualin, has shown a high rate of efficacy in two uncontrolled studies of refractory vasculitis [47] (B).

#### 4.5 Monitoring therapy and avoidance toxicity

##### 4.5a Assessment/monitoring disease activity

**Recommendation:** An initial assessment prior to starting treatment should be done. Assessment should then be performed approximately monthly for the first 3 months and then every 3–6 months for the next year according to clinical need. Thereafter as clinically indicated. (C) In the randomized trial of maintenance therapy in primary systemic vasculitis by Jayne and colleagues, assessment of remission was made at 3 months, with the aim of changing immunosuppression from cyclophosphamide to azathioprine if remission had been induced (A).

**Recommendation:** The primary systemic vasculitides are relapsing conditions, relapse can occur at anytime even many years after diagnosis and remission induction. Follow-up after 12 months should be as dictated by the clinical condition of the patient, but should not be less frequent than every 6 months (C).

**Rationale:** It is recommended that a validated tool is used to assess disease activity, especially in patients involved in publishable data or clinical trials. These tools have been reviewed recently [48]. The Birmingham Vasculitis Activity Score (BVAS) is a validated tool for the assessment of disease activity [49]. It is not an essential component for everyday clinical practice but represents a particularly useful checklist for patients with active vasculitis. It is a clinically determined score with each item given a weighted score. The weighting was determined by expert consensus and this tool has been adopted by the EUVAS group as the most practical for use in randomized clinical trials. A BVAS of 0 or 1 is defined as remission, and this definition was used in the EUVAS studies. Data shows poor outcome associated with high initial BVAS score [50].

The Disease Extent Index (DEI) records the number of organ systems affected by active WG. It has not been validated in other forms of vasculitis. Each organ system contributes a score of 1 or 2 points to a maximum value of 21. It has been shown to correlate with the BVAS and appears to have prognostic value in determining the likelihood of a good or poor treatment response [51, 52].

The five factor score (FFS) at presentation is a useful guide to prognosis. The following parameters are assessed (proteinuria >1 g/day, creatinine >140 µmol/l, cardiomyopathy, gastrointestinal symptoms, CNS involvement). A FFS of >2 in PAN is associated with a greatly increased mortality [53].

##### 4.5b Damage

**Recommendation:** Damage may occur as a result of vasculitis and lead to impairment of organ function. Damage may also be due to the treatment of vasculitis or occur as a result of the diagnosis of vasculitis having been made. Damage has a prognostic value and can also be used as a measure of success of treatment. We would recommend damage should be assessed

at 6 months and then annually using the vasculitis damage index (VDI) [54, 55].

**Rationale:** Measurement of damage provides a marker of long-term outcome of disease and its consequences. The damage index is being applied in the studies of vasculitis and provides evidence of progression of disease and worsening of status despite current treatments and is an important measure for future studies [56].

##### 4.5c Patient function and quality of life

**Recommendation:** Patient function and quality of life can be assessed on an annual basis using the SF-36 (C).

**Rationale:** The generic validated tool SF-36 has been shown to be sensitive to change in vasculitis activity and correlates with damage [57, 58].

##### 4.5d ANCA measurements

**Recommendation:** ANCA levels are not closely associated with disease activity. ANCA measurements do not have a high predictive value in terms of relapse, therefore, it is not justified to escalate immunosuppressive therapy solely on the basis of an increase in ANCA level, as determined by PR3/MPO ELISA. An increase should be taken as a warning of possible impending relapse and more frequent follow-up of the patient instigated. There is no evidence that induction therapy should be tailored against falling ANCA levels (B). Treatment withdrawal in patients with persistently positive ANCA is associated with relapse. ANCA by ELISA should probably be measured routinely every 3–6 months, whenever there is a significant change in therapy or clinical condition (C).

**Rationale:** The relationship between a rising ANCA titre and relapse has been studied. In a pooled analysis only 48% of rises in ANCA titres as measured by indirect immunofluorescence were followed by relapse and only 51% of relapses were preceded by rising titres [59].

Slot *et al.* [36] recently analysed ANCA status in an observational study at the time of switching from cyclophosphamide to AZA in ANCA-associated vasculitis and observed that a positive PR3 ANCA at this time was associated with an increased risk of relapse.

##### 4.5e Detection and prevention of potential adverse effects of immunosuppressive therapy

###### Cyclophosphamide induced bladder toxicity

**Recommendation:** Mesna treatment should be considered for patients on IV cyclophosphamide therapy. Patients should be encouraged to drink ~3l/day to minimize the risk of bladder toxicity (C). Surveillance with regular (3–6 monthly) urinalysis should be continued indefinitely after a course of cyclophosphamide (C). Haematuria (microscopic and macroscopic), or symptoms of recurrent cystitis should be investigated with urine microbiology and cytology and there should be a low threshold for referral for consideration of cystoscopy, if not considered due to active renal vasculitis (B).

**Rationale:** Bladder toxicity (haemorrhagic cystitis and bladder cancer) is a recognized complication of cyclophosphamide therapy. A recent epidemiology study from Sweden suggested a dose response relationship between cumulative cyclophosphamide dose and the risk of bladder cancer [60]. Older historical cohort data show that the risk of bladder toxicity is related to the cumulative dose administered and is greatest in patients receiving >100 g [61].

Mesna (sodium 2-mercaptoethane sulphonate) protects against the urothelial toxicity of cyclophosphamide by scavenging the toxic metabolite acrolein. There are no RCTs reporting its use in reducing urothelial toxicity of cyclophosphamide in vasculitis.

The current use of much lower cumulative cyclophosphamide doses and early change to alternative immunosuppressive agents for maintenance of remission should be associated with a lower risk of bladder toxicity. However, bladder cancer may develop many years after cyclophosphamide therapy and it is not known what the long term risk is for patients treated in these newer protocols (B).

Mesna may be given orally or intravenously. When cyclophosphamide is used intravenously, the oral dose of mesna should be 40% of the cyclophosphamide dosage in mg. It should be given 2 h prior to the pulse of cyclophosphamide and repeated 2 and 6 h after the pulse of cyclophosphamide. If the mesna is being given intravenously then the dose should be 20% of the pulsed cyclophosphamide dosage in mg and can be given with the cyclophosphamide and then at 2 h and 6 h (when it can be orally or intravenously). The same dosage of mesna is given each time the patient receives a pulse of IV cyclophosphamide.

#### 4.5f Infection with *Pneumocystis jiroveci* (previously known as *Pneumocystis carinii*)

**Recommendation:** Patients receiving cyclophosphamide and corticosteroids should receive trimethoprim/sulfamethoxazole 960 mg thrice weekly as prophylaxis against pneumocystis (C). In cases of trimethoprim/sulfamethoxazole intolerance monthly aerosolized pentamidine (300 mg) or dapsone 100 mg daily may be used as an equally effective alternative (B).

**Rationale:** *Pneumocystis jiroveci* is a common infectious complication in immunocompromised patients is associated with significant morbidity and mortality. Although there is no RCT data, observational data from trials and case series supports the approach that patients receiving cyclophosphamide and corticosteroids should receive trimethoprim/sulfamethoxazole 960 mg thrice weekly or aerosolized pentamidine/daily dapsone in patients allergic to trimethoprim/sulfamethoxazole, as prophylaxis against pneumocystis. The rate of pneumocystis infection reported in vasculitis patients receiving cyclophosphamide and corticosteroids has been reported to be as high as 20% [62] compared with 6% in the NIH cohort [63] and 1% in a German cohort [64]. This difference may be explained by the much higher doses of prednisolone used in the French study [62] (Guillevin 1997) and many patients in the German study received trimethoprim/sulfamethoxazole (Septrin) as part of their therapeutic regimen.

A cost-benefit analysis suggested that trimethoprim/sulfamethoxazole prophylaxis increased life expectancy and reduced overall costs. Replacing trimethoprim/sulfamethoxazole with aerosolized pentamidine in cases of acute drug reaction further increased life expectancy although at an increased cost [65].

The toxicity of prophylaxis with trimethoprim/sulfamethoxazole is due to the sulphonamide moiety. There is also an interaction with methotrexate resulting in an increased risk of myelosuppression. However, although there is a theoretical interaction between methotrexate and trimethoprim/sulfamethoxazole, the studies of methotrexate used in vasculitis have not shown that this is clinically relevant at these low doses of trimethoprim/sulfamethoxazole (C). However, extreme caution should be taken in using trimethoprim/sulfamethoxazole in patients on methotrexate.

The risks of pneumocystis are related to the doses of cyclophosphamide and corticosteroids, so the current use of lower cumulative doses of both drugs probably reduces the risk (C).

#### 4.5g Fungal infections

**Recommendation:** The EUVAS trials suggested that prophylactic treatment with anti-fungal agents such as nystatin, oral fluconazole and amphotericin should be considered for patients receiving immunosuppressive therapy.

**Rationale:** Patients receiving immunosuppressive therapy are at an increased risk of fungal infections.

#### 4.5h *Staphylococcus aureus* suppression

**Recommendation:** It is recommended that all patients receiving treatment for primary systemic vasculitis should be considered for treatment with long term nasal mupirocin treatment (C).

**Rationale:** Studies have shown that the nasal carriage of *staphylococcus aureus* is associated with an increased risk of relapse in patients with WG although the causal relation and mechanisms remain speculative [45].

#### 4.5i Cervical intraepithelial neoplasia (CIN)

**Recommendation:** Female patients receiving cyclophosphamide should be considered for an annual cervical smear for the first 3 yrs and then as per the national screening programme (C).

**Rationale:** Cervical carcinoma is a common malignancy associated with infection with human papilloma virus (serotypes 16, 19 and 31) which is sexually acquired. Immunosuppressive therapy is associated with development of secondary malignancies. A recent study in SLE patients reported a significant association between intravenous cyclophosphamide with prednisolone and development of CIN in the first 3 yrs following treatment [66]. Increased rates of CIN have been also observed in patients with lupus receiving azathioprine, results consistent with observations from the renal transplant population. There is no data on the occurrence of CIN in vasculitis patients.

Whether vasculitis patients are at an increased risk of cervical carcinoma/CIN irrespective of the type of immunosuppressive treatment like SLE patients is not known, but seems likely.

#### 4.5j Infertility

**Recommendation:** Patients should be counselled regarding the recognized complication of infertility and cyclophosphamide treatment. Sperm and oocyte cryopreservation should be considered in male patients wishing to father children and in premenopausal women. These procedures may take time to organize, and should be considered if the clinical condition of the patient permits (C).

**Rationale:** Both male and female infertility is a recognized complication of cyclophosphamide therapy. The majority of the evidence comes from other conditions such as SLE. Female infertility is associated with cumulative dose of cyclophosphamide and older age at time of treatment. In a study of 67 women with proliferative lupus nephritis (mean age  $31.1 \pm 8.4$  range 17–46 yrs) who received IV cyclophosphamide at a dose of  $0.5\text{--}0.75 \text{ mg/m}^2$ , the mean dose of cyclophosphamide administered and the mean number of pulses were  $888.1 \pm 268.8 \text{ mg}$  per pulse (range 750–1250) and  $8.8 \pm 2.4$  (range 2–12) over an 18 month period, it was shown that younger patients who receive relatively low cumulative doses infertility and amenorrhoea may be reversible [67]. The dose of cyclophosphamide should be kept, therefore, to a minimum. Male infertility after cyclophosphamide therapy for autoimmune disease is less well understood, because the majority of patients requiring cyclophosphamide therapy for SLE are female.

#### 4.5k Osteoporosis

**Recommendation:** It is recommended that all patients receiving standard treatment for primary systemic vasculitis should be commenced on bisphosphonate therapy with calcium and vitamin D supplementation because of the high doses of steroids used and prolonged treatment course involved in these patients (C). Care needs to be exercised in those with renal

impairment and in pre-menopausal women. Practice should be in line with current guidelines for the prevention of corticosteroid induced osteoporosis [68].

*Rationale:* Osteoporosis is a recognized consequence of high dose and/or prolonged treatment with corticosteroids. Care needs to be exercised in those with renal impairment and in premenopausal women.

#### 4.5l *Mycobacterium infection*

*Recommendation:* All patients should be assessed for risk of tuberculosis (TB) by taking a full history, physical examination and performing a chest X-ray. It is recommended that the guidelines provided by the British Thoracic Society for the assessment of risk and for managing mycobacterium tuberculosis infection and disease in patients due to start anti-TNF treatment should be adhered [69].

*Rationale:* Patients receiving intensive immunosuppressive therapy are potentially at an increased risk of reactivation of latent TB, or less commonly new infection.

#### 4.5m *Vaccinations*

*Recommendation:* Live vaccines should be postponed until at least 3 months after stopping immunosuppressive therapy [70].

It is recommended that patients receiving immunosuppressive therapy should receive pneumococcal and influenza vaccination. In contrast to the pneumococcal vaccine, the influenza vaccine must be given every year. Patients should have pneumococcal titres measured and undergo revaccination if required [71].

Varicella titres should be measured in all patients prior to patients commencing cyclophosphamide therapy; however, cyclophosphamide treatment should not be delayed for the result. Consider giving varicella specific immunoglobulin if contact risk is significant (C).

Further advice on the use of live vaccines in immunocompromised patients as per the BSR guidelines.

*Rationale:* Live vaccines should not be given to the immunocompromised patient as the response to vaccines may be reduced and there is risk of generalized infection.

Antibody titres tend to decline more rapidly in the immunocompromised patient and more frequent boosters may be required [70].

#### 4.5n *Cardiovascular risk*

*Recommendation:* It is recommended that patients with primary systemic vasculitis/ANCA-associated vasculitis should be screened and treated where appropriate for hypertension, hypercholesterolaemia and diabetes. Patients should also be strongly advised against smoking.

*Rationale:* There is emerging evidence that patients with primary systemic vasculitis/ANCA-associated vasculitis are at an increased risk of cardiovascular morbidity.

#### 4.5o *Thrombo-embolic risk*

*Recommendation:* It is recommended that patients with primary systemic vasculitis/ANCA-associated vasculitis should be considered for prophylactic anti-coagulation during periods of prolonged immobility. Attempts to avoid risk factors for thromboembolic disease should be undertaken and a high index of suspicion of thrombo-embolic disease should be used in these patients.

*Rationale:* Patients with primary systemic vasculitis/ANCA-associated vasculitis are at an increased risk of thrombo-embolic disease.

## Section 5: Applicability and utility

### 5.1 *A statement of potential organizational barriers to introduction*

Pulsed intravenous cyclophosphamide requires either inpatient or day unit facilities in which there is appropriate expertise to assess and provide treatment. The vasculitides are rare and are best looked after by physicians and nursing staff where there are sufficient numbers of patients to develop expertise.

### 5.2 *Potential costs implications for introduction of guideline*

There should be no major cost implications for the introduction of these guidelines as most of evidence reflects clinical practice.

### 5.3 *Mechanism for audit of the guideline*

Systemic vasculitis is rare, and therefore audit may need to be conducted on a collaborative basis. The following are areas that may be addressed by audit:

1. The long-term toxicity of cyclophosphamide is determined by the cumulative dose used. The cumulative dosage of cyclophosphamide used for induction and consolidation therapy should be audited on a regular basis.
2. The infection rate requiring hospital admission or intravenous antibiotics reflects cumulative cyclophosphamide and corticosteroid dose. Therefore, the number of patients being admitted during the induction and consolidation phases of treatment should be audited.
3. The major long-term toxicity of cyclophosphamide is bladder neoplasia and dysplasia. The use of mesna as prophylaxis and during long-term follow routine urinalysis and referral rates for cystoscopy should be audited.
4. Infection rates are reflected by nadir white counts, and therefore compliance with monitoring protocols for cyclophosphamide use should be audited.

## Section 6

### 6.1 *Working party membership, affiliations and conflicts of interest*

*Conflicts of interest.* Professor David GI Scott, Consultant Rheumatologist, Norfolk and Norwich University Hospital, Honorary Professor; University of East Anglia School of Medicine, Health Policy and Practice—no perceived conflicts of interest. Declaration of interest as follows; departmental sponsorship for research and travel by Schering-Plough, Abbott, Wyeth and Roche.

Dr Richard Watts, Consultant Rheumatologist, Ipswich Hospital; Senior Lecturer University of East Anglia School of Medicine, Health Policy and Practice (Advisor to Euro Nippon Kayaku pharmaceutical company—manufacturer of Gusperimus) Sponsorship for research and travel from Wyeth, Schering-Plough, Abbott and Roche.

Dr Chloe Lapraik, Rheumatology Research Fellow, Norfolk and Norwich University Hospital—no conflict of interest.

Dr Raashid Luqmani, Consultant Rheumatologist/Senior Lecturer, Nuffield Orthopaedic Centre and University of Oxford, Oxford—no perceived conflict of interest; declaration of interest as follows: departmental sponsorship for academic meetings; personal sponsorship for attendance at EULAR Amsterdam 2006, EULAR Berlin 2004, ACR Orlando 2003, ACR New Orleans 2002; honoraria for academic lectures; recruitment of patients for one commercial trial in rheumatoid arthritis, one commercial trial of NSAIDs in osteoarthritis, and one commercial trial of gusperimus in WG.

Professor Kuntal Chakravarty, Consultant Rheumatologist, Harrold Wood Hospital—no conflict of interest.

Dr David D'Cruz, Consultant Rheumatologist, St Thomas's Hospital—no conflict of interest.

Dr Lorraine Harper, Senior Lecturer in Nephrology, Birmingham—no conflict of interest.

Professor Paul Bacon, Emeritus Professor, Birmingham—no conflict of interest.

Dr David Carruthers, Consultant Rheumatologist, City Hospital Birmingham—no conflict of interest.

Professor Loic Guillevin, Professor of Medicine, Hospital Avicenne, University of Paris-Nord—no conflict of interest.

Dr David Jayne, Consultant Nephrologist, Addenbrooke's Hospital—no perceived conflict of interest; declaration of interest as follows—advisor to ARSEVA and Roche.

Mrs Janice Mooney, Nurse Lecturer, University of East Anglia—no conflicts of interest.

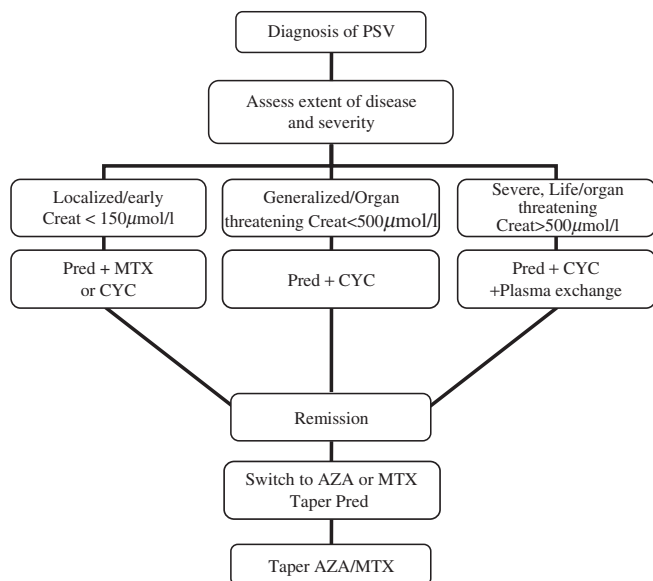
## 6.2 References with indication of 'Level of Evidence'

A = Evidence from at least one properly performed randomized controlled trial (quality of evidence Ib) or meta-analysis of several controlled trials (quality of evidence Ia).

B = Well-conducted clinical studies, but no randomized clinical trials; evidence may be extensive but essentially descriptive (evidence levels IIa, IIb, III).

C = Evidence (level IV) obtained from expert committee reports or opinions, and/or clinical experience of respected authorities. This grading indicates an absence of directly applicable studies of good quality.

## 6.3 Algorithm of guideline



## References

- Leavitt RY, Fauci AS, Bloch DA *et al.* The American college of Rheumatology criteria for the classification of Wegeners granulomatosis. *Arthritis Rheum* 1990;33:1101–7.
- Masi AT, Hunder GG, Lie JT *et al.* The American college of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome. *Arthritis Rheum* 1990;33:1094–100.
- Lightfoot RW, Micheal BA, Bloch DA *et al.* The American college of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990;33:1088–94.
- Jeanette JC, Falk RJ, Andrassy K *et al.* Nomenclature of systemic vasculitides: proposal of an international consensus conference. *Arthritis Rheum* 1994;37:187–92.
- Lanham JG, Elkon KB, Pusey CD, Hughes CR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine* 1984;63:65–81.

- Watts RA, Scott DGI. Epidemiology of vasculitis. In: Ball GV, Bridges L, eds. *Vasculitis*. Oxford: Oxford University Press, 2002;211–26.
- Luqmani RA, Bacon PA, Beaman M, Scott DGI, Emery P, Lee SJ. Classical versus non-renal Wegeners granulomatosis. *QJM* 1994;87:671–8.
- Reinhold-keller E, Kekow J, Schnabel A *et al.* Influence of disease manifestation and antineutrophil Cytoplasmic antibody titre on the response to pulse cyclophosphamide therapy in patients with Wegeners granulomatosis. *Arthritis Rheum* 1994;37:919–24.
- Walton EW. Giant cell granuloma of the respiratory tract. *Br J Med* 1958;2:265–70.
- Fauci A, Wolff S. Wegeners granulomatosis: studies in 18 patients and a review of the literature. *Medicine* 1973;52:535–61.
- Fauci AS, Haynes BF, Katz P, Wolff SM. Wegeners granulomatosis prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Inter Med* 1983;98:76–85.
- Vasallo M, Shepherd RJ, Iqbal P, Freehally J. Age related variations in presentation and outcome in Wegeners granulomatosis. *J R College Physicians* 1997;31:396–400.
- Westman K, Bygren P, Olsson H, Ranstam J, Weislander J. Relapse rate, renal survival and cancer morbidity in patients with Wegeners granulomatosis or microscopic polyangiitis with renal involvement. *J Am Soc Nephrol* 1998;9:842–52.
- Savage CO, Winearls CG, Evans DJ, Rees AJ. Microscopic polyarteritis presentation, pathology and prognosis. *QJM* 1985;56:467–83.
- Li KPT, Lui SF, Lai FM, Wang AYM, Leung CB, Lai KN. Microscopic polyarteritis has a poor prognosis in Chinese. *J Rheumatol* 1995;22:1295–9.
- Mahr A, Girard T, Agher R, Guillevin L. Analysis of factors predictive of survival based on 49 patients with systemic Wegeners granulomatosis and prospective follow up. *Rheumatology* 2001;40:492–8.
- Slot MC, Cohen A, Tervaert C, Franssen CF. Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. *Kidney Int* 2003;63:670–7.
- Maclaren JS, Stimson RH, McRorie ER, Coia JE, Luqmani RA. The diagnostic value of ANCA testing in a routine clinical setting. *QJM* 2001;94:615–21.
- Watts RA, Scott DGI. Overview of inflammatory vascular diseases. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt MH, Weisman MH, eds. *Rheumatology*, 3rd edn. Toronto: Mosby, 2003;1583–91.
- Cohen MD, Conn DL. An approach to the adult with suspected vasculitis. In: Ball GV, Bridges L, eds. *Vasculitis*. Oxford: Oxford University Press, 2002;227–34.
- Hagen EC, Daha MR, Hermans J *et al.* Diagnostic value of standardised assays for antineutrophil cytoplasmic antibodies in idiopathic systemic vasculitis: EC/BCR project for ANCA assay standardisation. *Kidney Int* 1998;53:743–53.
- Watts R, Lane S, Bentham G, Scott D. Epidemiology of systemic vasculitis—a 10 year study in the united kingdom. *Arthritis Rheum* 2000;43:265–70.
- Rasmussen N, Jayne DRW, Abramowicz D *et al.* European therapeutic trials in ANCA associated systemic vasculitis: disease scoring, consensus, regimens and proposed clinical trials. *Clin Exp Immunol* 1995;101(Suppl. 1):29–34.
- Jayne D, Rasmussen N, Andrassy K *et al.* A randomised trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Eng J Med* 2003;349:36–44.
- De Groot K, Muhler M, Reinhold-Keller E *et al.* Randomised controlled trial of daily oral versus pulsed cyclophosphamide for induction of remission in ANCA associated systemic vasculitis (abstract). *Kidney Blood Pressure Research* 2005;28:195.
- WGNET research group. The Wegener's granulomatosis etanercept trial. *N Eng J Med* 2006;352:4:351–61.
- Hall ND, Bird HA, Ring EFJ, Bacon PA. A combined clinical and immunological assessment of four cyclophosphamide regimens in rheumatoid arthritis. *Agents and Actions* 1979;9:97–102.
- Bolton WK, Sturgill BC. Methylprednisolone therapy for acute crescentic rapidly progressive glomerulonephritis. *Am J Nephrol* 1989;9:368–75.
- De Groot K, Rasmussen N, Bacon P *et al.* Randomised trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody associated vasculitis. *Arthritis Rheum* 2005;52:2462–8.
- Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of cyclophosphamide induction methotrexate maintenance regimen for the treatment of Wegeners granulomatosis: extended follow up and rate of relapse. *Am J Med* 2003;114:463–9.
- Chakravarty K, McDonald H, Pullar T, Taggart A, Chalmers R, Oliver S. BSR & BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology* 2006, doi:10.1093/rheumatology/ke216a.
- Gaskin G, Jayne D. Adjunctive plasma exchange is superior to methylprednisolone in acute renal failure due to ANCA associated glomerulonephritis. *J Am Soc Nephrol* 2002;13, F-FC010 (MEPEX).
- Mahr A, Pagnoux C, Cohen P *et al.* Treatment of ANCA associated vasculitides: corticosteroids and pulse cyclophosphamide followed by maintenance therapy with methotrexate or azathioprine a prospective multicentre randomised trial (Abstract). *Kidney Blood Press Res* 2005;28:194.
- Koukoulaki M, Jayne DR. Mycophenolate mofetil in anti-neutrophil cytoplasm antibodies-associated systemic vasculitis. *Nephron Clin Pract* 2005;102:c100–7.
- Hogan S, Falk R, Chin H, Cai J *et al.* Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody associated small vessel vasculitis. *Ann Internal Med* 2005;143: 9:621–31.
- Slot M, Cohen Tervaert JW, Boomsma MM, Stegeman CA. Positive classic antineutrophil cytoplasmic antibody (cANCA) titre at switch to azathioprine therapy associated with relapse in proteinase 3 related vasculitis. *Arthritis Rheum* 2004;51:269–73.

- 37 Booth A, Harper L, Hammad T *et al*. Prospective study of TNF-alpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol* 2004;15:717–21.
- 38 Bartolucci P, Ramanoelina J, Cohen P *et al*. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. *Rheumatology* 2002;41:1126–32.
- 39 Jayne DR, Chapel H, Adu D *et al*. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *QJM* 2000;93:433–9.
- 40 Jayne DR, Lockwood CM. Intravenous immunoglobulin as sole therapy for systemic vasculitis. *Br J Rheumatol* 1996;35:1150–53.
- 41 Ito-Ihara T, Ono T, Nogaki F *et al*. Clinical efficacy of intravenous immunoglobulin for patients with MPO- ANCA- associated rapidly progressive glomerulonephritis. *Nephron Clin Pract* 2006;102:c35–42.
- 42 Schmitt WH, Hagen EC, Neumann I *et al*. Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): an open study in 15 patients. *Kidney Int* 2004;65:1440–8.
- 43 Lockwood CM, Thiru S, Isaacs JD *et al*. Long-term remission of intractable systemic vasculitis with monoclonal antibody therapy. *Lancet* 1993;341:1620–2.
- 44 Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005;52:262–8.
- 45 Stegeman CA, Tervaert C, Sluiter WJ, Manson WL, de Jong M, Kallenberg CGM. Association of chronic nasal carriage of staphylococcus aureus and higher relapse rates in Wegeners granulomatosis. *Ann Internal Med* 1994;120:12–7.
- 46 Cohen A, Tervaert C, de Jong P *et al*. Trimethoprim-sulphamethoxazole (co-trimoxazole) for the prevention of relapses of Wegeners granulomatosis. *N Engl J Med* 1996;335:16–20.
- 47 Birk R, Warnatz K, Lorenz HM *et al*. 15-Deoxyspergualin in patients with refractory ANCA-associated systemic vasculitis: a six-month open-label trial to evaluate safety and efficacy. *J Am Soc Nephrol* 2003;14:440–7.
- 48 Bacon PA, Luqmani RA. Assessment of vasculitis. In: *Vasculitis*, Ball, Bridges, eds. Oxford: Oxford University Press, 2002:246–54.
- 49 Luqmani RA, Bacon PA, Moots RJ *et al*. Birmingham vasculitis activity score (BVAS) in systemic vasculitis. *QJM* 1994;87:671–8.
- 50 Gayraud M, Guillevin L, le Toumelin *et al*. Longterm follow up of polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome: analysis of 4 prospective trials including 278 patients. *Arthritis Rheum* 2001;44:668–77.
- 51 De Groot K, Gross WL, Heryin K, Reinhold-Keller E. Development and validation of a disease extent index for Wegeners granulomatosis. *Clin Nephrol* 2001;55:31–8.
- 52 Reinhold-Keller E, Kewok J, Schnabel A *et al*. Influence of disease manifestation and antineutrophil cytoplasmic antibody titre on the response to pulse cyclophosphamide therapy in patients with Wegeners granulomatosis. *Arthritis Rheum* 1994;37:919–24.
- 53 Guillevin L, le Duc THD, Godeau P, Jais P, Wechsler B. Clinical findings and prognosis of polyarteritis nodosa and Churg Strauss angiitis, a study in 165 patients. *Br J Rheumatol* 1988;27:258–66.
- 54 Exley AR, Bacon PA, Luqmani RA, Kitas GD, Gordon C, Savage COS, Adu D. Development and initial validation of the vasculitis damage index (VDI) for the standardised clinical assessment of damage in the systemic vasculitides. *Arthritis Rheum* 1997;40:371–80.
- 55 Exley A, Carruthers DM, Luqmani RA *et al*. Damage occurs early in systemic vasculitis and is an index of outcome. *QJM* 1997;90:391–9.
- 56 Seo P, Min YI, Holbrook JT *et al*. Damage from Wegener's granulomatosis and its treatment: prospective data from the Wegener's granulomatosis etanercept trial (WGET). *Arthritis Rheum* 2005;52:2168–78.
- 57 Ware JE, Snow KK, Kosinski M, Gandek B. Sf36 health survey manual and interpretation guide. Boston: The Health Institute New England Medical Centre, 1993.
- 58 Stewart AL, Hays RD, Ware JE Jr. The MOS short form general health survey. Reliability and validity in a patient population. *Medical Care* 1988;26:724–35.
- 59 Tervaert JW, Stegeman CA, Kallenberg CG. Serial ANCA testing is useful in monitoring disease activity of patients with ANCA associated vasculitides. *Sarcoidosis Vasc Dif* 1996;13:241–5.
- 60 Knight A, Askling J, Granath F, Sparen P, Ekblom A. Urinary bladder cancer in Wegeners granulomatosis risks and relation to cyclophosphamide. *Ann Rheum Dis* 2004;63:10:1183–5.
- 61 Taylor-Williams C, Hijazi YM, Walther MM *et al*. Cyclophosphamide –induced cystitis and bladder cancer in patients with Wegeners granulomatosis. *Ann Inter Med* 1996;124:477–84.
- 62 Guillevin, Cordier JF, Lhote F *et al*. A prospective multicentre, randomised trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalised Wegeners granulomatosis. *Arthritis Rheum* 1997;40:2187–9.
- 63 Ognibene FP, Shelhamer JH, Hoffman GS *et al*. Pneumocystis carinii pneumonia: a major complication of immunosuppressive therapy in patients with Wegeners granulomatosis. *Am J Resp Crit Care Med* 1995;151:795–9.
- 64 Reinhold-keller E, Beuge N, Latza U *et al*. An interdisciplinary approach to the care of patients with Wegeners granulomatosis: longterm outcome in 155 patients. *Arthritis Rheum* 2000;43:1021–32.
- 65 Chung JB, Armstrong K, Schwartz SJ, Albert D. Cost effectiveness of prophylaxis in patients with Wegeners granulomatosis undergoing immunosuppressive therapy. *Arthritis Rheum* 2000;43:1841–8.
- 66 Ogeneovski VM, Marder W, Somers EC, Johnston CM, Farrehi J, Selvaggi SM, McCune WJ. Increased incidence of cervical intraepithelial neoplasia in women with systemic lupus erythematosus treated with intravenous cyclophosphamide. *J Rheumatol* 2004;31:1763–7.
- 67 Park MC, Park YB, Yung SY, Choi KH, Lee SK. Risk of ovarian failure and pregnancy outcome in patients with lupus nephritis treated with intravenous cyclophosphamide pulse therapy. *Lupus* 2004;13:569–74.
- 68 Royal College of Physicians, National Osteoporosis Society, Bone and Tooth Society of Great Britain. Glucocorticoid induced osteoporosis – guidelines for the prevention and treatment. London: Royal College of Physicians, 2002.
- 69 British Thoracic society standards of care committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF treatment. *Thorax* 2005;60:800–5.
- 70 British society for Rheumatology (2002) vaccinations in the immunocompromised person. Guidelines for the patient taking immunosuppressant, steroids and the new biologic therapies. [www.rheumatology.org.uk](http://www.rheumatology.org.uk)
- 71 Gluck T. Vaccinate your immunocompromised patients. *Rheumatology* 2006;45:9–10.