Rheumatology

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Modern management of primary systemic vasculitis

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Background

The systemic vasculitides are a group of heterogeneous, relatively uncommon conditions characterised by inflammation and necrosis of blood vessel walls. They are classified according to vessel size (Table 1).[1] Primary systemic vasculitis (PSV) (comprising Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS) and microscopic polyangiitis (MPA)) typically involves medium and small vessels and is associated with the presence of antineutrophil cytoplasmic antibodies (ANCA). This group is sometimes described as ANCA-associated vasculitis (AAV).

Most data on the incidence and prevalence of PSV have come from Europe. The consensus is that:

- the overall annual incidence is approximately 10–20 per million
- the peak age of onset is 65–74 years
- it is slightly more common in men
- it is very rare in childhood.[2,3]

Table 1. Classification of systemic vasculitis. Reprinted with permission from Elsevier.[1]

	Vasculitis	
Dominant vessel	**Primary**	**Secondary**
Large arteries	Giant cell arteritis Takayasu's arteritis	Aortitis associated with RA, infection (eg syphilis, TB)
Medium arteries	Classical PAN Kawasaki disease	Hepatitis B-associated PAN
Small vessels and medium arteries	Wegener's granulomatosis Churg-Strauss syndrome Microscopic polyangiitis	Vasculitis secondary to RA, SLE, Sjögren's syndrome, drugs, infection (eg HIV)
Small vessels	Henoch-Schonlein purpura Cryoglobulinaemia Cutaneous leucocytoclastic angiitis	Drugs Hepatitis C-associated infection

PAN = polyarteritis nodosa; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; TB = tuberculosis.

The aetiology is unknown but, like most autoimmune diseases, involves a complex interaction between environmental factors and a genetically predisposed host.

Investigation and diagnosis of primary systemic vasculitis (Table 2)

Symptoms can be non-specific in the early phases of the disease and a high index of suspicion is required. 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.

Acute-phase reactants such as C-reactive protein and erythrocyte sedimentation rate are typically elevated in the acute phase. Urinalysis should be performed as soon as the diagnosis of vasculitis is suspected because renal involvement may progress silently and it is associated with a worse prognosis. Full blood count should be measured, looking particularly for eosinophilia. It is essential to investigate critical organ function for renal, cardiac and pulmonary involvement, with appropriate organ-specific tests (Fig 1).

Autoantibodies including ANCA are useful in the appropriate clinical setting. It is important to recognise that a negative ANCA does not exclude vasculitis and a positive ANCA does not necessarily prove vasculitis.[4]

Infection should be excluded by blood culture and appropriate serology because treatment for PSV involves intense immunosuppression.

The choice of biopsy site depends on the clinical features, but skin and renal biopsies are often helpful for diagnosis. Treatment should not be delayed for a biopsy if there are strong clinical grounds for a diagnosis of vasculitis.

Imaging investigations including angiography should be carefully considered in appropriate cases. Coeliac axis angiography has an important role in the diagnosis of polyarteritis nodosa.

There are a number of conditions that may mimic systemic vasculitis and these

Table 2. Investigation of vasculitis.

Assessment of inflammation	Blood count and differential cell count (total white cell count, eosinophils) Acute-phase response (ESR, CRP) Liver function
Assessment of organ involvement	Urinalysis (proteinuria, haematuria, casts) Renal function (creatinine clearance, 24-hour protein, excretion, biopsy) Chest radiograph Liver function Nervous system (nerve conduction studies, biopsy) Muscle (EMG, creatinine kinase, biopsy) Cardiac function (ECG, echocardiography) Gut (angiography) Skin (biopsy)
Serological tests	ANCA (including proteinase 3, myeloperoxidase) Antinuclear antibodies Rheumatoid factor Anticardiolipin antibodies Complement Cryoglobulins
Differential diagnosis	Blood cultures Viral serology (HBV, HCV, HIV, CMV) Echocardiography (2-dimensional, transoesophageal or both)

ANCA = antineutrophil cytoplasmic antibody; CMV = cytomegalovirus; CRP = C-reactive protein; EMG = electromyography; ESR = erythrocyte sedimentation rate; HBV = hepatitis B virus; HCV = hepatitis C virus.

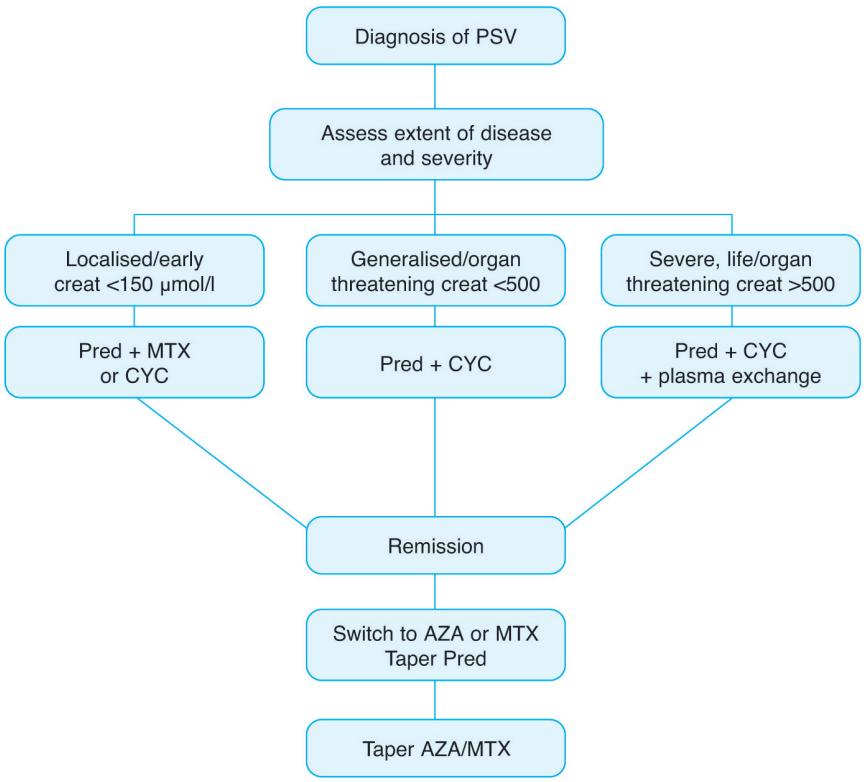

Fig 1. Algorithm for the management of primary systemic vasculitis (PSV).[7]
AZA = azathioprine; creat = creatinine; CYC = cyclophosphamide; MTX = methotrexate; Pred = prednisolone.

must be considered in the differential diagnosis (Table 3).

Treatment

The natural history of untreated PSV is of a rapidly progressive, usually fatal disease. With modern treatment regimens the five-year survival rates are 45% for MPA, 76% for WG and 68% for CSS.[5] The European Vasculitis Study Group (EUVAS) has recently completed a series of multicentre randomised controlled trials (RCTs).[6] Detailed guidelines for the management of the PSV have recently been developed by the British Society for Rheumatology.[7]

Current treatment is based on assessing severity and extent of disease, subdividing the disease into three groups as adopted by EUVAS (Table 4). Treatment can be divided into three stages: induction, consolidation and maintenance of remission.

Treatment for remission induction

Localised/early systemic disease

Cyclophosphamide (CYC) (maximum dose oral 200 mg/day or intravenous pulse 15 mg/kg) and methotrexate (MTX) (maximum 20–25 mg/week) are the most established treatments for this category. MTX is effective but may be associated with a higher relapse rate; any evidence of progression or relapse should be treated with CYC.[8] Localised disease can have significant local destructive consequences and these patients require CYC treatment.

Generalised/threatened organ involvement

Initial treatment of patients with generalised/organ-threatening disease should include CYC and steroids. CYC may be given as continuous low-dose oral treatment (2 mg/kg/day, maximum 200 mg/day) or by intravenous (iv) pulse (15 mg/kg, maximum 1,500 mg per pulse), initially at two-weekly intervals and then three-weekly. Dose reductions should be made for age and renal

function. The recently completed EUVAS trial of pulse versus continuous low-dose oral CYC showed no difference in remission rates and no increased risk of relapse in the iv treated patients.[9] Continuous low-dose oral CYC was associated with a higher total CYC dosage and a significant increase in infection risk. The cumulative dose of CYC was lower for the iv pulse regimen than for the continuous oral regimen when administered for the same period of time.

Current clinical practice considers transfer to maintenance therapy after 3–6 months of CYC therapy if successful disease remission has been achieved. The aim should be for a maximum duration of therapy of six months where successful disease remission has been achieved.

Table 3. Differentiation to be made from conditions that may mimic primary systemic vasculitis. Reprinted with permission from Elsevier.[1]

Multisystem disease	Infection	Subacute bacterial endocarditis
		Neisseria
		Rickettsiae
	Malignancy	Metastatic carcinoma
		Paraneoplastic
	Other	Sweet's syndrome
Occlusive vasculopathy	Embolic	Cholesterol crystals
		Atrial myoma
		Infection
		Calciphylaxis
	Thrombotic	Antiphospholipid syndrome
		Procoagulant states
		Cryofibrinogenaemia
	Others	Ergot
		Radiation
		Degos syndrome
		Severe Raynaud's
		Acute digital loss
		Buerger's disease
Angiographic	Aneurysmal	Fibromuscular dysplasia
		Neurofibromatosis
	Occlusion	Coarctation

Severe/life-threatening disease

Patients with PSV presenting with severe renal failure (creatinine >500 μmol/l) should be treated with CYC (either pulsed iv or continuous low-dose oral) and steroids, with adjuvant plasma exchange.[10] Plasma exchange should also be considered in those with other life-threatening manifestations of disease such as pulmonary haemorrhage.

Corticosteroids

Steroids in combination with standard immune suppression are useful for the early control of disease activity in PSV but are ineffective as sole therapy for the induction of remission. The optimal initial dosage of steroids and the rate of steroid taper are currently controversial. Steroids are usually given as daily oral prednisolone, starting initially at relatively high doses (1 mg/kg up to about 60 mg) and tapered to about 10 mg/day at six months.[10] Steroids (250–500 mg iv methylprednisolone) are sometimes given with the first two pulses of iv CYC.

Patients intolerant of cyclophosphamide

For patients intolerant of CYC alternative treatments such as MTX, azathioprine (AZT), leflunomide or mycophenolate mofetil may be used, but there is little evidence for their use as induction therapy except for MTX.

Maintenance therapy

CYC should be withdrawn in patients who have achieved successful remission and either AZT or MTX substituted. A recent trial comparing CYC and AZT found them equally effective at maintaining remission, with similar relapse rates but increased toxicity in the CYC group.[11] MTX may be used in patients intolerant of AZT, with mycophenolate or leflunomide as alternatives for intolerance or lack of efficacy of AZT or MTX.

Maintenance therapy should continue for at least 24 months following successful disease remission. It is advisable that patients who remain ANCA-positive continue immunosuppression for up to five years.

Relapsing disease

Minor relapse is treated with an increase in prednisolone dosage, followed by

Table 4. Categorisation of disease severity and induction therapy.[6]

Clinical subgroup	Constitutional symptoms	Typical ANCA status	Threatened vital organ function	Serum creatinine (μmol/l)	Treatment induction*
Localised/early systemic	Yes	+ or –	No	<150	MTX or CYC
Generalised	Yes	+	Yes	<500	CYC
Severe	Yes	+	Yes	>500	CYC/plasma exchange Methylprednisolone

* All induction regimens include oral/intravenous steroids.
ANCA = antineutrophil cytoplasmic antibody; CYC = cyclophosphamide; MTX = methotrexate.

gradually tapering of the dose and optimisation of concurrent immunosuppression. Major relapse is treated with CYC as for remission induction with an increase in prednisolone; iv methylprednisolone or plasma exchange may also be considered.

Nasal carriage of *Staphylococcus aureus* is associated with increased risk of relapse in patients with WG, although the causal relation and mechanism remain speculative.[12] Cyclical application of mupirocin should be considered in patients with WG.

Refractory disease

Disease refractory to full-dose CYC and prednisolone is rare. More commonly, optimal doses are not tolerated or a prolonged relapsing disease course with high cumulative exposure to CYC and prednisolone are the indications for alternative agents.

The use of infliximab, iv immunoglobulin, antithymocyte globulin, CAMPATH-1H (alemtuzumab, anti-CD52), deoxyspergualin and rituximab in refractory disease is still under investigation. It is important to identify potential underlying factors influencing persistent or relapsing disease, including intercurrent infection and malignancy as well as non-compliance.

Assessment and monitoring of disease activity

The PSVs are relapsing conditions; relapse may occur any time after diagnosis and remission induction. Various tools may be used to assess disease activity and extent of disease: for example the Birmingham Vasculitis Activity Score.[13,14] The Vasculitis Damage Index[15] provides a long-term outcome of disease and its consequences.

ANCA measurements are not closely associated with disease activity. Treatment should not be escalated solely on the basis of an increase in ANCA but it should be taken as a warning of possible impending relapse.[16] Treatment withdrawal in patients with persistently positive ANCA is associated with relapse.[17]

Key Points

- **Symptoms of systemic vasculitis at presentation are often non-specific and diagnosis requires a high index of suspicion**
- **A negative antineutrophil cytoplasmic antibody (ANCA) does not exclude primary systemic vasculitis**
- **Critical organ function is damaged early in disease, so a careful assessment for renal, cardiac and pulmonary involvement, with appropriate tests, is essential**
- **Studies have included large numbers and have significantly influenced current management**
- **Treatment regimens are based on early systemic/localised, generalised/organ-threatening or severe/life-threatening disease**
- **Localised disease may have local destructive consequences and these patients require cyclophosphamide (CYC) treatment**
- **For both oral and intravenous CYC the aim is a maximum duration of therapy of six months where successful disease remission has been achieved**
- **Maintenance therapy should continue for at least 24 months or longer in patients who remain ANCA-positive**
- **ANCA titre does not always correlate with disease activity**
- **Treatment should not be altered solely according to changes in ANCA titre; the exception is treatment withdrawal which should not be considered in the presence of a persistently positive ANCA because of a high risk of relapse**

KEY WORDS: cyclophosphamide, diagnosis, treatment, vasculitis

Detection and prevention of potential adverse effects of immunosuppressive therapy

Cyclophosphamide-induced bladder toxicity

Haemorrhagic cystitis and bladder cancer are recognised complications of therapy. The risk is related to the cumulative dose of CYC administered and is greatest in patients receiving more than a cumulative dose of 100 g CYC.[18] Treatment with [sodium-2-] mercaptoethanesulfonate (MESNA), which protects against the urothelial toxicity of CYC, should be considered in all patients receiving CYC therapy.

Pneumocystis jiroveci infection

Immunosuppressed patients are at risk of *Pneumocystis jiroveci*. There are no RCT data but observational data support the approach that patients receiving CYC and corticosteroids should receive trimethoprim/sulfamethoxazole 960 mg thrice weekly (or aerolised pentamidine/daily dapsone in patients allergic to trimethoprim/sulfamethoxazole) as prophylaxis against pneumocystis.[19–21]

Osteoporosis

All patients receiving corticosteroids for systemic vasculitis should be started on a bisphosphonate with calcium and vitamin D supplementation.

Vaccinations

Immunocompromised patients should not receive live vaccines, but should be vaccinated against influenza and pneumococcal infections.[22,23]

Conclusions

CYC has transformed the prognosis of many of the systemic vasculitides. Early diagnosis and treatment improve the outcome. Recently published clinical

trials and smaller case series provide evidence for new treatment options and treatment stratification, but there is a continued need for better and less toxic treatment regimens.

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