ABC of arterial and vascular disease
Vasculitis

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Vasculitis is inflammation of blood vessel walls. The clinical and pathological features are variable and depend on the site and type of blood vessels that are affected. Diseases in which vasculitis is a primary process are called primary systemic vasculitides.

The main types of vasculitides can be described using clinical features and pathological findings according to the Chapel Hill Consensus Conference. These names and definitions will be followed in this article. Definitive classification of systemic vasculitis is unsatisfactory since aetiology and pathogenesis are rarely known, and clinical and histological features overlap. Vasculitis may also occur as a secondary feature in other diseases, such as systemic lupus erythematosus and rheumatoid arthritis.

Fever, night sweats, malaise, myalgia, and arthralgia are common in all types of vasculitis. Active vasculitis is usually associated with an acute phase response with an increase in C reactive protein concentration, erythrocyte sedimentation rate, or plasma viscosity.

Large vessel vasculitis

Giant cell arteritis (temporal arteritis)

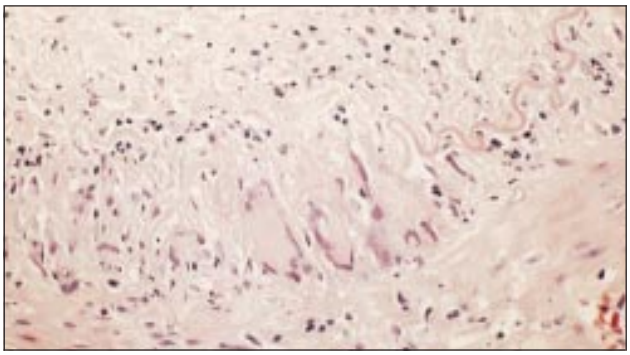
Clinical features include unilateral throbbing headache, facial pain, and claudication of the jaw when eating. Visual loss is a feared symptom and may be sudden and painless, affecting part or all of the visual field. Diplopia may also occur. Giant cell arteritis is the most common type of primary systemic vasculitis with an incidence of 200/million population/year.

Treatment is with high dose corticosteroids (40-60 mg/day), which should be started as soon as the diagnosis is suspected to avoid visual loss. The diagnosis is confirmed by biopsy of the affected artery, done within 24 hours of starting corticosteroids. The corticosteroid dose may be reduced to 10 mg/day over six months and then more slowly to a maintenance of 5-10 mg/day. Maintenance treatment may be required for two years. The disease is monitored by measuring C reactive protein concentrations, erythrocyte sedimentation rate, or plasma viscosity.

Takayasu's arteritis

Takayasu's arteritis is most common in Asia and the Far East and affects women more than men. Disease of the arteries supplying the arms, head, neck, and heart leads to the aortic arch syndrome with claudication of the arm, loss of arm pulses, variation in blood pressure of more than 10 mm Hg between the arms, arterial bruits, angina, aortic regurgitation, syncope, stroke, and visual disturbance. The descending aortic syndrome may cause bowel ischaemia or infarction, renovascular hypertension, and renal impairment.

Diagnosis is by angiography or magnetic resonance angiography. Treatment of acute disease in patients with high C reactive protein concentration or erythrocyte sedimentation rate is with corticosteroids. Cytotoxic drugs such as cyclophosphamide can be added if steroids alone do not control the disease. Surgery or angioplasty may be required for stenoses once active inflammation has been controlled.

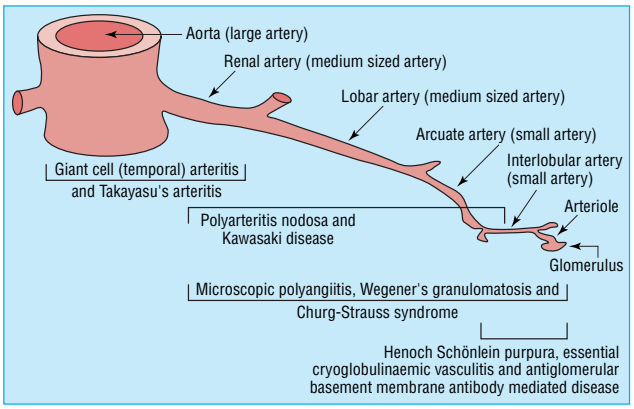


Temporal artery biopsy specimen with giant cell inflammation

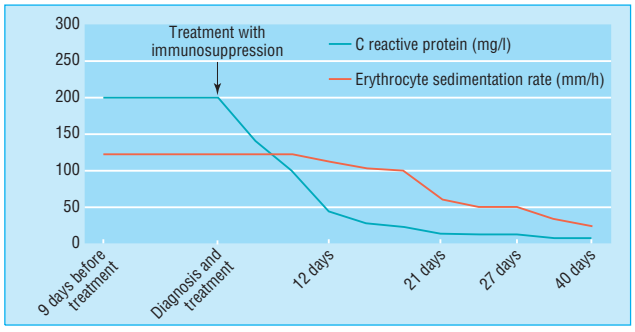
Definitions of large vessel vasculitis

Giant cell arteritis (temporal arteritis)
- Granulomatous arteritis of aorta and its major branches, especially extracranial branches of carotid artery
- Often affects temporal artery
- Usually occurs in patients older than 50 years
- Often associated with polymyalgia rheumatica

Takayasu's arteritis
- Granulomatous inflammation of aorta and its major branches
- Usually occurs in patients younger than 50 years



Spectrum of systemic vasculitides organised according to predominant size of vessels affected (adapted from Jennette et al, Arthritis Rheum 1994;37:187-92)



C reactive protein concentration (>10 mg/l) and erythrocyte sedimentation rate (>18 mm/h) are raised at time of diagnosis of giant cell arteritis but fall to normal levels after starting immunosuppressant therapy

Medium vessel vasculitis

Polyarteritis nodosa

Polyarteritis nodosa is uncommon in the United Kingdom. It is associated with hepatitis B virus in some patients. Arterial disease leads to ischaemia or infarction within affected organs. The condition can affect the gut causing bleeding or perforation, the heart causing angina or myocardial infarction, the kidneys causing cortical infarcts leading to hypertension and renal failure, and the peripheral nerves causing mononeuritis multiplex. Hepatitis may reflect the presence of hepatitis B virus.

Diagnosis is based on the presence of arterial aneurysms on angiography of the renal, hepatic, splanchnic, or splenic circulations. Biopsy of affected muscle or nerve may confirm the presence of vasculitis. Treatment of polyarteritis associated with hepatitis B virus requires an antiviral drug such as interferon alfa combined with short course, high dose corticosteroids and plasma exchange. Non-hepatitis B virus polyarteritis usually responds to corticosteroids alone, although cyclophosphamide may be required for patients with more severe disease.

Kawasaki disease

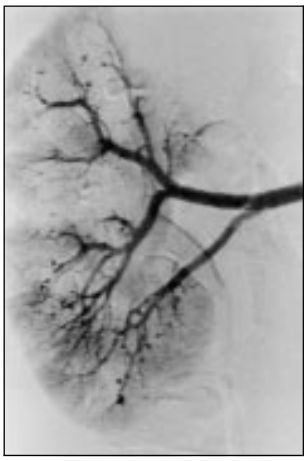
Kawasaki disease affects children, usually under the age of 12 years. In Japan the incidence exceeds 100/100 000 children younger than 5 years but is less than 5/100 000 in this age group in the United Kingdom.

The most serious feature of Kawasaki disease is coronary artery disease; aneurysms occur in a fifth of untreated patients and may lead to myocardial infarction. They can be detected by echocardiography. High dose intravenous immunoglobulins reduce the prevalence of coronary artery aneurysms, provided that treatment is started within 10 days of onset of the disease. Low dose aspirin is recommended for thrombocythaemia.

Definitions of medium sized vessel vasculitis

Polyarteritis nodosa
- Necrotising inflammation of medium and small arteries without glomerulonephritis, pulmonary capillaritis, or disease of other arterioles, capillaries, or venules

Kawasaki disease
- Arteritis affecting large, medium, and small arteries and associated with mucocutaneous lymph node syndrome
- Coronary arteries are usually affected and aorta and veins may be affected
- Usually occurs in children



Renal angiogram showing multiple arterial aneurysms

Small vessel vasculitis associated with antineutrophil cytoplasmic antibody

Small vessel vasculitides are being recognised more frequently, mainly because of increased awareness. Estimates of incidence have increased from fewer than 5 cases per million population in the early 1980s to over 20 per million. The early symptoms of these disorders are non-specific with fever, malaise, arthralgia, myalgia, and weight loss, and patients in whom such symptoms are persistent should be screened for antineutrophil cytoplasmic antibodies (ANCA); have their erythrocyte sedimentation rate and C reactive protein concentration measured; and have their urine tested for blood with a dipstick. Early diagnosis is essential to prevent potentially life threatening renal and pulmonary injury. Delays in diagnosis are unfortunately common, and this often leads to serious morbidity. Once respiratory or renal disease develops, the course is usually rapidly progressive.

Wegener's granulomatosis

Upper respiratory tract disease occurs in more than 90% of cases and includes sinusitis; nasal crusting, bleeding, obstruction, and collapse of the nasal bridge; serous otitis media with conductive deafness; and tracheal stenosis. Limited Wegener's refers to disease that affects only the respiratory tract at the time of diagnosis; many cases evolve to systemic disease. Lung disease is common with cough, haemoptysis, and dyspnoea and may progress to life threatening pulmonary haemorrhage. The kidneys are affected in up to 80% of cases; blood, protein, and casts are present in the urine and should be examined by dipstick testing and microscopy. If untreated, there is loss of renal function, often within days. Other features include purpuric rashes, nail fold infarcts, and ocular manifestations including

Features of mucocutaneous lymph node syndrome in Kawasaki disease

- Fever for >5 days
- Conjunctival congestion
- Changes to lips and oral cavity: dry, red, fissured lips; strawberry tongue; reddening of oral and pharyngeal mucosa
- Changes of peripheral extremities: red palms and soles; indurative oedema; desquamation of finger tips during convalescence
- Macular polymorphous rash on trunk
- Swollen cervical lymph nodes

At least five features must be present

Definitions for diagnosis of vasculitides often associated with antineutrophil cytoplasm antibodies

Wegener's granulomatosis
- Granulomatous inflammation of the respiratory tract
- Necrotising vasculitis affecting small to medium sized vessels (capillaries, venules, arterioles, and arteries)
- Necrotising glomerulonephritis is common

Microscopic polyangiitis (microscopic polyarteritis)
- Necrotising vasculitis with few or no immune deposits affecting small vessels (capillaries, venules, arterioles, and arteries)
- Necrotising arteritis of small and medium sized arteries may be present
- Necrotising glomerulonephritis very common
- Pulmonary capillaritis often occurs

Churg-Strauss syndrome
- Eosinophil rich and granulomatous inflammation of respiratory tract
- Necrotising vasculitis affecting small to medium sized vessels
- Blood eosinophilia ($>1.5\times10^9/l$)
- Usually associated with asthma

conjunctival haemorrhages, scleritis, uveitis, keratitis, proptosis, or ocular muscle paralysis due to retro-orbital inflammation. The disease can affect the gut causing haemorrhage, the heart causing coronary artery ischaemia, and the neurological system causing sensory neuropathy or mononeuritis multiplex.

The two pathological hallmarks of Wegener's disease are chronic granulomatous inflammation and vasculitis. Granulomas (localised microscopic collections of macrophages) are not always present. Granulomas in the lung may coalesce into large masses which cavitate. The vasculitis affects capillaries particularly in the lung, causing lung haemorrhage, and glomeruli, causing glomerulonephritis that may be segmental, global, focal, or diffuse with thrombosis, necrosis of capillary loops, and accumulation of cells in Bowman's space. Affected arteries or arterioles show an inflammatory infiltrate and fibrinoid necrosis. There is no deposition of immunoglobulins within the kidney or vessel walls.

Microscopic polyangiitis (microscopic polyarteritis)

Microscopic polyangiitis has many similarities to Wegener's granulomatosis, but disease of the upper respiratory tract is uncommon in microscopic polyangiitis, although pulmonary haemorrhage may occur. Patients with microscopic polyangiitis usually have glomerulonephritis, and, rarely, disease may be limited to the kidney. No granuloma formation is seen.

Diagnosis

Diagnosis is based on typical clinical features, biopsy (usually of kidney, occasionally of nasal mucosa or lung) and presence of antineutrophil cytoplasmic antibodies. These antibodies usually have specificity for the enzymes proteinase-3 or myeloperoxidase and can be detected by enzyme linked immunosorbent assay (ELISA). In indirect immunofluorescence tests, antineutrophil cytoplasmic antibodies against proteinase-3 produce a cytoplasmic staining pattern (cANCA) and antibodies against myeloperoxidase produce perinuclear staining pattern (pANCA). Combined testing by ELISA and indirect immunofluorescence is recommended as this increases specificity at the cost of a 10% reduction of sensitivity. Sometimes antineutrophil cytoplasmic antibody tests are negative, particularly if disease is limited to the upper respiratory tract. Antibody titres usually fall and may disappear completely when the disease is in remission.

Treatment

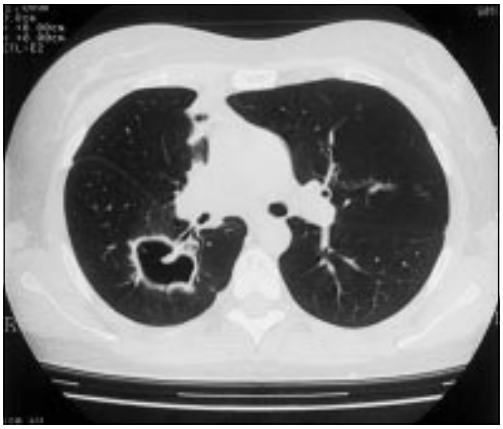
Treatment of Wegener's granulomatosis and microscopic polyangiitis comprises induction of remission and then maintenance of remission. Multicentre trials are in progress to assess the place of pulse cyclophosphamide, plasma exchange, and methylprednisolone in treatment and to assess the optimum duration of maintenance therapy. Methotrexate is sometimes used instead of cyclophosphamide for patients with no renal disease. Relapses occur in 40-50% of patients during the first five years, so lifelong monitoring for recurring disease activity is essential. The five year survival rate is over 80%.

Churg-Strauss syndrome

Churg-Strauss syndrome is associated with an atopic tendency, usually asthma. It may affect coronary, pulmonary, cerebral, and splanchnic circulations. Rashes with purpura, urticaria, and subcutaneous nodules are common. Glomerulonephritis may develop, but renal failure is uncommon.

Diagnosis depends on presence of typical clinical features, biopsy of skin, lung, and kidney, and blood eosinophilia. About 25% of patients are positive for cANCA, 50% for pANCA, and 25% have no antineutrophil cytoplasmic antibodies.

Many patients respond to high dose corticosteroids alone, although cyclophosphamide may be required for patients with



Cavitating granulomatous lesion in right lung of patient with Wegener's granulomatosis

Specificity and sensitivity of ANCA serology testing for Wegener's granulomatosis and microscopic polyangiitis (adapted from Hagen et al, *Kidney Int* 1998;53:743-53)

	Specificity/ sensitivity (%)
Specificity of assays (related to disease controls)	
Indirect immunofluorescence:	
cANCA	95
pANCA	81
ELISAs:	
PR3-ANCA	87
MPO-ANCA	91
Combined indirect immunofluorescence and ELISA:	
cANCA/PR3-ANCA positive	99
pANCA/MPO-ANCA positive	99
Sensitivity of combined testing	
Wegener's granulomatosis	73
Microscopic polyangiitis	67

Treatment of small vessel vasculitis

***Induction therapy* (to 3 months after remission, usually 6 months from diagnosis)**

- Cyclophosphamide, 2.0 mg/kg/day (maximum 200 mg/day). Age > 60 years, reduce dose by 25%, > 75 years by 50%
- Prednisolone, 1 mg/kg/day (maximum 80 mg/day) reduced weekly to 25mg/day by 8 weeks and then more slowly to 10 mg/day by 6 months

In severe, life threatening disease (eg, pulmonary haemorrhage, severe crescentic glomerulonephritis with creatinine >500 µmol/l), consider plasma exchange, 7-10 treatments over 14 days, or three pulses of methylprednisolone, 15 mg/kg/day for 3 days

***Maintenance therapy* (to 18-24 months, longer if clinically indicated)**

- Azathioprine, 2.0 mg/kg/day (maximum 200 mg/day). Age > 60 years, reduce dose by 25%, > 75 years by 50%
- Prednisolone, 5-10 mg/day

Relapse therapy

- Major relapse: return to induction therapy
- Minor relapse: increase dose of corticosteroids

Stop cyclophosphamide or azathioprine if white blood count $4x10^9$/l; restart with a dose reduced by at least 25 mg when white blood count $>4x10^9$/l on two consecutive tests

Consider gastric and bone protection, and fungal and *Pneumocystis carinii* prophylaxis

more severe disease. Asthma requires conventional treatment but the recently introduced leukotriene receptor antagonist drugs have been causally linked with the Churg-Strauss syndrome and should be avoided in these patients.

Small vessel vasculitis without antineutrophil cytoplasmic antibodies

Henoch-Schönlein purpura

Henoch-Schönlein purpura is most common in children but can occur at any age. Typical clinical features are purpura over the lower limbs and buttocks, haematuria, abdominal pain, bloody diarrhoea, and arthralgia.The pathological hallmarks are deposition of immunoglobulin A at the dermoepidermal junction and within the glomerular mesangium, with a mesangial hypercellular glomerulonephritis. Some patients develop a glomerular lesion resembling that seen in small vessel vasculitis. Renal disease may occur without the rash or other typical features.

The disease is usually self limiting and only supportive treatment is required. Corticosteroids and immunosuppression may be needed for vasculitic glomerulonephritis or serious gut haemorrhage and ischaemia.

Cryoglobulinaemic vasculitis ("mixed, essential")

Cryoglobuins are immunoglobulins that precipitate in the cold. The mixed cryoglobulin consists of a monoclonal immunoglobulin M rheumatoid factor complexed to polyclonal immunoglobulin G. Vasculitis develops when cryoglobulins deposit in blood vessels. Mixed essential cryoglobulinaemia is due to hepatitis C virus infection in over 80% of cases. Other causes of cryoglobulinaemia include dysproteinaemias, autoimmune diseases, and chronic infections. Serum complement C4 and C3 concentrations are reduced. Clinical features include palpable purpura, arthralgia, distal necroses, peripheral neuropathy, abdominal pain, and glomerulonephritis. Renal biopsy specimens typically have the appearance of subendothelial membranoproliferative glomerulonephritis with intraglomerular deposits.

In cryoglobulinaemia associated with hepatitis C, treatment is directed at the viral infection. Interferon alfa over six months is beneficial, but many patients relapse when treatment is stopped. Prednisolone with or without immunosuppressants has been used successfully in acute severe disease. The role of plasma exchange remains unsubstantiated.

Isolated cutaneous leukocytoclastic vasculitis

This is often associated with a drug hypersensitivity response and improves when the drug is stopped. Occasional patients may require corticosteroids for severe disease.

Antiglomerular basement membrane antibody mediated disease (Goodpasture's disease)

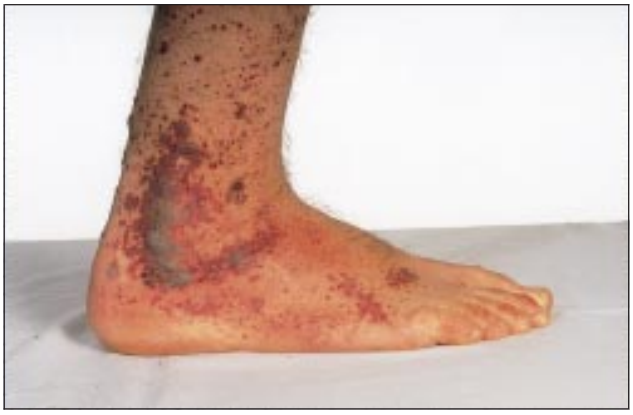
No Chapel Hill definition exists for this rare disease, which has considerable overlaps with antineutrophil cytoplasmic antibody associated vasculitis. The hallmarks are a rapidly progressive global and diffuse glomerulonephritis, as seen in small vessel vasculitides, or presence of pulmonary haemorrhage, or both. Diagnosis depends on finding antibodies to glomerular basement membrane in the serum and linear staining for immunoglobulin G along the glomerular basement membrane. The antibodies have been implicated in disease pathogenesis. About 15-30% of patients have detectable antineutrophil cytoplasmic antibodies. Treatment is as for small vessel vasculitis with addition of daily plasma exchange until antiglomerular basement membrane antibodies are no longer detectable.

Definitions of non-ANCA associated small vessel vasculitis

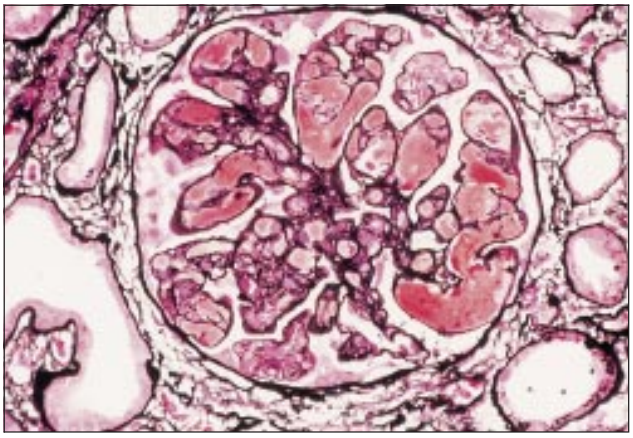
Henoch-Schönlein purpura
- Vasculitis with IgA dominant immune deposits affecting small vessels (capillaries, venules, or arterioles)
- Affects skin, gut, and glomeruli
- Associated with arthralgia or arthritis

Cryoglobulinaemic vasculitis
- Vasculitis with cryoglobulin immune deposits affecting small vessels
- Associated with cryoglobulins in serum
- Skin and glomeruli often affected

Isolated cutaneous leukocytoclastic vasculitis
- Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis
- May evolve into systemic vasculitis



Purpuric rash on lower limb of patient with Henoch-Schönlein purpura



Renal biopsy specimen showing intraglomerular deposit of cryoglobulins

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The ABC of arterial and venous disease is edited by Richard Donnelly, professor of vascular medicine, University of Nottingham and Southern Derbyshire Acute Hospitals NHS Trust (richard.donnelly@nottingham.ac.uk) and Nick J M London, professor of surgery, University of Leicester, Leicester (sms16@leicester.ac.uk). It will be published as a book later this year.

BMJ 2000;320:1325-8