Vasculitis: an update

The systemic vasculitides are uncommon but serious diseases. Early recognition can be difficult because they mimic many conditions. Aggressive immunosuppression is toxic but effective; a targeted approach with biological agents may improve the outcome.

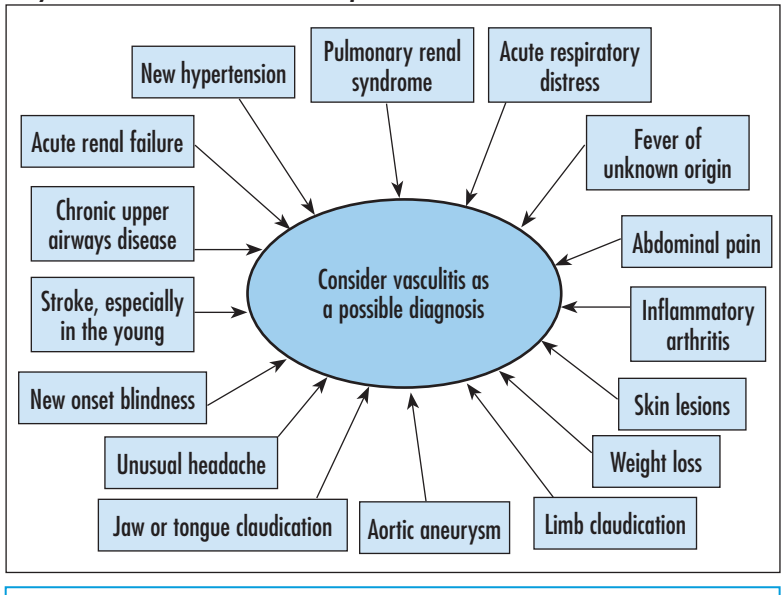
The systemic vasculitides are characterized by blood vessel inflammation leading to organ or tissue damage, which in severe cases causes organ failure or death (Phillip and Luqmani, 2008). This review focuses on the overall approach to diagnosis, characterization of disease, assessment, initial therapy and outcome. The main role of the generalist is in recognizing the possibility that a patient may have a form of vasculitis as well as being involved in the acute management of patients who have established disease and are admitted urgently either as a result of complications of the vasculitis or its treatment. Being able to distinguish between vasculitis and other conditions can be challenging; when patients with established vasculitis become acutely unwell, it is important to consider the possible reasons for this deterioration.

Although a flare of vasculitis is possible (around 30–50% of patients flare), a complication of treatment (such as infection from immunosuppression) or as a result of comorbidity is more likely. By taking a pragmatic view of the assessment of each case it should be possible to determine the likely cause of the acute presentation and have an effective plan to manage the patient, with the support of an expert in vasculitis.

Table 1. The spectrum of problems in the diagnosis and management of vasculitis

V	vast array of possible differential diagnoses
a	ANCA (anti-neutrophil cytoplasmic antibody) test is useful but can be over-interpreted
s	start treatment early
c	clinical features affecting many systems
u	unclassified cases can have incomplete features but still need treatment
l	life threatening or organ threatening if untreated
i	idiopathic in most cases (drugs, hepatitis B and C can cause specific forms of vasculitis)
t	tests including biopsy, imaging and serology are important
i	inflammation of blood vessels is characteristic, leading to tissue or organ damage
s	serial assessment of patients is important to control disease, limit damage, treat flares and prevent or manage long term complications

Figure 1. Multiple clinical presentations, alone or in combination, can raise the possibility of systemic vasculitis as a cause of the patient's condition.



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Background

The vasculitides are uncommon but serious conditions which can be difficult to diagnose and treat (*Table 1* lists some of the complexities). They can present with clinical features which are difficult to distinguish from other causes (*Figure 1*). Some forms such as giant cell arteritis are more frequent (around 220/million/annum in older persons), while others are much less common (classical polyarteritis nodosa and Takayasu arteritis occur in fewer than 5 patients/million/year). In different ethnic groups and also in different parts of the world, the incidence of the vasculitides varies (Scott and Watts, 2013). For example, giant cell arteritis is most common in patients of Scandinavian descent. The underlying pathology includes inflammatory vessel occlusion leading to tissue or organ damage as a result of ischaemia, but the nature of the inflammatory process varies. Cutaneous vasculitis is a different entity and far less serious than the multi-system vasculitides. Vasculitis can also occur as a secondary form in patients with other diseases (e.g. rheumatoid arthritis and systemic lupus erythematosus). This article focuses on the primary multi-system vasculitides.

In giant cell arteritis, transmural inflammation with CD4 positive T cells and macrophages progresses from the adventitia towards the lumen (*Figure 2*), eventually resulting in luminal narrowing or occlusion (Weyand et

al, 2004). In patients with immune complex-associated vasculitis such as cryoglobulinaemic vasculitis, the formation of immune complexes in situ causes occlusion of small blood vessels where the complexes lodge and obstruct blood flow. In microscopic polyangiitis and granulomatosis with polyangiitis, two types of anti-neutrophil cytoplasmic antibody-(ANCA) associated vasculitis, ANCA, cellular immunity, neutrophil extracellular traps, fibroblasts, vascular endothelial cells and several cytokines and chemokines all play a significant role (Csernok and Gross, 2013), resulting in local tissue destruction in the capillary bed of organs such as the kidney or lung. By contrast, in eosinophilic granulomatosis with polyangiitis, the eosinophil is the key cell in the inflammatory process.

Classification and diagnosis

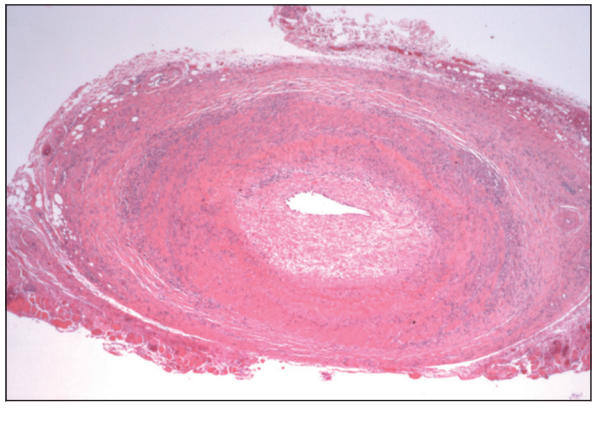
The different forms of vasculitis are confusing to the majority of clinicians. However, the differences between different vasculitides are important, reflecting different causes, pattern of organ involvement, treatment and outcome. However, some of the conditions have overlapping features (e.g. the ANCA-associated vasculitides share many of the same clinical and histological abnormalities) and indeed the treatment options, which are still limited, are often the same.

There is no satisfactory classification or diagnostic system. A set of definitions is widely used to separate different forms of vasculitis from each other (Jennette et al, 2013). Many physicians will know these diseases under their former eponymous or other names (such as Wegener's granulomatosis, Churg–Strauss syndrome, Henoch–Schönlein purpura). *Table 2* lists new and former names for the primary vasculitides.

There are many pitfalls in the diagnosis and management of vasculitis (*Table 3*). In making a diagnosis, it is necessary to consider the possibility of vasculitis in the first place, and then to take an adequate history, perform a thorough examination and request appropriate laboratory or imaging tests. Symptoms and signs (*Table 4*) should be elicited and the pattern reviewed to see if it conforms to one of the vasculitides or not. Further tests such as imaging (*Figure 3*), biopsy or serology are not always confirmatory, leaving some uncertainty about the diagnosis. It is most important to rule out other causes such as infection, cancer, drug toxicity or other autoimmune conditions.

It is very important to involve a specialist in vasculitis at an early stage to give advice or help manage the patient, to guide the choice of which further tests (if any) are helpful, avoid unnecessary tests, reduce delays in starting definitive treatment, and prevent inappropriate treatment.

Figure 2. Cross section of temporal artery in a patient with giant cell arteritis showing transmural inflammation, occasional giant cells and significant luminal narrowing (haematoxylin and eosin staining).



Large vessel vasculitis

Giant cell arteritis is the most common form of systemic vasculitis in adults. It is usually present in older adults (above the age of 50 years), and presents with new unaccustomed temporal headache, scalp tenderness and systemic illness. A minority of patients have neuro-ischaemic complications such as jaw or tongue claudication, and in 20–25% of patients there is a risk of

Table 2. The primary vasculitides

Vessel size	Disease	Former or other name	ANCA status
Large vessel vasculitis	Giant cell arteritis	Horton's disease	Negative
	Takayasu arteritis	Aortic arch syndrome, non-specific aortoarteritis, pulseless disease	Negative
Medium vessel vasculitis	Kawasaki disease	Mucocutaneous lymph node syndrome	Negative
	Polyarteritis nodosa	Periarteritis nodosa	Negative
Small vessel vasculitis	Granulomatosis with polyangiitis	Wegener's granulomatosis	Up to 90% cANCA/PR3 ANCA positive
	Eosinophilic granulomatosis with polyangiitis	Churg–Strauss syndrome	Approximately 40% pANCA/MPO positive
	Microscopic polyangiitis	Microscopic polyarteritis	Up to 90% pANCA/MPO positive
	Anti-glomerular basement membrane (GBM) disease	Goodpasture's syndrome	ANCA negative (but occasionally double positive for ANCA and anti-GBM antibody)
	Cryoglobulinaemic vasculitis	Mixed essential cryoglobulinaemic vasculitis	Negative
	IgA vasculitis	Henoch–Schönlein purpura	Negative
	Hypocomplementaemic urticarial vasculitis, also termed C1q vasculitis		Negative

ANCA = anti-neutrophil cytoplasmic antibody; MPO = myeloperoxidase; PR3 = proteinase 3. Main forms of primary vasculitis including where appropriate, the names that were previously used to describe some of these conditions and the typical ANCA status (there will always be exceptions, but they are usually not clinically relevant). There are also other forms of vasculitis not included in the table (see Jennette et al (2013) for a more comprehensive overview)

permanent visual loss as a result of ciliary artery occlusion leading to ischaemic optic neuropathy. The latter makes giant cell arteritis a medical emergency, because prompt introduction of steroids can be sight saving. Patients will typically complain of tenderness when brushing or combing their hair. About 30% of patients will have features of associated widespread aches and pains as a result of polymyalgia rheumatica.

Most patients in the UK are initially managed by their GPs, using high dose glucocorticoid (typically 40–60 mg/day), but this should be followed or accompanied by urgent referral to secondary care so that the diagnosis can be confirmed by temporal artery biopsy. If more than 10 days elapse from steroid therapy to biopsy, or the specimen is too small (less than 1 cm), the result may be uninterpretable in up to 40% of cases with good clinical

Table 3. Common pitfalls in diagnosing and managing vasculitis

Problem	Explanation
Missing the diagnosis of vasculitis	Patients can present to any hospital department and it may not be immediately obvious that the problem is vasculitis. A clue would be the presence of features in more than one body system, but this depends on adequate history and examination of the patient
Over-diagnosing vasculitis	There can be an over-reliance on laboratory investigations for vasculitis. Don't forget that more common explanations should be considered in a patient with multi-system presentation, e.g. cancer or infection; and don't necessarily equate anti-neutrophil cytoplasmic antibody (ANCA) positivity with vasculitis
Inadequate history and examination	In general medicine it is unusual to undertake a full vasculitis history or examination. It is necessary to consider past events in conjunction with current clinical features to see if they fit together to suggest a diagnosis of vasculitis. For current features there is a need to ask about involvement of all systems. Clinicians often forget to ask about the upper airways, e.g. nasal crusting, discharge, sinusitis and deafness, or if these features are volunteered by the patient, their relevance to vasculitis may be overlooked. If vasculitis is suspected, a suggested checklist is shown in *Table 4*
A vasculitis screen is commonly recommended	It is tempting to think that with one fell swoop you can order a series of blood tests to rule in or rule out vasculitis. In practice, this is not useful and can mislead as well as being very inefficient. Much more valuable is time spent evaluating the clinical manifestations including checking urine for evidence of blood and protein
Starting treatment before contacting expert	There is a common misunderstanding that treatment must be given immediately on suspicion of the diagnosis; it is very important to investigate the patient urgently to ascertain the diagnosis and only then initiate definitive therapy, unless the patient has immediate organ-threatening or life-threatening manifestations. The injudicious use of high doses of glucocorticoid can make it difficult to confirm the diagnosis (steroids will rapidly alter the outcome of the investigations) but may also contribute to morbidity because of toxicity. It is essential to discuss such cases as soon as they are suspected and not to embark on treatment until expert advice has been sought. For some conditions, such as suspected giant cell arteritis, it may be appropriate to commence high dose steroids before definitive investigations are performed, but this should be done in conjunction with experts, so that a plan is in place to organize the relevant tests in a timely fashion

Table 4. Clinical manifestations which suggest the possibility of vasculitis

System	Examples
General systemic features	These are general systemic manifestations that are not exclusive to vasculitis but are often accompaniments to the disease, including muscle pains, joints pains, fevers, significant weight loss
Skin	Small infarcts, purpura, ulceration, gangrene. Other skin lesions can occur such as erythema nodosum in many forms of vasculitis
Mucus membranes and eyes	Oral and/or genital ulceration occur; inflammation of the salivary and lacrimal glands; inflammatory eye disease including scleritis, episcleritis, iritis and keratitis; sudden visual loss may occur in giant cell arteritis; retinal haemorrhage and thrombosis can occur in some diseases
Ear, nose and throat	This is commonly involved in granulomatosis with polyangiitis giving blood-stained nasal discharge, nasal crusting, sinusitis, subglottic stenosis or hearing loss (conductive or sensorineural)
Chest	Patients with late onset asthma may have eosinophilic granulomatosis with polyangiitis; haemoptysis or breathlessness are common symptoms of lung involvement. Imaging is used to show the presence of nodules, cavities, infiltrates and bronchial involvement. In extreme cases, patients have massive haemoptysis as a result of alveolar haemorrhage resulting in respiratory failure
Cardiovascular	Loss of pulses or bruits typically occurs in large vessel vasculitis; some patients experience severe artery pain or tenderness (e.g. tender temporal arteries in giant cell arteritis or carotid artery tenderness in Takayasu arteritis). Some patients develop pericarditis, valvular heart disease, ischaemic cardiac pain and heart failure as a result of direct heart muscle involvement
Abdominal	Patients may experience peritonitis, bloody diarrhoea as a result of ischaemic colitis or ischaemic abdominal pain associated with eating. Imaging examination may show the presence of smooth narrowing of vessels and/or microaneurysms
Renal	Most important system for small vessel vasculitis; it is often asymptomatic and therefore it is important to measure blood pressure and check urine for the asymptomatic presence of blood and protein as well as measuring renal function with serum creatinine or glomerular filtration rate
Nervous system	Patients with giant cell arteritis often complain of unaccustomed new onset of headache. Several other neurological manifestations affect patients with vasculitis, including peripheral neuropathy, stroke and seizures

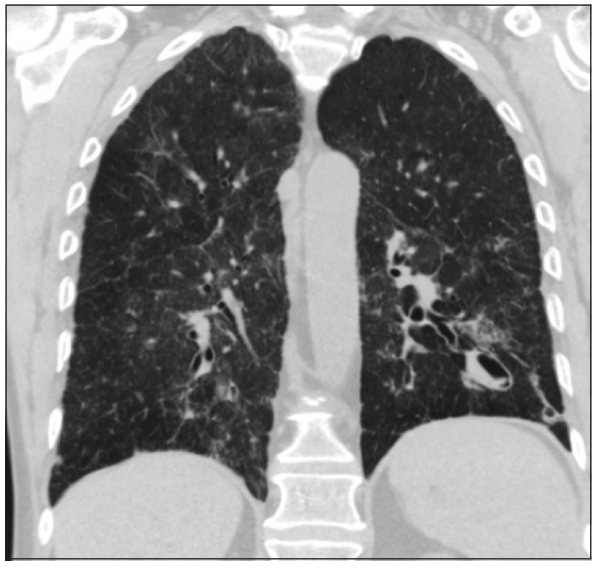


Figure 3. Extensive cavitating and non-cavitating nodules in a patient with granulomatosis with polyangiitis.

evidence of the disease. Therefore, a fast track service for giant cell arteritis is being developed, and alternative investigation strategies such as using ultrasound to image the vessels are being tested.

Takayasu arteritis, by contrast, is much less common in the UK and Europe, and is more common in young women of Asian and Oriental descent. The presentation is often insidious with tiredness, occasionally with fever and weight loss plus pain over affected arteries such as the carotids (carotidynia). More often, patients will present at a much later stage of the condition, by which time they have developed ischaemic claudication of their limbs and reduced pulses are noted. Imaging of the great vessels is the most common way of confirming the diagnosis.

Another group of patients with large vessel inflammation is increasingly being recognized as a cause of systemic otherwise unexplained non-organ-specific illness, especially in the elderly. These patients have 18 fluoro-deoxyglucose positron emission tomography-computed tomography (FDG PET-CT) scan appearances (*Figure 4*) similar to those seen in Takayasu arteritis, and it is unclear at present whether or not they have a separate form of large vessel vasculitis, or if this is a subgroup of unusual patients with older onset Takayasu arteritis.

Medium vessel vasculitis

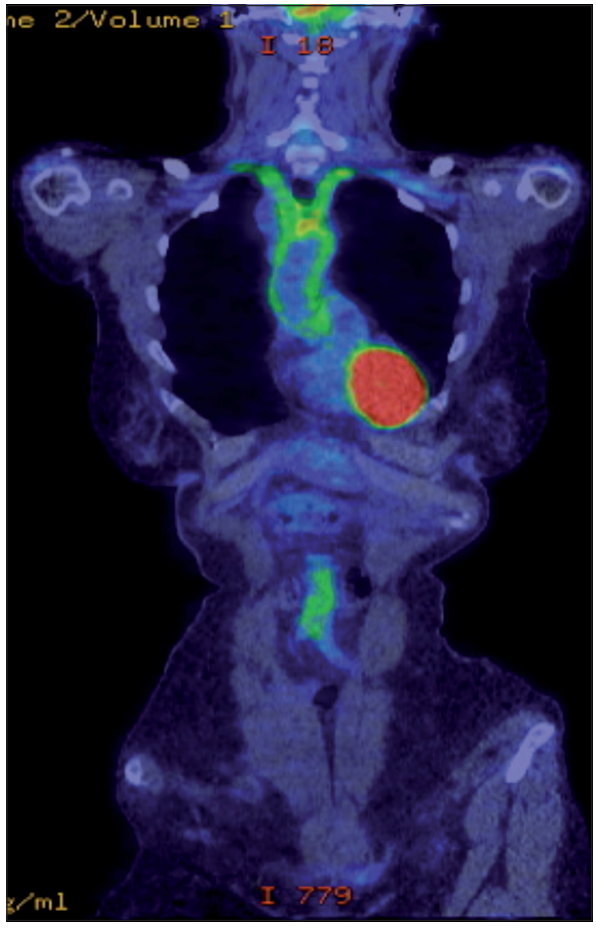
Kawasaki disease occurs in children and presents with acute unexplained fever, lymphadenopathy and mucosal inflammation, followed by desquamation. The most important aspect of this rare disease which mimics an acute infection is the presence of coronary arteritis, which can lead to coronary artery rupture and sudden death without prompt and adequate treatment with intravenous immunoglobulin and high dose aspirin.

Polyarteritis nodosa is a very rare disease. Previously, when hepatitis B was more prevalent, polyarteritis nodosa was slightly more common, but with eradication of hepatitis B, the main subtype of polyarteritis nodosa is disappearing. Non-hepatitis B-associated polyarteritis nodosa does still occur, presenting with systemic upset, and typically resulting in skin rashes, peripheral neuropathies, gastrointestinal ischaemia and infarction or other organ infarction, as a result of medium vessel inflammation and occlusion.

Small vessel vasculitis

The discovery of antibodies to neutrophil cytoplasm (ANCA) in the 1980s has been strongly associated with three forms of small vessel vasculitis: microscopic polyangiitis, granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis (Van der Woude et al, 1985; Hagen et al, 1998; Mouthon et al, 2014). Not all patients are ANCA positive, and not all ANCA-positive individuals have vasculitis, but there is no doubt that the ability to test for this antibody has increased recognition of vasculitis, as well as leading to the development of effective targeted therapy designed to reduce antibody production. ANCA occur

Figure 4. Combined 18 fluoro-deoxyglucose positron emission tomography-computed tomography scan from a patient with active large vessel vasculitis. The image shows abnormal enhancement of the ascending aorta and its proximal branches as well as parts of the descending aorta.

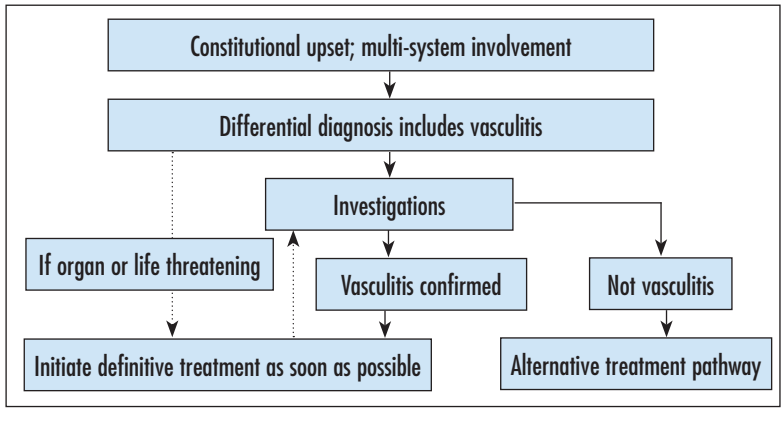


in many forms, but the most disease specific are those directed against proteinase 3 (PR3) and those against myeloperoxidase (MPO). PR3 and MPO are normal enzymes present in the primary granules of neutrophil polymorphs. PR3 ANCA usually produces a cytoplasmic staining pattern on immunofluorescence (cANCA), whereas MPO ANCA produces a perinuclear pattern (pANCA). PR3 ANCA is typical in most but not all cases of granulomatosis with polyangiitis; MPO ANCA is more commonly found in about 50% of cases of microscopic polyangiitis and about 30–40% of patients with eosinophilic granulomatosis with polyangiitis. The three conditions have an overlapping clinical spectrum, but with distinct differences. They can all present with constitutional features (fever, malaise, weight loss, muscle and joint pains).

Eosinophilic granulomatosis with polyangiitis usually results in late onset asthma and the patient typically has a significant peripheral eosinophilia. Asthma (sometimes combined with lung infiltrates) and nasal polyps or nasal congestion may occur, together with more specific features of vasculitis involving peripheral nerves (mononeuritis multiplex), the skin, the gastrointestinal tract, and less commonly affecting the kidney.

By contrast, in granulomatosis with polyangiitis, patients suffer from chronic upper respiratory tract features of chronic nasal congestion, blood-stained discharge, hearing loss, stridor combined with lower respiratory tract evidence of disease (cough, occasional haemoptysis, nodules or infiltrate on chest imaging). The majority of patients with granulomatosis with polyangiitis will have renal involvement, detected as asymptomatic microscopic haematuria and proteinuria and newly developed hypertension. Patients with microscopic polyangiitis are similar to those with granulomatosis with polyangiitis but without the upper respiratory tract features.

Figure 5. Initial management pathway for patients with suspected systemic vasculitis. In severe cases, treatment may be started before definitive evidence of disease is proven. This is a judgment call that needs to be made with advice from an expert. Waiting too long may allow disease to progress, but immunosuppressive therapy can alter the outcome of tests, obscuring the diagnosis; in addition, if patients have other causes for their condition, e.g. sepsis, this may be worsened by therapy.



Small vessel vasculitis can occur in response to the presence of antibodies to glomerular basement membrane. Anti-glomerular basement membrane disease only occurs in smokers, and typically presents with haemoptysis, which can be life threatening, and varying degrees of renal impairment. The glomerular basement membrane antibodies cross react with the respiratory tract.

Immune complex-mediated small vessel vasculitis affecting the skin and some other organs can occur in adult patients with IgA disease, but this is uncommon compared to the equivalent problem in children where it is much more common and often in association with streptococcal throat infections. Long-term effects on the kidney as a result of renal deposition of IgA can lead to renal failure in a significant number of patients over a long period of time.

If patients present with obvious renal disease (haematuria, proteinuria and renal impairment) the prognosis is less good than if there is no sign of renal disease. Isolated skin vasculitis is common and often resolves without treatment. Hepatitis C infection can induce the presence of cryoglobulins (proteins which precipitate out in the cold). Immune complexes are deposited in small capillary beds, usually in cooler peripheries, leading to tissue infarction. Patients present with rashes, muscle pains and can have renal involvement. Mixed cryoglobulins are found (a mixture of polyclonal and monoclonal antibodies, the latter often has rheumatoid factor activity).

Other forms of vasculitis

There are many other forms of vasculitis, some more common but most are less common and characterized by different patterns of organ involvement and less specific laboratory investigations

Management of vasculitis

An outline of the general approach is shown in *Figure 5*.

Evaluation

There are no reliable circulating biomarkers of disease activity in vasculitis. Inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein levels can be helpful in managing these illnesses (especially giant cell arteritis and granulomatosis with polyangiitis); PR3 ELISA levels can be helpful in managing granulomatosis with polyangiitis – these levels can rise in advance of the clinical flare and act as a warning sign. However, the clinical context is always important; high erythrocyte sedimentation rate and C-reactive protein levels may indicate the presence of infection rather than a flare of vasculitis; PR3 levels may change independent of any change in clinical state (Tomasson et al, 2012). On the contrary, patients may experience a flare without any obvious acute phase response, especially if they are already on treatment. Clinical methods to assess disease

are reliable if used by trained assessors with expertise in vasculitis and can be used to guide treatment. Disease activity is quantified using a checklist of items. However, the skill comes in interpreting whether or not the item actually represents active vasculitis, because many of the features on the checklist would occur in other conditions such as infection which may complicate the patient's condition. Use of these evaluation tools is a good guide to clinical management of the patient and proficiency can be attained through training.

Increasingly, it is becoming necessary to formally document disease status for patients who are going to be treated with expensive and potentially toxic therapy, as well as repeating the documentation after the patient has received treatment. The Birmingham Vasculitis Activity Score is the most robust clinical measure of disease activity (Luqmani et al, 1994; Mukhtyar et al, 2009a). As well as providing a numeric score, it serves as an important guide in evaluating and documenting the pattern of problems that the patient is currently suffering so that it can form the basis of a treatment plan (Mukhtyar et al, 2009b).

Accrual of damage from the effects of vasculitis and its treatment, or from comorbidity is an increasingly recognized problem, which has a significant impact on future prognosis. Using a similar checklist to the Birmingham Vasculitis Activity Score, it is possible to record the impact of vasculitis in the Vasculitis Damage Index. Recording damage allows separation of clinical problems not resulting from active vasculitis, as well as providing a basis for managing the patient's comorbidity (Exley et al, 1997).

Therapy

The overall strategy for managing vasculitis requires careful evaluation of disease status (see above). A summary of the drug treatments used is shown in *Table 5*.

Steroids

Glucocorticoids are important and currently required therapy for most forms of vasculitis, except for Kawasaki disease, which responds most effectively to intravenous gammaglobulin and high dose aspirin. In fact glucocorticoids can worsen the outcome in some cases. For giant cell arteritis, steroids are usually the only therapy required, given at doses above 0.75 mg/kg/day (typically 1 mg/kg) and progressively reducing over a period of about 15–24 months (Mukhtyar et al, 2009c; Dasgupta et al, 2010).

Immunosuppressive agents

Cyclophosphamide is the key drug which has transformed the outcome in ANCA vasculitis as well as being effective for other forms of vasculitis (Berden et al, 2012). It acts as a cytotoxic agent, killing immune cells (because they are among the most rapidly dividing cells). Lower cumulative doses are possible as a result of pulse therapy, but the disadvantage is in relapse risk, which is higher on lower cumulative doses of cyclophosphamide. It is the main form of induction therapy in small vessel vasculitis with significant organ involvement, but rituximab is being used increasingly for patients who are unable to receive cyclophosphamide, or in those who are relapsing (Ntatsaki et al, 2014).

Other agents

Other agents can be used for non-life- or organ-threatening forms of systemic vasculitis, such as methotrexate, mycophenolate, leflunomide or ciclosporin. All of these agents can also be suitable maintenance therapies after disease has been controlled with induction therapy, but azathioprine is probably the most commonly used maintenance agent.

Biological therapies are increasingly being used and tested in vasculitis. Rituximab, a B cell antibody, targets CD20 and induces remission in ANCA vasculitis as effectively as cyclophosphamide (Guerry et al, 2012; Ntatsaki et al, 2014). Newer agents are being developed based on the biology of these diseases, but they are being tested in clinical trials.

Outcomes

The prognosis in vasculitis has been transformed from over 80% fatality in ANCA vasculitis to over 90% survival in the first year with effective treatment. Early intervention as a result of more rapid diagnosis can prevent permanent sight loss in giant cell arteritis, and irreversible kidney failure or catastrophic lung haemorrhage in small vessel vasculitis. However, relapse is common in these diseases, as is comorbidity (such as infection, hypertension, diabetes and cardiovascular disease).

Use of toxic agents can increase the risk of future malignancy, although this risk is also enhanced by the disease itself. Management requires long-term surveillance of patients in expert care, in order to detect and treat relapses, manage comorbidity and improve quality of life.

Conclusions

The systemic vasculitides remain a challenge in clinical practice. Because of the wide range of clinical manifestations, patients can present to many different clinical specialties, and therefore recognition of the disease is often difficult. Development of diagnostic criteria and improved classification criteria may improve the situation but it is important to remain vigilant for the possibility of vasculitis especially in the setting of patients with unexplained multi-organ disease.

Diagnostic testing for vasculitis is improving. The availability of the ANCA test has allowed earlier identification of small vessel vasculitis such as microscopic polyangiitis, granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis but this also confuses the picture because ANCA are not exclusive

Table 5. Common immune therapies used to treat systemic vasculitis

Drug	Phase of therapy	Dose	Indication and comments
Glucocorticoids	Induction and maintenance	Varies but usually required at high dose initially (0.75–1 mg/kg/day) tapering after 4 weeks if there is evidence of good disease control. Subsequent reduction of steroids is typically rapid in the first 4–6 months (e.g. 5–15 mg every 1–2 weeks), then much slower (e.g. 1 mg every 1–2 months). Pulse high dose intravenous methylprednisolone (500–1000 mg) may be indicated for organ- or life-threatening manifestations, but the evidence for its use is poor	For giant cell arteritis, this may be the only immunosuppression given. For most other forms of systemic vasculitis, additional immunosuppressive agents are mandatory
Cyclophosphamide	Induction	Usually given intravenously as high dose intermittent pulses of 15 mg/kg/dose on 6–10 occasions, 2–3 weeks apart. Oral pulse therapy is also feasible and delivers more drug (as a result of first pass metabolism in liver to active compound). Continuous daily oral cyclophosphamide is also effective but the cumulative dose is much higher after 6 months compared to pulse therapy	Most forms of small vessel ANCA vasculitis, some patients with polyarteritis nodosa and some with large vessel vasculitis require therapy with cyclophosphamide. Rituximab is increasingly used for patients with ANCA vasculitis who have failed cyclophosphamide or in whom it is contraindicated. Long-term risk of malignancy related to cumulative dose exposure
Plasmapheresis	Induction	Additional to other immunosuppression. No standard volume of exchange. x7–10 4-litre exchanges in first 10 days of induction therapy is typical	Increases risk of infection when combined with glucocorticoids and cyclophosphamide. Avoid plasmapheresis shortly after administration of other intravenous therapies (otherwise they are removed)
Intravenous immunoglobulin	Induction	2 g/kg single dose or divided over 5 days is typical therapy in Kawasaki disease. These doses are much higher than those used for immunodeficiency	Kawasaki disease is the main form of vasculitis responding to intravenous immunoglobulin, in combination with high dose aspirin. Other forms such as ANCA vasculitis will respond transiently; this may be useful if patients are also septic, as it is an immunomodulating therapy. Check serum IgA to avoid allergic reactions in IgA-deficient patients (there is usually some IgA contamination). Intravenous immunoglobulin is prepared from pooled human serum, typically from thousands of donors. Viral screening is now highly effective (previous intravenous immunoglobulin therapy use has been associated with hepatitis C transmission)
Rituximab	Induction or maintenance	375 mg/m^2 every week for 4 weeks or 1 g x2 14 days apart are typical induction regimens. Maintenance therapy is often given every 4–6 months afterwards on four occasions	Increasingly used in place of cyclophosphamide as induction therapy at initial presentation or during relapse for ANCA vasculitis
Methotrexate	Induction or maintenance	15–25 mg/week oral or subcutaneous	Can be used as effective induction therapy for non-organ- or non-life-threatening ANCA vasculitis. Provides some extra benefit in control of giant cell arteritis. Avoid in patients with significant renal impairment
Leflunomide	Induction or maintenance	10–40 mg/day	This drug is used for inflammatory arthritis but has shown benefit in patients with localized granulomatosis with polyangiitis
Mycophenolate mofetil	Induction or maintenance	2–3 g per day	Less effective than azathioprine as a maintenance agent, but has a place in management of ANCA vasculitis. As an induction agent it appears as effective as cyclophosphamide
Co-trimoxazole	Induction or maintenance	960 mg twice a day or 960 mg three times per week if used in combination with methotrexate	This antibiotic has immunomodulatory effects in patients with mild granulomatosis with polyangiitis and improves upper airways disease, usually in combination with steroids. At a reduced dose it can be used as prophylaxis against *Pneumocystis jirovecii* in patients receiving other immunosuppressive agents
Azathioprine	Maintenance	2 mg/kg/day	This is a common maintenance agent, following successful induction therapy with either cyclophosphamide or rituximab
Ciclosporin	Maintenance	2–4 mg/kg/day in two divided doses	Less commonly used, largely because of its nephrotoxicity
Gusperimus	Relapse	0.5 mg/kg/day until neutropenia develops or for up to 21 days repeated every month for up to 6 months	Unlicensed in Europe, this immunomodulator therapy has been effective in relapsing granulomatosis with polyangiitis

ANCA = anti-neutrophil cytoplasmic antibody. Usually patients receive intense induction therapy followed by maintenance. Most patients also require additional agents to manage comorbidity and prevent drug toxicity. All induction therapies can be repeated for relapse.

to vasculitis; therefore rational use and interpretation of tests as in all aspects of clinical investigation, remains an important underlying principle.

Diagnostic imaging tools are being used in vasculitis, particularly for large vessel disease. Ultrasound examination is being evaluated in the diagnosis of giant cell arteritis. Magnetic resonance angiography, computed tomography angiography and FDG PET CT scanning have allowed more effective identification of patients with Takayasu arteritis as well as a new subgroup of patients with previously unexplained illness who have large vessel vasculitis.

Therapy is still based on the use of glucocorticoids but usually requires supplementation with other agents. Steroids are often sufficient for giant cell arteritis, but for most forms of small and medium vessel vasculitis other agents are necessary. Cyclophosphamide or rituximab are recommended for ANCA-associated vasculitis. For the small number of patients where there is a clear aetiological factor such as infection or prescribed or illicit drug use, removal of these agents or factors should modify the course of the disease, usually to resolution. Long-term outcome in vasculitis remains unsatisfactory with a mortality of around 30% after 5 years in ANCA-associated vasculitis but the more common problems are relapse and chronic damage as a result of either the disease or its therapy. Improvements in treatment should address these issues in the future. **BJHM**

Figure 2 *is supplied courtesy of Dr Brendan McDonald.*

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KEY POINTS

- The vasculitides are a group of uncommon disorders characterized by blood vessel inflammation, leading to tissue and organ damage.
- Some forms of vasculitis are life threatening or organ threatening.
- Early diagnosis and treatment, before damage occurs, will improve the outcome; late recognition and delayed therapy leads to poor prognosis.
- Clinical features of poor prognosis at presentation in small and medium vessel vasculitis include older age, the presence of renal impairment, cardiac or gastrointestinal involvement.
- Treatment of the vasculitis depends on the subtype and also the severity of the disease and should be tailored to it.
- The early use of effective immunosuppression using cyclophosphamide or rituximab combined with glucocorticoid remains the cornerstone of management for small vessel multisystem vasculitis.
- There has been a major improvement in survival from systemic vasculitis as a result of modern immunosuppression, but patients continue to experience chronic morbidity with frequent relapses and accumulating damage.
- Newer targeted therapies based on the pathophysiology of the disease are being introduced with the promise of more effective control of disease but with less long-term toxicity.