**An Update on The General Management Approach to Common Vasculitides**

Mooikhin Hng1, Sizheng Steven Zhao1,2, Robert J Moots1,3

1 Department of Rheumatology, Aintree University Hospital, Liverpool University Hospitals NHS Foundation Trust, Lower Lane, L9 7AL

2 Institute of Life Course and Medical Sciences, University of Liverpool, 6 West Derby Street, L7 8TX

3 Faculty of Health, Social Care and Medicine, Edge Hill University, ST Helen’s Road, L39 4QP

Corresponding

Prof Robert J Moots

Department of Rheumatology, Aintree University Hospital, Liverpool University Hospitals NHS Foundation Trust, Lower Lane, L9 7AL

Abstract

Primary systemic vasculitides are multisystem diseases attributed to inflammation of the blood vessels. They are associated with high morbidity and mortality particularly if not recognized and treated in a timely manner. Over the decades, more clinical trials have delivered better evidence and thus improved diagnostic and therapeutic approaches to vasculitis. This article provides a general overview of vasculitis in adults, including the latest updates in recommendations for the management of ANCA-associated vasculitis and giant cell arteritis.

Keywords: primary systemic vasculitides, ANCA-associated vasculitis, giant cell arteritis

**Introduction**

Primary systemic vasculitides (PSV) are a group of rare, chronic diseases characterised by inflammation of the blood vessels([1](#_ENREF_1)). Vessels of any size in any organ can be affected. The disease spectrum ranges from mild, localised disease to potentially life- or organ-threatening manifestations. Due to their heterogeneity and rarity, the recognition and management of vasculitis poses a considerable challenge to non-rheumatologists. In this review, we begin with a general overview of vasculitis in adults, including classification and general management approaches. We then focus on two comparatively common diseases - antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and giant cell arthritis (GCA) - with the latest update on their management guidelines.

**Types of vasculitis**

Although this review focuses on PSV, the general approach to vasculitis requires consideration and exclusion of vasculitis mimics and secondary vasculitis. Vasculitis mimics are caused by certain drugs, infections, malignancy, and thromboembolic disease. Secondary vasculitis develops in the context of some inflammatory rheumatic diseases, such as rheumatoid arthritis and systemic lupus erythematosus. Their management can differ completely from that of PSV; for example, immunosuppressive medication used for the treatment of presumed vasculitis may aggravate infectious diseases. Therefore, it is imperative to exclude them before making a diagnosis of PSV. **Table 1** provides a non-exhaustive summary of mimics ([2](#_ENREF_2), [3](#_ENREF_3)).

Currently, there are no validated diagnostic criteria for PSV. The Chapel Hill Consensus Conference (CHCC) in 2012 updated the definitions and nomenclature for vasculitis (**Table 2**). Vasculitides are categorised not only by vessels size, but also by aetiology, pathogenesis, pathology, demographics and clinical features([1](#_ENREF_1)). The ongoing Diagnostic and Classification Criteria for Vasculitis (DCVAS) project is anticipated to develop and validate diagnostic criteria and to improve classification criteria for PSV ([4](#_ENREF_4)).

**Approach to a patient with possible PSV**

Diagnosis of PSV is based on a combination of clinical, laboratory, histopathological and radiographic features. There are several clinical manifestations that should raise suspicion of vasculitis. The most common are constitutional symptoms such as fever, malaise, unintentional weight loss, and anorexia, although they are not unique to PSV because chronic infection, malignancy, and autoimmune connective tissue diseases may present similarly. Symptoms indicating organ ischemia (i.e. limb claudication, digital ulcer, stroke, or myocardial infarction) are more specific, especially if they occur in young patients without conventional cardiovascular risk factors. Vasculitis should be suspected in a constitutionally ill patients with multi-organ dysfunctions.

A systematic and comprehensive history **(Table 3)** and examination **(Table 4)** are essential. Laboratory tests are crucial for excluding mimics or secondary vasculitis, and determining extent of organ involvement. The more specific serological, histopathological, and angiographic investigations are helpful in categorizing PSV (**Table 5).**

**ANCA-Associated Vasculitis**

AAV is characterised by necrotizing vasculitis predominantly affecting small vessels, with few or no immune deposits. It is usually associated with ANCA specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA) and commonly involves the respiratory tract and kidneys ([1](#_ENREF_1)).

The estimated prevalence of AAV in England is 14.6/100,000 population. The prevalence of granulomatosis with polyangiitis (GPA) is 9.97/100,000, microscopic polyangiitis (MPA) 1.40/100,000 and eosinophilic granulomatosis polyangiitis (EGPA) 3.18/100,000. The median age of these patients is 65.3 years with approximately equal gender ratio ([5](#_ENREF_5)).

**Management of AAV**

The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) published revised guidelines for the management of adults with AAV in 2014 ([6](#_ENREF_6), [7](#_ENREF_7)). The European League Against Rheumatism and European Renal Association – European Dialysis and Transplant Association (EULAR/ERA-EDTA) updated similar recommendations in 2016 ([8](#_ENREF_8), [9](#_ENREF_9)).

These latest guidelines and recommendations have simplified the stratification of AAV disease severity into non-severe and severe groups, namely, ‘non-organ threatening disease’ and ‘organ- or life-threatening disease’. The EULAR/ERA-EDTA recommendations grouped the ‘rapidly progressive renal failure or pulmonary haemorrhage’ as third category.

The general principles of managing AAV are to induce and maintain disease remission using least cytotoxic medications. Latest BSR/BHPR and EULAR/ERA-EDTA recommendations also highlight the importance of patient education and participation in disease management.

**Remission induction**

**Organ- or life-threatening AAV**

Latest guidelines advocate combination of either cyclophosphamide (CYC) or rituximab (RTX) with glucocorticoid in inducing remission in patients with organ- or life-threatening AAV.

In the CYCLOPS study, pulsed CYC was associated with fewer leukopenia episodes and lower cumulative dose than oral regimens and thus deemed to have lower toxicity ([10](#_ENREF_10)). Although pulsed CYC was associated with a higher relapse risk than oral CYC in extended follow-up study, it was not associated with increased mortality or long-term morbidity ([11](#_ENREF_11)). Therefore, oral CYC is no longer a preferred choice for induction therapy. The recommended protocol is intravenous CYC 15mg/kg at 2-week intervals and then every 3 weeks, reduced for age and renal function.

Rituximab (RTX) has emerged as a new remission induction option for severe AAV after it was proven non-inferior to CYC in RAVE ([12](#_ENREF_12)) and RITUXVAS ([13](#_ENREF_13)) trials. This B-cell-depleting anti-CD20 monoclonal antibody is now recognized as a first-line alternative by BSR/BHPR and EULAR/ERA-EDTA. The RAVE trial, which recruited younger AAV patient and with less severe renal disease, demonstrated similar rates of adverse events compared to oral CYC([12](#_ENREF_12)). RAVE long-term follow-up data reported that single course of RTX was as effective as conventional CYC-azathioprine therapy in maintaining disease remission over the course of 18 months ([14](#_ENREF_14)). RITUXVAS trial, using intravenous CYC as comparator, showed equivalent sustained-remission and infection rates ([13](#_ENREF_13)). The RITUXVAS 2-year-follow-up study showed comparable disease remission, adverse events and mortality ([15](#_ENREF_15)). The BSR/BHPR highlighted that RTX is preferred when CYC avoidance is needed, i.e pre-existing high cumulative dose of CYC, infection, intolerant, uroepithelial malignancy or infertility concern. Dosing regimens are either 375mg/m2/week for 4 weeks or two infusion of 1g, two weeks apart ([7](#_ENREF_7), [16](#_ENREF_16)). The BSR and EULAR/ERA-EDTA guidelines both highlighted the lack of strong data on the use of RTX for EGPA.

High dose glucocorticoid at 1mg/kg/day or equivalent remains a cornerstone of remission induction therapy. Both treatment groups in RAVE and RITUXVAS trials received one to three pulses of methylprednisolone (1g each), followed by prednisolone taper. Some physicians favour intravenous methylprednisolone due to the rapid onset of effect and relative short-term safety despite poor evidence ([17](#_ENREF_17)). A retrospective cohort study showed that pulsed methylprednisolone may not confer any clinical benefit, while leading to higher incidence of infection and diabetes mellitus ([18](#_ENREF_18)). The BSR/BHPR guidelines advocate intravenous methylprednisolone 250-500mg to be given prior to the first two pulses of CYC. The BSR/BHPR and EULAR/DRA-EDTA guidelines recommend tapering prednisolone to 15mg or 7.5mg-10mg at 12 weeks, respectively.

Newer therapies continue to emerge. The ADVOCATE trial investigated avacopan - a novel orally-administered selective antagonist of complement fragment C5a receptor (C5aR) – against prednisolone for remission induction, each in combination with CYC or RTX, followed by azathioprine for maintenance. The avacopan combination was non-inferior to prednisolone combination at week 25 and superior in sustained remission at week 52. A remarkable reduction in glucocorticoid-related toxicity was observed in the avacopan arm ([19](#_ENREF_19)).

**Severe organ-threatening / life-threatening AAV**

Both BSR/BHPR and EULAR/ERA-EDTA recommended consideration of plasma exchange (PLEX) for patients with new or relapsing AAV and severe renal failure (creatinine > 500 µmol/L) or severe diffuse alveolar haemorrhage, in addition to pulsed CYC and glucocorticoid. In the MEPEX trial, PLEX improved rate of renal recovery at 3 months when compared with intravenous methylprednisolone, while patient survival and severe adverse event rates were similar at 12 months ([17](#_ENREF_17)). However PEXIVAS - a factorial trial design comparing PLEX vs no PLEX among patients with severe AAV receiving CYC or RTX - did not show adjuvant PLEX to reduce death or end-stage renal failure after up to 7 years of follow up ([20](#_ENREF_20)). Results did not support a treatment effect for the 191 participants with pulmonary haemorrhage. The design also allowed comparison of reduced vs standard dose glucocorticoid regimes; outcomes were non-inferior when using 50% reduced disease glucocorticoids.

**Localized AAV**

Mycophenolate mofetil (MMF) or methotrexate (MTX) in combination with glucocorticoids are recommended for remission induction in AAV patients without evidence of organ damage. In the MYCYC trial, MMF was non-inferior to CYC for remission induction in patients with AAV but resulted in higher relapse rate, especially in those with PR3-ANCA positivity ([21](#_ENREF_21)). MMF may therefore be suitable for patients at low risk of relapse, e.g., those with MPO-ANCA. Long-term data from the NORAM study showed that MTX was safe and as effective as CYC in remission rates, but the median time to relapse and cumulative relapse-free survival were shorter in MTX-treated patients ([22](#_ENREF_22)). Regarding long-term CYC toxicity, both BSR/BHPR and EULAR/ERA-EDTA have phased out CYC, instead recommending a combination of glucocorticoids with either MTX (up to 25-30mg once per week) or MMF (up to 3g/day) for localized AAV. MMF is preferred over MTX in moderate or severe renal impairment.

**Refractory disease**

Treatment for refractory disease remains challenging and should be managed at expert centres. EULAR/ERA-EDTA recommended a switch from CYC to RTX or vice versa. NHS clinical commissioning policy approves use of RTX if severe AAV disease has remained active or progressed despite 3-6 months of CYC. Adjunctive IVIG has been advocated by EULAR/ERA-EDTA and BSR/BHPR for patients who fail to achieve remission or have persistent low activity. BSR/BHPR also suggest leflunomide, alemtuzumab (anti-CD52) and gusperimus (a T-cell inhibitor) in patients with refractory AAV.

**Remission maintenance**

Once remission is achieved, low dose glucocorticoid combined with azathioprine, MTX, MMF, leflunomide or RTX are recommended for maintenance.

Rituximab was superior to azathioprine in maintaining remission (after CYC induction) for AAV in the MAINRITSAN trial, where more patients had sustained remission at month 28 with comparable safety ([23](#_ENREF_23)). The advantage of RTX over azathioprine in preventing relapse continued at 60 months’ follow-up([24](#_ENREF_24)). RITAZAREM trial demonstrated RTX to be superior to azathioprine in achieving sustained-remission among patients with baseline relapse disease and given RTX as induction therapy ([25](#_ENREF_25)). BSR released consensus guidelines on the use of RTX for maintenance in new and relapsing AAV following RTX or CYC induction. They advocate the fixed interval dosing, either 500mg or 1000mg administered every 6 months for a period of 2 years ([26](#_ENREF_26)).

Azathioprine, the standard-of-care therapy for remission maintenance, was superior to MMF in the IMPROVE study ([21](#_ENREF_21)). Although leflunomide was proved superior to MTX, it is preferred as second line due to its adverse effects profile ([27](#_ENREF_27)).

BSR/BHPR and EULAR/ERA-EDTA recommend at least 24 months of remission maintenance therapy. Some experts advocate 36 months in patient who are anti-PR3-ANCA positive. In patients who relapse after a prior course of rituximab maintenance, with persistent ANCA positivity, or where the effect of relapse would be organ- or life- threatening despite 2 years of rituximab maintenance therapy, an extended duration of rituximab up to 5 years could be considered ([26](#_ENREF_26)). If sustained-remission is achieved for at least one year on maintenance therapy, BSR/BHPR suggests tapering glucocorticoids, followed by withdrawing immunosuppressant 6 months later.

**Relapse of AAV**

Latest BSR/BHPR guidelines advocate the use of RTX or further course of CYC in major relapse. The EULAR/ERA-EDTA, concerned about cumulative CYC dose, more strongly recommends RTX over CYC. RAVE long-term follow-up data showed that those with severe relapsing disease treated with RTX had higher rate of maintaining remission and fewer severe relapses at 6 and 12 months ([14](#_ENREF_14)). Both BSH/BHPR and EULAR/ERA-EDTA recommend optimization or modification of remission maintenance agent and increase glucocorticoid dose for minor relapse, without specifying choice of immunosuppressant and duration of therapy.

**Long term follow-up and monitoring**

Long-term follow-up and monitoring for disease relapse and its complications is imperative since AAV is a chronic relapsing disease. The role of biomarkers (e.g. ANCA, PR3-ANCA, MPO-ANCA, CD19) in predicting disease relapse requires further research. Regular monitoring and assessment for infections, haemorrhagic cystitis, cancer (i.e., bladder or cervical), infertility, cardiovascular and thromboembolic risk, and osteoporosis is warranted.

**Giant Cell Arteritis**

GCA is a large vessel vasculitis, primarily affecting aorta and its extracranial branches, with a predilection for temporal artery ([1](#_ENREF_1)). GCA commonly occurs in patients older than 50 years with highest incidence among persons 70-79 years of age. The incidence of GCA in UK is approximately 2.2 /10 000 ([28](#_ENREF_28)).

Polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease characterized by pain, aching, and morning stiffness in the shoulder, pelvic girdle, and neck ([29](#_ENREF_29)). PMR manifestations are observed in about 40-50% of patients with temporal artery biopsy (TAB)-proven GCA([30](#_ENREF_30)). It was found that 11% of patients who developed GCA had a background history of isolated PMR ([31](#_ENREF_31)).

**Recognition and Diagnosis of GCA**

EULAR and BSR updated the recommendations on diagnosis and treatment of GCA in 2018 and 2020, respectively ([32](#_ENREF_32), [33](#_ENREF_33)).

GCA has been distinguished into three phenotypes, namely cranial GCA, large vessel GCA (LV-GCA) and isolated PMR. Patients aged over 50 years, presenting with abrupt-onset headache, scalp tenderness, visual loss, jaw claudication, limb claudication, polymyalgia or constitutional symptoms should raise suspicion of GCA. Several mimics of GCA and PMR **(Table 6)** should be excluded via thorough history, physical examination, and investigations **(Table 3, 4 and 5)** ([2](#_ENREF_2), [34](#_ENREF_34), [35](#_ENREF_35)).

High erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are hallmark for the diagnosis of GCA. A small proportion of patients with GCA (<4%) have normal ESR and CRP ([36](#_ENREF_36), [37](#_ENREF_37)). Normal acute-phase reactants make a diagnosis of GCA very unlikely but do not rule it out.

**Confirmatory Diagnostic Test for GCA**

Latest guidelines advocate utilizing either TAB or ultrasound of the temporal or / and axillary arteries to confirm diagnosis of GCA ([32](#_ENREF_32), [33](#_ENREF_33), [38](#_ENREF_38)).

TAB has been regarded as the gold standard to diagnose GCA for decades. In one meta-analysis of studies investigating TAB positivity among patients satisfying the 1990 American College of Rheumatology classification criteria of GCA, the estimated sensitivity of temporal artery biopsy for GCA diagnosis was 77%, with high between-study heterogeneity ([39](#_ENREF_39), [40](#_ENREF_40)).

**Vascular Imaging as an Emerging Diagnostic Tool for GCA**

High resolution colour Doppler sonography (CDS) of the temporal or axillary arteries, showing concentric hypoechoic mural thickening ‘halo sign’ , and ‘compression sign’ where the hypoechoic wall swelling is non-compressible upon application of pressure with ultrasound probe, are the most important sonographic abnormalities for GCA ([41](#_ENREF_41)). These findings are interpreted as inflammatory vessel wall oedema ([42](#_ENREF_42)). Using CDS, LV-GCA was observed in 53% of one GCA cohort, where circumferential, homogenous, hypoechogenic mural thickening was most frequently observed in the axillary arteries ([43](#_ENREF_43)). In the TABUL study, CDS of temporal and axillary arteries had a higher sensitivity (54% vs. 39%) than TAB but with a lower specificity (81% vs. 100%) in diagnosing GCA ([44](#_ENREF_44)). In short, CDS of temporal or axillary arteries, best done within 1 week of glucocorticoid initiation, is valuable to confirm GCA in high probability cases.

High resolution magnetic resonance imaging (MRI) of cranial arteries can be considered as an alternative to CDS for GCA diagnosis ([32](#_ENREF_32), [33](#_ENREF_33), [38](#_ENREF_38)). MRI can detect vessel wall oedema and contrast enhancement, signifying vessel inflammation. Using TAB as reference standard, MRI of the cranial arteries had a sensitivity of 94% and specificity of 78% in diagnosing GCA. The corresponding negative predictive value of MRI cranial arteries was 98%, suggesting it potentially useful to rule out GCA if the result is negative([45](#_ENREF_45)).

The use of imaging tests to evaluate involvement of the aorta and its proximal branches in GCA is limited due to lack of direct evidence. Most of the published evidence is extrapolated from other diseases, such as Takayasu arteritis ([38](#_ENREF_38)).

Computed tomography angiogram of aorta and its major branches can reveal vessel wall thickening with contrast enhancement, and structural lesions (stenosis, dilatation or aneurysms) ([46](#_ENREF_46)). Contrast-enhanced magnetic resonance angiography was found to reliably identify aortitis in LVV but changes were very sensitive to glucocorticoid ([47](#_ENREF_47)). Positron emission tomography-computed tomography (PET-CT) can demonstrate inflammatory cell infiltration of the aorta and its branches ([48](#_ENREF_48)). It has the advantage of being able to screen for malignancy or occult infections ([38](#_ENREF_38)).

Conventional angiography is not recommended for the diagnosis of GCA because there are safer modalities available. It is mainly used for vascular intervention such as angioplasty or stenting ([38](#_ENREF_38)).

**Management of GCA**

Glucocorticoids remain the mainstay of treatment for GCA. Glucocorticoids at 1mg/kg/day (oral prednisolone 40-60mg daily) should be initiated immediately while referring patients for urgent specialist evaluation ([32](#_ENREF_32), [33](#_ENREF_33)). Patients with ischemic presentation (eg. vision loss) may be initiated with intravenous methylprednisolone 250mg - 1g daily for up to 3 consecutive days after ophthalmologist’s evaluation ([32](#_ENREF_32), [34](#_ENREF_34)). High dose glucocorticoid is continued until resolution of symptoms and normalization of inflammatory markers, which may take 2 – 4 weeks. Despite the lack of data regarding the optimal duration of glucocorticoid therapy, BSR recommended to tapered over 12 to 18 months, whereas EULAR advocated 24 months or more ([32](#_ENREF_32), [33](#_ENREF_33)).

A substantial number of patients with GCA have refractory or relapsing disease when glucocorticoid is tapered. They are conventionally treated with glucocorticoid dose increment, which subject them to excessive cumulative adverse effects of glucocorticoids. Methotrexate might be combined with glucocorticoid taper for those at high risk of glucocorticoid toxicity or who relapse, however the evidence remains equivocal ([49](#_ENREF_49)).

Tocilizumab, an IL-6 inhibitor, is approved for GCA by European regulatory authorities in 2017. In the GiACTA trial, one-year of tocilizumab weekly plus 26-week prednisolone taper (56%) had higher rate of sustained remission at 1 year, compared to placebo and 26-week prednisolone taper (14%) or 52-week taper (18%) (P<0.001) ([50](#_ENREF_50)). Results from 2-year long-term extension of GiACTA trial showed 47% of patients in tocilizumab weekly plus 26-week prednisolone taper maintained clinical remission, with similar safety profile compared to placebo and prednisolone taper. This arm of patients had the lowest cumulative glucocorticoid dose over the 3-year study ([51](#_ENREF_51)). Subcutaneous tocilizumab 162mg weekly has been approved by NHS England for patient with relapsing or refractory GCA for one year.

Contrary to previous recommendations, anticoagulant, antiplatelet, or cholesterol-lowering agents are not routinely recommended for treatment of GCA unless indicated ([32](#_ENREF_32), [33](#_ENREF_33)).

**Summary**

Significant advancement has been made in the management approach to common vasculitides, especially toward AAV and GCA. Diagnosis of PSV depends largely on excluding mimics and secondary vasculitis, recognizing a combination of clinical, laboratory, histopathological and radiographic features. A validated diagnostic criteria and improvement on classification criteria for PSV is much anticipated.

Intravenous CYC is favoured over oral CYC due to lower cumulative toxicity. Rituximab has provided a treatment revolution for AAV, both for remission induction and maintenance, among patients with organ- / life-threatening or relapsing disease. There is still a lack of robust data to support the use of PLEX in imminent life-threatening AAV. More research is needed to guide treatment for refractory or relapsing AAV, and to identify biomarkers indicating a predisposition to poorly-controlled disease.

CDS of temporal or axillary arteries has equal diagnostic value as TAB in diagnosis GCA.Tocilizumab has been approved for relapsing or refractory GCA, lowering risk of glucocorticoid toxicity in susceptible patients. Further cost-effectiveness analyses are needed to support the extension commissioning of tocilizumab in GCA.

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**Table 1. Vasculitis mimics**

|  |  |
| --- | --- |
| **Vasculitis mimics**  | **Example**  |
| Infections  | -Infective endocarditis-Bacterial infections: meningoccemia, gonococcemia-Spirochetes infections-Fungal infections-Mycobacterial infection-Viral infections |
| Drugs / therapy | -Ergotamine-Cocaine-Phenylpropanolamine -Warfarin-Radiation therapy |
| Malignancy  | -Leukaemia cutis-Plasma cell dyscrasia-Metastatic carcinoma-Paraneoplastic syndrome-Lymphoma, especially involving nasal or paranasal cavity |
| Thromboembolic disorders | -Atrial myxoma-Cholesterol emboli from an atheroma-Antiphospholipid syndrome-Thrombotic thrombocytopenic purpura-Sickle cell disease-Procoagulant states-Calciphylaxis |
| Other vasculopathy | -fibromuscular dysplasia-amyloid angiopathy -neurofibromatosis type I-coarctation of aorta-chronic ergotism-scurvy -sweet’s syndrome-Köhlmeier-Degos disease |

**Table 2. Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the nomenclature of vasculitides**

**Large vessel vasculitis (LVV)**

* Takayasu arteritis (TAK)
* Giant cell arteritis (GCA)

**Medium vessel vasculitis (MVV)**

* Polyarteritis nodosa (PAN)
* Kawasaki disease (KD)

**Small vessel vasculitis (SVV)**

* Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)
	+ Microscopic polyangiitis (MPA)
	+ Granulomatosis with polyangiitis (Wegener’s) (GPA)
	+ Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
* Immune complex small vessel vasculitis
	+ Anti-glomerular basement membrane (anti-GBM) disease
	+ Cryoglobulinemia vasculitis (CV)
	+ IgA vasculitis (Henoch-Schönlein) (IgAV)
	+ Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)

**Variable vessel vasculitis (VVV)**

* Behçet’s disease (BD)
* Cogan’s syndrome (CS)

**Single-organ vasculitis (SOV)**

* Cutaneous leukocytoclastic angiitis
* Cutaneous arteritis
* Primary central nervous system vasculitis
* Isolated aortitis
* Others

**Vasculitis associated with systemic disease**

* Lupus vasculitis
* Rheumatoid vasculitis
* Sarcoid vasculitis
* Others

**Vasculitis associated with probable aetiology**

* Hepatitis C virus-associated cryoglobulinemic vasculitis
* Hepatitis B virus-associated vasculitis
* Syphilis-associated aortitis
* Drug-associated immune complex vasculitis
* Drug-associated ANCA-associated vasculitis
* Cancer-associated vasculitis
* Others

**Table 3. Summary of clinical history enquired when approaching patient with probably having vasculitides**

|  |  |
| --- | --- |
| **History**  | **Descriptions**  |
| General | * Onset of symptoms, progression
* Preceding infection, illness or trauma
* Previous medical illness
* Previous drug usage
* Family history of autoimmune rheumatic disease or chronic hepatitis infection
* Travel history
* Occupational history
* Recreational drug consumption or high risk behaviour
 |
| Constitutional symptoms  | * Fever, sweats
* Weight loss, anorexia
* Malaise, fatigue
 |
| Skin, extremities | * New, persistent skin rashes
* Raynaud’s phenomenon
* Digital ulcer
* Cutaneous ulcer
 |
| Musculoskeletal | * Myalgia, muscle weakness, stiffness
* Arthralgia
 |
| ENT  | * Persistent, recurrent, blood-stained nasal discharge or epistaxis
* Nasal crusting
* Sinusitis
* Nasal bridge collapse
* Ear discharge
* Hearing impairment
 |
| Eye  | * Painful, red eye
* Sight loss, changes to colour vision
* Diplopia
 |
| Nervous system  | * Wrist drop, foot drop
* Stroke
* Seizure
* Headache
 |
| Extracranial  | * Scalp tenderness / hyperaesthesia
* Jaw claudication, tongue claudication
 |
| Pulmonary  | * Asthma
* Breathless
* Haemoptysis
 |
| Cardiovascular  | * Limb claudication
* Chest pain
 |
| Gastrointestinal  | * Abdominal pain
* Diarrhoea
* Haematemesis, malaena, haematochezia
 |
| Renal  | * Frothy urine, haematuria
* Hypertension
 |
| Genitourinary  | * Scrotal pain
 |

**Table 4. Summary of possible clinical findings in patients with PSV**

|  |
| --- |
| * General: cachexia, fever, pallor, facial puffiness, pedal oedema
* Skin: splinter haemorrhage, nodules, papules, erythema nodosum, cutaneous ulcers / necrosis, digital ulcer or gangrene, purpuric, petechial or urticarial rash, maculopapular rash, scalp necrosis
* Blood pressure: different blood pressure between two arms
* Peripheral pulses: absent pulses, arterial bruit or thrill
* Lung: crepitation, rhonchi or sign of consolidation.
* Abdominal: tenderness, absent of bowel sound, organomegaly or audible bruit.
* Lymphadenopathy
* Musculoskeletal: synovitis, muscle weakness or muscle wasting
* Ear and nose: discharge, crusting, ulcer, nasal bridge collapse or hearing loss
* Eye: opthalmoplegia, proptosis, visual loss, optic neuritis, scleritis, episcleritis, uveitis
* Extracranial: temporal artery tenderness / thickened / nodularity / reduced or absent pulsation, carotid artery tenderness, scalp necrosis, tongue necrosis
* Neurological: peripheral neuropathy, neurological deficit or cranial nerve palsy
* Fundoscope: microvascular infarct or hypertensive retinal changes
 |

**Table 5. List of laboratory investigations useful in the evaluation of suspected vasculitides**

|  |  |
| --- | --- |
| **Preliminary investigations** | **More specific investigations**  |
| -Full blood count-Urinalysis, urine protein: creatinine ratio-Renal profile-Liver function test-Creatinine kinase-Fasting lipid profile, fasting blood sugar-C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)-Procalcitonin level-Blood culture-Hepatitis B and hepatitis C screening-Human immunodeficiency virus test-Other serology such as Parvovirus B19, cytomegalovirus or specific fungal serology test-Antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), extractable nuclear antigen (ENA)-Antiphospholipid antibodies-Rheumatoid factor-Complements level-Urine toxicology screening-Chest radiograph or computed tomography (CT) of thorax-Sinus radiograph or CT scan-Electrocardiogram, echocardiogram-Serum protein electrophoresis, serum free light chains, urine Bence-Jones protein | -Perinuclear-ANCA (p-ANCA) and cytoplasmic-ANCA (c-ANCA)-anti-proteinase 3 (anti-PR3) and anti-myeloperoxidase (anti-MPO) test-Anti-glomerular basement membrane antibody-Serum cryoglobulins-Immunoglobulin E level -Appropriate tissue biopsy -Bronchoscopy, bronchoalveolar lavage-Angiographic examinations -MRA / MRI-PET scan-Nerve conduction studies or electromyography |

**Table 6. List of mimics of GCA and PMR.**

|  |  |
| --- | --- |
| **Mimics of GCA** | **Mimics of PMR** |
| - Sinusitis - Dental or temporo-mandibular local disease- Non-arteritic anterior ischemic optic neuropathy- Subacute thyroiditis - Chronic infections- Trigeminal neuralgia- Malignancy - artherosclerotic cardiovascular disease | - Elderly-onset rheumatoid arthritis- Osteoarthritis- Fibromyalgia - Shoulder bursitis / tendinitis- Cervical spondylosis - Ankylosing spondylitis - Statin-induced myositis- Systemic lupus erythematosus- Hypothyroidism - Chronic infections - Polymyositis - Malignancy (e.g multiple myeloma)- Amyloidosis |