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REVIEW

Wegener's Granulomatosis: A comprehensive review

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ABSRACT

Wegener's Granulomatosis (WG) is a systemic multi-organ disease that is specifically characterised by inflammation of small and medium – sized vessels that could lead to tissue damage. Most commonly affected systems are the upper respiratory tract, the pulmonary, renal and ocular systems. Even though no diagnostic criteria have been established, the Chapel Hill Consensus definitions and the American College of Rheumatology classification criteria are widely used in clinical practice to identify WG. Definite diagnosis is confirmed by biopsy of the affected organ. This article reviews the epidemiology, pathophysiology, clinical manifestations, laboratory markers, diagnosis and disease assessment and, finally, the conventional and therapeutic options in WG.

List of Abbreviations:
WG: Wegener's Granulomatosis,
ANCA: Anti-Neutrophil Cytoplasmic Antibody,
MPA: microscopic polyangiitis,
CSS: Churg-Strauss Syndrome,
AASV: ANCA Associated Systemic Vasculitis,
PR3: proteinase 3,
MPO: myeloperoxidase,
BVAS: Birmingham Vasculitis Activity Score

KEY WORDS: *Wegener's Granulomatosis, vasculitis, pulmonary, renal, Anti-Neutrophil Cytoplasmic Antibody, Birmingham Vasculitis Activity Score, cyclophosphamide*

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INTRODUCTION

Systemic vasculitis comprises a group of multi-organ chronic diseases defined histologically as inflammation of the blood vessels that eventually results in organ damage [1]. Primary vasculitis is not related to any known underlying disorder while secondary vasculitis occurs as a manifestation of a co-existing disorder. The spectrum of organ involvement along with severity is quite diverse, complicating both the diagnosis and especially the treatment. The first case of systemic vasculitis was reported in 1866 by Kussmaul and Maier who described a disorder of nodular inflammation along the muscular arteries that they called "periarteritis nodosa" (later renamed polyarteritis nodosa) [2]. The first cases of Wegener's Granulomatosis were described in the 1930s.

DEFINITION AND CLASSIFICATION CRITERIA

Several classification schemes have been proposed for primary vasculitis. These are based on either the size of the vessels predominantly involved or the classification criteria by the American College of Rheumatology (ACR) or the Chapel Hill Consensus Conference (CHCC) on nomenclature.

Three categories are recognised for the classification of vasculitis according to size of vessel involved; large, medium and small vessel vasculitis [2,3]. In 1990, the ACR developed classification criteria for seven forms of vasculitis (polyarteritis nodosa [PAN], Churg-Strauss syndrome [CSS], Wegener's Granulomatosis [WG], hypersensitivity vasculitis, Henöch Schölein Purpura [HSP], giant cell [temporal] arteritis, and Takayasu's arteritis) [4] aiming to identify patients with a particular type

of vasculitis (sensitivity) and to exclude those who do not have vasculitis but suffer from other disorders (specificity). These criteria would establish uniform standards for the inclusion of patients in clinical, research or epidemiological trials. The determination of the classification criteria was based on the analysis of clinical data collected from 807 patients diagnosed with one of the seven forms of vasculitis over a five-year time period. Different combinations of clinical features of each form of vasculitis were evaluated before selecting the most discriminating variables to be considered as classification criteria [5]. It was clearly suggested that the ACR classification criteria were not diagnostic criteria, which was later confirmed at an audit using the ACR classification criteria as diagnostic criteria [6]. It was reported that applying ACR criteria for diagnosis of vasculitis led to identification of patients with vasculitis in 75% of the examined cases, but also another 21% of the patients met the ACR criteria without having vasculitis. Therefore, ACR criteria should not be used for the diagnosis of vasculitis.

In 1994, the CHCC on the Nomenclature of Systemic Vasculitides proposed names and definitions for the most common forms of vasculitis based on the consensus of a committee of clinicians [7]. Except for the seven vasculitic types included in the ACR criteria, three more types of vasculitis were added: microscopic polyangiitis (MPA), Kawasaki disease [KD] and essential cryoglobulinaemic vasculitis.

Even though no diagnostic criteria have been developed for the diagnosis of vasculitides, the definitions of the CHCC along with the classification criteria of the ACR are widely used in clinical and research studies. It should be noted that CHCC definitions are based exclusively on pathological biopsy features while the ACR criteria take into account both clinical presentation and biopsy findings.

More specifically, according to the Chapel Hill Consensus Conference on nomenclature (CHCC) definitions, WG is defined as vasculitis characterised by granulomatous inflammation of the respiratory tract and necrotising vasculitis affecting small to medium-sized vessels (e.g. capillaries, venules, arterioles and arteries) while a common finding is necrotising glomerulonephritis [7]. Classification criteria were developed by the American College of Rheumatology (ACR) by comparing 85 cases of WG with 722 control cases that were diagnosed with other types of vasculitis [8]. Criteria for the classification of WG are: 1) nasal or oral inflammation, defined as the development of painful or painless ulcers or purulent or bloody nasal discharge, 2) abnormal chest radiograph defined as a chest radiograph showing the presence of nodules, fixed infiltrates or cavities, 3) urinary sediment defined as microhaematuria (more than five red blood cells per high power field) or red cell casts in urine sediment, and 4) granulomatous inflammation on biopsy, defined as histological changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole) (Table 1). For the purposes of classification a patient shall be said to have WG if at least two of these four criteria are present. The presence of any two or more criteria is associated with a sensitivity of 88.2% and specificity of 92%.

EPIDEMIOLOGY

The incidence and prevalence of systemic vasculitis are not well documented worldwide. Several reports suggest that in Europe, the overall annual incidence of primary systemic vasculitis including WG, microscopic polyangiitis (MPA) and Churg-Strauss Syndrome (CSS) is approximately 10-20/million and also that the incidence increases with age showing a peak at the age group 65–74 [9-11]. More specifically, in the UK, the incidence of WG is 10.2/million, MPA 5.8/million and CSS 4.2/million [12]. A joint study by the Departments of Rheumatology in Norwich (Great Britain) and Lugo (Spain) showed that even though the incidence of primary systemic vasculitis is the same in the two regions, there are differences between certain types of vasculitis [13]. WG was more common in Norwich with an incidence 10.6/million compared to 4.9/million in Lugo while the incidence of MPA was greater in Lugo (11.6/million) than in Norwich (8.4/million). This

TABLE 1. Definition and classification criteria of Wegener's Granulomatosis adopted by the Chapel Hill Consensus Conference and the American College of Rheumatology respectively.

CHCC definition of Wegener's granulomatosis
Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g. capillaries, venules or arterioles). Necrotizing glomerulonephritis is common.
ACR Criteria for the classification of Wegener's granulomatosis
1) nasal or oral inflammation, defined as the development of painful or painless ulcers or purulent or bloody nasal discharge;
2) abnormal chest radiograph defined as a chest radiograph showing the presence of nodules, fixed infiltrates or cavities;
3) urinary sediment defined as microhaematuria (more than five red blood cells per high power field) or red cell casts in urine sediment, and
4) granulomatous inflammation on biopsy, defined as histological changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole).

geographical pattern of incidence of vasculitis may reflect the impact of climatological factors.

Additionally, other environmental or infectious parameters have been associated with systemic vasculitis. Exposure to high levels of silica or inhalation of fumes, particulates and pesticides have been identified as risk factors for the development of anti-neutrophil cytoplasmic antibodies (ANCA) - associated systemic vasculitis (AASV) and WG [14,15]. Furthermore, nasal carriage of Staphylococcus aureus has been associated with a high relapse rate in WG patients suggesting a potential role in the pathogenesis of WG [16,17]. Finally, clinical observations and individual case reports note the onset of vasculitis following vaccination for influenza, smallpox, diphtheria, tetanus or hepatitis B [18,19].

PATHOPHYSIOLOGY

The aetiology and pathophysiology of vasculitis is not well understood. However, both immune complexes of immunoglobulins and complement as well as autoantibodies have been reported as mediators of the pathogenesis of vasculitis. In the early 1980s, the identification of autoantibodies directed against enzymes of the neutrophil cytoplasm provided a potential explanation of the mechanism that underlies the autoimmune response in vasculitis [20,21]. They were named anti-neutrophil cytoplasmic antibodies (ANCA) and up to date several types of ANCA have been described on the basis of their target. Two types of ANCA are the most important clinically and both have been correlated with systemic vasculitis. ANCA against proteinase 3 (PR3), a 29 kD serine protease found in neutrophils and monocytes, produce a diffuse granular cytoplasmic immunofluorescent staining (C-ANCA) and they are associated predominantly with Wegener's Granulomatosis. ANCA that target myeloperoxidase (MPO), a 140 kD enzyme of neutrophils, generate a perinuclear immunofluorescent staining (P-ANCA) and they are linked mainly to MPA and renal limited vasculitis [22,23].

The mechanisms that lead to the breakdown of tolerance and the formation of ANCA remain uncertain. It is assumed that a genetic predisposition is essential but environmental factors are also important for disease onset. Clinical evidence suggests an association between bacterial (Staph. aureus) infection and vasculitis [16,17]. Potential pathways in the pathogenesis of ANCA that also apply to the pathogenesis of autoimmunity involve two mechanisms, molecular mimicry or infection-induced activation. Antigenic mimicry of host antigens (autoantigens) by microbial molecules may lead to activation of naove T-cells resulting in autoreactivity. In addition, microbial infection can lead to tissue damage and release of host antigens and further activation of innate immunity and antigen-presenting-cells (APC). Up-regulation of host-antigens and major histocompatibility complex (MHC) by APC along with secretion of cytokines promote T-cells activation and recruitment of autoreactive lymphocytes. These mechanisms could trigger autoimmune reactions only in cases that innate regulatory mechanisms fail to recognise self antigens [24,25].

In vitro studies have revealed that ANCA can activate healthy neutrophils to produce oxygen radicals and release cytotoxic enzymes [26]. Pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNFα) interleukin (IL)-1 beta and IL-8 have been reported to induce degranulation of neutrophils [27-29]. Degranulation of neutrophils leads to the expression of the target antigens (PR3 and MPO) on the cell surface membrane which subsequently interacts with circulating ANCA [30,31]. Binding of ANCA to their target antigens results in activation of neutrophils, apoptosis and the release of lytic enzymes. This interaction between PR3 and ANCA also seems to prevent the binding of PR3 to its natural inhibitor α1-antitrypsin [32]. Further on in the molecular pathway both F(ab)2 and Fc fragment are involved in this interaction, each activating a different pattern of gene expression [33,34].

In addition, ANCA can activate monocytes in vitro in a similar manner to neutrophils, via the production of oxygen radicals [35]. Furthermore, interaction of ANCA with its target antigen on endothelial cells leads to the expression of adhesion molecules and further adhesion of neutrophils and monocytes to endothelial cells which consecutively induces vascular endothelium injury [36-38].

In vivo studies will be required to definitely identify the immunological mechanisms underlying vasculitis but so far no experimental animal model of spontaneous vasculitis has been developed. MPO-knockout mice immunised with murine MPO develop antibodies against MPO, and transfer of anti-MPO splenocytes to immunodeficient Rag2-/- mice results in small vessel vasculitis and necrotising crescentic glomerulonephritis suggesting a causative role of MPO-ANCA in the pathogenesis of vasculitis [39].

In conclusion, ANCA seems to play a pivotal role in the pathogenesis of systemic vasculitis but the mechanisms that trigger disease onset have yet to be determined.

CLINICAL MANIFESTATIONS

Symptoms of WG can be non-specific leading to a delay in the definite diagnosis of the disease. Organ involvement usually includes the upper respiratory tract, ears, eyes, lungs and kidneys. Systemic symptoms of fatigue, weakness, arthritis and skin manifestations are common while nervous system, cardiovascular or gastrointestinal involvement is less frequent [1,40,41].

The majority of patients with WG have upper respiratory tract symptoms that include nasal blockade with or without bloody nasal discharge, rhinitis, epistaxis, tenderness or pain over the paranasal sinuses. Inflammation of the nasal septum with septic sinusitis may lead to perforation and collapse of the nasal bridge resulting in saddle-nose deformity. Histologically, WG involves necrosis of medium size vessels with infiltration

by neutrophils and multinucleated giant cells specifically in the upper airway. Typically ear involvement includes either conductive or sensorineural hearing loss if the middle or inner ear is affected respectively. Subglottic stenosis presents with hoarseness, difficulty in breathing, cough or inspiratory stridor, and can be a life-threatening complication.

The pulmonary system is the second most commonly affected system following ENT (ear, nose, throat) in WG. Symptoms like cough, dyspnoea or haemoptysis are not diagnostic, but lung imaging with radiology or computed tomography usually reveals nodules, cavities, infiltrates, and in more severe cases alveolar haemorrhage. Respiratory failure requiring artificial ventilation can be fatal. On lung biopsy, a classic necrotizing granulomatous vasculitis is usually seen that is characterised by pulmonary angiitis with inflammation and necrosis of blood vessels with associated granuloma formation. The granuloma consists of infiltrates of lymphocytes, plasma cells, epithelioid cells, or histiocytes with or without the presence of multinucleated giant cells and sometimes tissue necrosis. A small vessel capillaritis and intralveolar haemorrhage may also be found.

Renal involvement presents with active urine sediment (haematuria) and a rise in serum creatinine. Kidney biopsy shows ischemic injury predominantly in the glomeruli and crescentic glomerulonephritis. Because of the absence of deposits of immunoglobulin or complement, renal vasculitis is called "pauci-immune" glomerulonephritis.

Ocular features of WG commonly include conjunctivitis, episcleritis or orbital mass and proptosis due to retrobulbar inflammatory deposits. Scleritis, keratitis, uveitis may also be manifestations attributable to WG.

Patients with WG quite frequently suffer from non-specific systemic symptoms like fatigue, musculoskeletal pains, arthralgia or fever. Cutaneous manifestations include palpable purpura and occasionally ulcers or nodules. Sensory peripheral neuropathy and motor mononeuritis are features of nervous involvement. Finally, WG may also affect the cardiovascular system causing aortic valve regurgitation.

LABORATORY MARKERS

ANCA are the only characteristic biomarker used in clinical practice for both confirming the diagnosis and monitoring of systemic vasculitis. ANCA are not diagnostic for systemic vasculitis, nor does their absence exclude the possibility of vasculitis. As mentioned previously, two types of ANCA (C-ANCA and P-ANCA) have been associated with primary systemic vasculitis. This led to the definition of ANCA-Associated Systemic Vasculitis (AASV) which includes WG, MPA and CSS. The pattern of ANCA is determined by indirect immunofluorescent staining producing either a cytoplasmic staining C-ANCA or a perinuclear staining P-ANCA. Enzyme-linked immunosorbent assays (ELISA) are used for detecting PR3-ANCA and MPO-ANCA and quantifying their titers. C-ANCA has been associated with WG and P-ANCA with MPA. However, 10% of the WG patients may present positivity for P-ANCA. Even though the presence of ANCA can be useful to confirm diagnosis, their titer does not predict or correlate with disease activity. However, persistent positive ANCA after therapy for active disease or conversion to positive of previously tested negative ANCA is associated with an increased risk of disease relapse [42,43]. It has also been reported that monitoring of ANCA can be helpful in predicting relapse, suggesting pre-emptive modification of immune suppression in cases with four-fold increase of ANCA to prevent such relapse [44].

Acute–phase parameters or inflammatory markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually elevated in cases with active disease but they are non-specific biomarkers and are certainly not diagnostic. They may be taken into consideration in assessing disease remission or monitoring disease flares but their value is quite questionable.

DIAGNOSIS – DIFFERENTIAL DIAGNOSIS

Diagnosis of the systemic vasculitides can be difficult since they are multi-organ diseases and also due to the fact that there is no consensus on diagnostic criteria. Because of the presentation of non-specific general symptoms at disease onset, vasculitis may not be diagnosed immediately, leading to subclinical progression of organ injury and damage.

A definite diagnosis of WG is usually based on histological evidence of necrotizing granulomatous inflammation of the organs involved along with clinical features of upper and lower respiratory tract disease and frequently renal manifestations of glomerulonephritis.

Differential diagnosis of WG can be challenging. Because of its multi-organ character, it has to be differentiated from other diseases with multi-organ involvement and inflammation. Firstly, it has to be discriminated from other forms of vasculitis like MPA, CSS, anti-glomerular basement membrane disease, and drug-induced AASV. Then, other autoimmune disorders like systemic lupus erythematosus (SLE) and secondary forms of vasculitis like rheumatoid vasculitis have to be excluded. Further, infections that can cause granulomata such as mycobacterium tuberculosis, mycobacterium avium or fungi have to be taken into consideration at the time of diagnosis. Finally, lymphomas and lung tumours are also in the differential diagnosis.

ASSESSMENT OF DISEASE ACTIVITY

As already mentioned, systemic vasculitis is a multi-organ disorder that presents with differing severity and organ involvement. Serological and immunological parameters do not usually represent disease activity or indicate whether a therapeutic intervention is required. Moreover, vasculitis is a chronic disease characterised by periods of active disease,

remission or relapse that require different treatments. In other autoimmune diseases clinical indices are routinely used to assess disease activity, more specifically the Disease Activity Score is widely used in rheumatoid arthritis [45] and the British Isles Lupus Assessment (BILAG) is used in SLE [46]. Likewise, in systemic vasculitis, the Birmingham Vasculitis Activity Score (BVAS) was developed in the early 90s to assess vasculitic manifestations [47]. The main objective of these scores is to transform qualitative data collected from clinical evaluation into quantitative measurements. The score is representative of disease activity and can be used to indicate or monitor the effectiveness of therapeutic intervention, to compare between different time points in disease progression, as an unambiguous means of communication between physicians, and as a widely accepted clinical measure in clinical trials.

BVAS is an assessment tool that aims to standardise current disease activity and persisting clinical features that contribute to ongoing disease activity. Manifestations attributed to vasculitis are reported after excluding other possible causes. Sixty-six clinical features grouped into nine organ systems (general, cutaneous, mucous membranes/eyes, ENT, pulmonary, cardiovascular, abdominal, renal and nervous system) are included (Table 2). The presence of each one of the clinical features has a numerical value and each organ has a maximum score. A glossary of terms along with their values has been developed to accompany the BVAS form (Table 3). The European Vasculitis Study Group (EUVAS) has amended the BVAS so that it provides two scores; the BVAS 1 score reflects present or worse features and the BVAS 2 score shows disease activity due to persistent manifestations of vasculitis within the last three months [48]. The main objective of BVAS 2 is to report grumbling and ongoing disease activity. Patients should be evaluated monthly when treated for newly diagnosed disease and three-monthly when disease is in remission. In clinical practice any increase of BVAS scores should be indicative of disease activity and treatment should be modified accordingly.

Given that systemic vasculitis can lead to permanent damage of the tissue and organs involved, another scoring system, the Vasculitis Damage Index (VDI), has been developed to document features attributable to systemic damage and not to current disease activity [49]. Damage is defined as any non-healing scar that developed as a result of active vasculitis and which is unlikely to respond to further immune suppressive therapy. VDI is considered an assessment tool for measuring damage due to either vasculitis activity or treatment and includes 64 features grouped into 11 organ systems (Table 4). VDI differs from BVAS because it reports any manifestation that has remained for more than three months. Each feature of VDI has the same numeric value and the VDI score is a cumulative assessment of organ dysfunction. The main utility of VDI is a predictor of mortality and since the items included are due to irreversible damage, the score would remain the same or increase but definitely not improve [50]. Any naove patient would have zero VDI score and, thereafter, should be evaluated every six months or more to monitor permanent organ damage.

Both BVAS and VDI are used in clinical trials and every day practice to record disease activity and chronic systemic damage in order to evaluate the progress of disease, efficacy of drug therapy and predict long-term survival. It should be mentioned that although both BVAS and VDI can be applied to all forms of systemic vasculitis, recently the International Network for Study of Systemic Vasculitis (INSSYS) has reviewed BVAS and developed a version to be specifically used in WG [51].

THERAPY OF WEGENER'S GRANULOMATOSIS

Systemic vasculitides are usually characterised by a relapsing-remitting course of disease progression. Even though the general principles of treatment apply to all types of vasculitis, the therapeutic options for WG will be thoroughly described. At presentation, induction therapy is administered to induce remission with potent regimens including cyclophosphamide (CYC) or methotrexate (MTX) complemented with corticosteroids. Maintaining remission can be challenging but crucial to avoid relapse and after the completion of induction therapy, alternative immune suppressive agents, such as azathioprine (AZA) or mycophenolate mofetil (MMF), are administered to maintain remission. In cases of relapse or grumbling disease, therapeutic intervention is required either with conventional or novel treatments.

Corticosteroids were the first immune modulator to be used in the treatment of vasculitis and they still remain a major component of most immune suppressive regimens used to treat WG today [52]. While they rapidly control disease activity, they do not induce remission when administered as monotherapy and, therefore, they are administered in combination with other immune suppressive drugs. Steroids such as prednisolone are given at a dose of around 1 mg/kg in mostly newly diagnosed cases. This dose is slowly tapered to avoid the severe adverse events associated with their continuous administration. Intravenous methylprednisolone may be beneficial, especially, in active vasculitic glomerulonephritis [53].

First line therapy for induction of remission in active WG is the use of CYC. Daily oral administration of 2 mg/kg/day CYC with prednisolone has proven efficacy to achieve complete remission in 75% of patients and significant improvement in 91% [40]. CYC can cause significant cytotoxic events both in the short-term, including the suppression of bone marrow, neutropenia and infection and in the long-term such as infertility, bladder malignancy and myelodysplastic disorders [54]. It has been suggested that intermittent intravenous bolus treatment with CYC may eliminate these adverse reactions especially if adjusted for age and renal impairment [55,56].

TABLE 2. Birmingham Vasculitis Activity Score (BVAS)

VASCULITIS ACTIVITY SCORE

oTick box **only** if abnormality is **newly present** since last assessment or **worse** in the last **few weeks** (use the Vasculitis Damage Index, VDI to score items of damage)
□Tick box **only** if abnormality is due to **active** (but not new or worse) vasculitis
◊ Tick box if more information (specialist opinion/tests) is requested
@ oral/axillary temperatures; rectal temperatures are 0.5°C higher

DEMOGRAPHY
Trial Number
Visit Date / /
Investigator

	PERSISTENT	NEW/WORSE
1. GENERAL	□ (none)	
malaise	□	○
myalgia	□	○
arthralgia/arthritis	□	○
headache	□	○
fever (< 38.5°C) @	□	○
fever (≥ 38.5°C) @	□	○
wt loss (≥ 2kg)	□	○
2. CUTANEOUS	□ (none)	
Infarct	□	○
purpura	□	○
other skin vasculitis	□	○
ulcer	□	○
gangrene	□	○
multiple digit gangrene	□	○
3. MUCOUS MEMBRANES/EYES	□ (none)	
mouth ulcers	□	○
genital ulcers	□	○
significant proptosis	□	○
red eye- conjunctivitis	□	○
red eye- epi/scleritis	□	○
blurred vision	□	○
sudden visual loss	□	○
ophthalmic opinion	◊	
no active vasculitis	○	
uveitis	○	
retinal exudates	○	
retinal haemorrhage	○	
4. ENT	□ (none)	
Nasal obstruction	□	○
Bloody nasal discharge	□	○
Nasal crusting	□	○
Sinus involvement	□	○
Hearing loss	□	○
Hoarseness/stridor	□	○
ENT opinion	◊	
no active vasculitis	○	
Granulomatous sinusitis	○	
Conductive hearing loss	○	
Sensorineural hearing loss	○	
Significant Subglottic inflammation	○	

	PERSISTENT	NEW/WORSE
5. CHEST	□ (none)	
persistent cough	□	○
dyspnoea or wheeze	□	○
Haemoptysis/haemorrhage	□	○
chest radiology performed	◊	
no active vasculitis	○	
nodules or cavities	○	
pleural effusion/pleurisy	○	
Infiltrate	○	
massive haemoptysis or alveolar haemorrhage	□	○
respiratory failure	□	○
6. CARDIOVASCULAR	□ (none)	
aortic incompetence	□	○
pericardial pain/rub	□	○
ischaemic cardiac pain	□	○
congestive cardiac failure	□	○
cardiology opinion/tests	◊	
no active vasculitis	○	
pericarditis	○	
myocardial infarct/angina	○	
cardiomyopathy	○	
7. ABDOMINAL	□ (none)	
severe abdominal pain	□	○
bloody diarrhoea	□	○
surgical opinion/tests	◊	
no active vasculitis	○	
gut perforation/infarct	○	
acute pancreatitis	○	
8. RENAL	□ (none)	
hypertension (diastol>95)	□	○
proteinuria >1+/>0.2g/24h)	□	○
haematuria>1+/>10rbc/ml)	□	○
creatinine 125-249 umol/l		○
creatinine 250-499 umol/l		○
creatinine >500 umol/l		○
rise in creatinine >30% or fall in creatinine clearance>25%		○
9. NERVOUS SYSTEM	□ (none)	
organic confusion/dementia	□	○
seizures(not hypertensive)	□	○
stroke	□	○
cord lesion	□	○
sensory peripheral neuropathy	□	○
cranial nerve palsy	□	○
motor mononeuritis multiplex	□	○
10. OTHER		
	□	○

TABLE 3. Glossary and definition of terms as well as score for each item included in the Birmingham Vasculitis Activity Score (BVAS)

GLOSSARY for BVAS

GENERAL RULE: disease features are scored only when they are due to active vasculitis, after exclusion of other obvious causes (e.g. infection, hypertension, etc.). If the feature has occurred afresh or represents a recent deterioration of status since last visit, it is scored in the NEW/WORSE boxes. It is essential to apply these principles to each item below. Scores have been weighted according to the severity which each symptom or sign is thought to represent. Tick box (Persistent) if the abnormality indicates the presence of active (but not new or worse) vasculitis. For some features, further information (from specialist opinion or further tests) is required if abnormality is newly present or worse. Remember that in most instances, you will be able to complete the whole record when you see the patient. However, on occasions, you may require further information before entering some items. We would suggest that you leave these items blank, and once the information is available, please remember to take the time to fill in the information. For example, if the patient has new onset of stridor, you would usually ask an ENT colleague to investigate this further to determine whether or not it is due to active Wegener's granulomatosis.

DERIVATION of BVAS.1 (new/worse) BVAS.2 (persistent) scores. The data from the score sheet will be used to derive indices of disease activity as follows:

BVAS.1 - This represents a score of new/worse disease activity attributable to vasculitis

BVAS.2 - This represents a score of disease activity due to persisting or grumbling disease, which is neither new nor worse, compared to the previous assessment.

Scores are calculated using the values given to each item as shown; each section has a maximum score, corresponding to the total value for BVAS (new/worse) and BVAS (persistent).

TERM	DEFINITION	BVAS persis-tent	BVAS new/ worse
1. General	**Maximum scores**	2	3
Malaise	A general feeling of tiredness, illness & discomfort.	1	1
Myalgia	Pain in the muscles	1	1
Arthralgia or arthritis	Pain in the joints or joint inflammation.	1	1
Headache	New, unaccustomed & persistent	1	1
Fever <38.5	Documented oral/axillary temperature elevation. Rectal temperatures are 0.5 C higher	1	1
Fever >=38.5	Documented oral/axillary temperature elevation. Rectal temperatures are 0.5 C higher	2	2
Weight Loss	At least 2kg loss of body weight (not fluid) having occurred since last assessment or in the 4 weeks not as a consequence of dieting	2	2

2. Cutaneous	Maximum scores	3	6
Infarct	Area of tissue necrosis or splinter haemorrhages	1	2
Purpura	Petechiae (small red spots), palpable purpura, or ecchymoses (large plaques) in skin or oozing (in the absence of trauma) in the mucous membranes.	1	2
Other skin vasculitis	e.g., livedo reticularis, nodules etc.	2	2
Ulcer	Open sore in a skin surface.	1	4
Gangrene	Extensive tissue necrosis (e.g. digit)	1	6
Multiple digit gangrene	Extensive tissue necrosis occurring in more than one digit or limb.	2	6

3. Mucous membranes/eyes	Maximum score	3	6
Mouth ulcers	Ulcers localised in the mouth. Exclude other causes, such as drugs, Crohn's disease, pemphigus etc.	1	1
Genital ulcers	Ulcers localised in the genitalia or perineum.	1	1
Significant proptosis	Protrusion of the eyeball due to significant amounts of inflammatory in the orbit. This may be associated with diplopia due to infiltration of extra-ocular muscles.	2	4
Red eye conjunctivitis	Inflammation of the conjuctivae (exclude infectious causes); (specialist opinion not usually required).	1	1
Red eye (Epi)scleritis	Inflammation of the scleras (specialist opinion not usually required).	1	2
Blurred vision	Significant impairment of vision.	2	2
Sudden visual loss	Sudden loss of vision requiring ophthalmological assessment.	-	6
Ophthalmic opinion	To diagnose & score retinal exudates, haemorrhages, uveitis & reason for sudden visual loss. This data must be entered on score sheets subsequently.		
Uveitis*	Inflammation of the uvea (iris, ciliary body, choroid) confirmed by ophthalmologist.	-	6
Retinal exudates*	Any area of soft retinal exudates (exclude hard exudates) seen on ophthalmoscopic examination.	-	6
Retinal haemorrhages*	Any area of retinal haemorrhage seen on ophthalmoscopic examination.	-	6

4. ENT	Maximum scores	3	6
Nasal obstruction	A history of nasal blockage	1	2
Bloody nasal discharge	Blood stained secretions from the nose, irrespective of severity, or frequency & severity of previously occurring bleeding since last visit.	2	4
Nasal crusting	Discharge of large serous or serosanguinous crusts from either nostril.	2	4
Sinus involvement	Tenderness or pain over paranasal sinuses or X-ray evidence of sinusitis. If nasal bridge collapse is observed, this may be recorded separately (in 10. Other).	1	2
Hearing loss	Significant new hearing loss requiring specialist opinion.	-	3
Hoarseness/ stridor	Increasing hoarseness & inspiratory stridor.	2	5
ENT opinion	To ascribe otitis media, deafness, or diagnose subglottic involvement due to vasculitis. This data can be entered on score sheets subsequently.		
Granulomatous sinusitis*	Characteristic appearance on nasal examination	-	4
Conductive hearing loss*	Any hearing loss due to middle ear involvement preferably confirmed by audiometry.	-	3
Sensorineural hearing loss*	Deafness attributable to auditory nerve or cochlear damage.	-	6
Significant subglottic inflammation*	Inspiratory stridor with significant narrowing of subglottic space confirmed by further examination (usually by an ENT specialist) or by radiological assessment	-	6

5. Chest	Maximum scores	3	6
Persistent cough	Cough for more than 2 weeks (other causes for the cough having been excluded e.g. infection)	1	2
Dyspnoea or wheeze	Shortness of breath or audible wheeze on exercise, by history &/or clinical examination.	1	2
Haemoptysis/ haemorrhage	Production of blood stained sputum. Other causes (e.g. infection, cancer) should be excluded.	1	3
Chest radiology performed	A chest radiograph should be performed if there are significant signs or symptoms to suggest chest disease or in the presence of a generalised flare – to determine the following three:		
Nodules or cavities*	New lesions, detected by CXR.	-	3
Pleural effusion/pleurisy*	Pleural pain &/or friction rub on clinical assessment or new onset of radiologically confirmed pleural effusion. Other causes (e.g. infection, cancer) should be excluded.	-	4
Infiltrate	By CXR, CT scan.	-	4
Massive haemoptysis/ Alveolar haemorrhage	Major pulmonary bleeding, with shifting pulmonary infiltrates & usually associated with signs of shock; other causes of bleeding should be excluded.	-	6
Respiratory failure	Dyspnoea which is sufficiently severe as to require artificial ventilation; arterial blood gases should be performed to confirm the presence of hypoxaemia & or hypercapnia.	3	6

6. Cardiovascular	Maximum scores	3	6
Aortic incompetence	Significant aortic valve regurgitation, detected clinically or echocardiographically.	2	4
Pericardial pain/ rub	Pericardial pain &/or friction rub on clinical assessment.	2	3
Ischaemic cardiac pain	Typical clinical history of cardiac pain. Consider the possibility of more common causes (e.g. atherosclerosis).	2	4
Congestive cardiac failure	By history or clinical examination	2	4
Cardiology opinion or tests	Specialist opinion/tests are usually required to determine the following features		
Pericarditis*	Pericardial pain &/or friction rub on clinical assessment.	-	4
Myocardial infarction/angina*	Typical history of cardiac pain.	-	6
Cardiomyopathy*	Heart failure by history or clinical examination		6

7. Abdominal	Maximum scores	4	9
Severe abdominal pain	Of recent onset & attributed to vasculitis.	2	3
Bloody diarrhoea	Of recent onset, not due to known inflammatory bowel disease, etc.	2	3
Surgical opinion/ tests	Specialist opinion/tests required to determine the cause of abdominal pain or diarrhoea if they are of recent onset or worse since last visit.		
Gut perforation/ infarction*	Typical pain & peritonism includes gall bladder or appendix. Confirmed by X-ray or at surgery.	-	9
Acute pancreatitis*	Typical history & clinical examination findings of acute abdominal pain & tenderness with guarding. Confirmed by elevated serum amylase & a surgical opinion	-	9

8. Renal	Maximum scores	6	12
Hypertension	Diastolic BP>95, accelerated or not, with or without retinal changes.	1	4
Proteinuria	>1+ on urinalysis; >0.2g/ 24 hours. Infection should be excluded.	2	4
Haematuria	>1+ on urinalysis; >10 rbc/ ml, or red cell casts seen on urine microscopy. Infection should be excluded.	3	6
Creatinine 125-249	Serum creatinine values 125-249 umol/l at first assessment only.	2	4
Creatinine 250-499	Serum creatinine values 250-499 umol/l at first assessment only.	3	6
Creatinine >=500	Serum creatinine values 500 umol/l or greater at first assessment only.	4	8
Rise in creatinine > 30% or creatinine clearance fall > 25%	Significant deterioration in renal function attributable to active vasculitis.	-	6

9. Nervous system	Maximum scores	6	9
Organic confusion/ Dementia	Impaired orientation, memory or other intellectual function in the absence of metabolic, psychiatric, pharmacological or toxic causes.	1	3
Seizures (not hypertensive)	Paroxysmal electrical discharges in the brain & producing characteristic physical changes including tonic & clonic movements & certain behavioural changes.	3	9
Stroke	Cerebrovascular accident resulting in focal neurological signs such as paresis, weakness, etc. A stroke due to other causes (eg atherosclerosis) should be considered & appropriate neurological advice is recommended	3	9
Cord lesion	Transverse myelitis with lower extremity weakness or sensory loss (usually with a detectable sensory level) with loss of sphincter control (rectal & urinary bladder).	3	9
Sensory Peripheral neuropathy	Sensory neuropathy resulting in glove &/or stocking distribution of sensory loss. Other causes should be excluded (e.g. idiopathic, metabolic, vitamin deficiencies, infectious, toxic, hereditary).	3	6
Cranial nerve palsy	Isolated acute cranial nerve palsy, excluding sensorineural hearing loss, or optic nerve lesion secondary to retro-orbital mass.	3	6
Motor mononeuritis multiplex	Simultaneous neuritis of many peripheral nerves, only scored if motor involvement. Other causes should be excluded (diabetes, sarcoidosis, carcinoma, amyloidosis).	3	9

10. Other	Significant features attributable to active vasculitis not listed above.		
	Total maximum score	33	63

TABLE 4. Vasculitis Damage Index (VDI)

VASCULITIS DAMAGE INDEX (VDI)

This is for recording organ damage that has occurred in patients ***since the onset of vasculitis***
Patients often have co-morbidity before they develop vasculitis, **which must not be scored**
Record features of active disease using the Birmingham Vasculitis Activity Score (BVAS)
A new patient should ***usually have a VDI score of zero,*** unless:
(a) they have had vasculitis for more than three months of onset of disease. **and**
(b) the damage has developed or become worse since the onset of vasculitis

1. Musculoskeletal	**No**	**Yes**
None	☐	
Significant muscle atrophy or weakness		○
Deforming/erosive arthritis		○
Osteoporosis/vertebral collapse		○
Avascular necrosis		○
Osteomyelitis		○
2. Skin/Mucous membranes		
None	☐	
Alopecia		○
Cutaneous ulcers		○
Mouth ulcers		○
3. Ocular		
None	☐	
Cataract		○
Retinal change		○
Optic atrophy		○
Visual impairment/diplopia		○
Blindness in one eye		○
Blindness in second eye		○
Orbital wall destruction		○
4. ENT		
None	☐	
Hearing loss		○
Nasal blockage/chronic discharge/crusting		○
Nasal bridge collapse/septal perforation		○
Chronic sinusitis/radiological damage		○
Subglottic stenosis (no surgery)		○
Subglottic stenosis (with surgey)		○
5. Pulmonary		
None	☐	
Pulmonary hypertension		○
Pulmonary fibrosis		○
Pulmonary infarction		○
Pleural fibrosis		○
Chronic asthma		○
Chronic breathlessness		○
Impaired lung function		○
6. Cardiovascular		
None	☐	
Angina/angioplasty		○
Myocardial infarction		○
Subsequent myocardial infarction		○
Cardiomyopathy		○
Valvular disease		○
Pericarditis ≥ 3 mths or pericardectomy		○
Diastolic BP ≥ 95 or requiring antihypertensives		○

Name
Trial Number
Date
Centre

7. Peripheral vascular disease	**No**	**Yes**
None	☐	
Absent pulses in one limb		○
2nd episode of absent pulses in one limb		○
Major vessel stenosis		○
Claudication >3 mths		○
Minor tissue loss		○
Major tissue loss		○
Subsequent major tissue loss		○
Complicated venous thrombosis		○
8. Gastrointestinal		
None	☐	
Gut infarction/resection		○
Mesenteric insufficiency/pancreatitis		○
Chronic peritonitis		○
Oesophageal stricture/surgery		○
9. Renal		
None	☐	
Estimated/measured GFR ≤ 50%		○
Proteinuria ≥ 0.5g/24hr		○
End stage renal disease		○
10. Neuropsychiatric		
None	☐	
Cognitive impairment		○
Major psychosis		○
Seizures		○
Cerebrovascular accident		○
2nd cerebrovascular accident		○
Cranial nerve lesion		○
Peripheral neuropathy		○
Transverse myelitis		○
11. Other		
None	☐	
Gonadal failure		○
Marrow failure		○
Diabetes		○
Chemical cystitis		○
Malignancy		○
Other		○

Total VDI Score. Record the number of positive Items (1 point for each). The VDI score can either increase or remain the same over time. Remember to carry forward any previous items of damage.	☐

MTX has been evaluated as an alternative treatment for active AASV (WG and MPA) in a prospective randomised trial against CYC. This showed that MTX induced remission in 90% of patients [57]. However, a slightly, albeit non-significant, higher rate of relapse was also reported, perhaps indicating the need for longer periods of maintenance therapy. Formerly, reports by Langford et al. and Reinhold-Keller et al. reviewed the use of MXT as a remission maintaining agent [58,59]. Even though MTX was relatively well tolerated, the relapse rate with renal involvement warranted further study.

Maintaining remission in WG is an essential factor of patient survival. The safety and efficacy of AZA, a metabolite of 6-mercaptopurin inhibiting purine synthesis, as a remission maintenance therapy has been assessed by EUVAS [60]. It was shown that replacement of CYC after induction of remission with AZA did not have an impact on disease relapse and that AZA may be used to prevent long-term exposure to CYC.

MMF, the prodrug of mycophenolic acid, which non-competitively reversibly inhibits inosine monophosphate dehydrogenase and purine synthesis, has also been introduced in the therapy of WG either as a remission maintenance agent or as a treatment for disease relapse. Preliminary reports indicated that MMF had variable efficacy of (10 - 43%) in sustaining remission for more that twelve months [61,62]. In a recent retrospective study, it was demonstrated that MMF can induce remission in WG when administered for disease flare but it was observed that low MMF doses could be responsible for higher relapse rates [63].

Additional therapy with intravenous immunoglobulin (IVIg) can supplement induction immune suppressive regimens in cases of relapsing or refractory WG. In a randomized trial comparing IVIg with placebo when administered with steroids and another immune suppressive agent, it was shown that IVIg can improve clinical response [64]. The impact of IVIg on clinical outcome appears to be temporary, but it can be used for critical cases where there is an urgent need to rapidly control disease activity.

Novel therapeutic options that target specific parts in the pathogenesis pathway of vasculitis have become available for clinical investigation. Alemtuzumab (CAMPATH-1H), a humanised monoclonal antibody against CD52, a surface antigen of T- and B-lymphocytes, leads to lymphocyte depletion and has been used successfully in difficult refractory cases of WG, but its toxicity, namely infections and infusion reactions, has restrained its further use [65]. Tumour necrosis factor alpha (TNFα) is considered an important component in the pathophysiology of vasculitis and, as a result, treatment with anti-TNFα agents such as the monoclonal antibody infliximab, and the soluble TNF receptor etanercept, has been examined. Infliximab has proven efficacy in 88% of refractory or relapsing cases of vasculitis [66]. However, it was shown that etanercept did not improve relapse rates when administered as concomitant treatment with CYC and steroids [67]. Furthermore, the role of B-cells in WG has received special interest. B-cell depletion with rituximab, a chimeric monoclonal antibody targeting CD20 that is expressed on B-cells, has been effective in inducing remission in refractory cases of WG [68,69]. Rituximab satisfactorily controlled disease activity, ANCA titers fell, the daily steroid dose was significantly decreased and the drug was very well-tolerated. It was noted that in the majority of cases remission was sustained as long as the B-cells were undetectable, suggesting that repeated courses of rituximab may be necessary to prevent disease flares. Initial studies of 15-deoxyspergualin (DSG) have shown its safety and efficacy in refractory WG [70]. A European clinical trial of DSG in WG has been recently completed indicating particular specificity of DSG to control manifestations of the upper and lower respiratory tract (personal communication Dr O Flossmann).

In addition to the medical treatments described, non-pharmacological interventions like plasma exchange or dilatation of the trancheo-bronchial tree can be useful, especially in life-threatening cases. Plasma exchange removes pathogenic autoantibodies and other factors that may trigger disease activity and has proven beneficial in cases of severe glomerulonephritis and alveolar haemorrhage [71], although there is still no specific indication for plasma exchange in WG and no definite protocol for its use. In addition, subglottic stenosis is a frequent clinical feature of WG patients and usually indicates permanent scarring and fibrosis that is unlikely to respond to drug therapy. Dilatation of stenotic areas and possibly in situ steroid injections, can secure the patency of airways [72].

SUMMARY

Wegener's Granulomatosis (WG) as a systemic multi-organ disease, targets small and medium-sized vessels that could lead to tissue damage. The upper respiratory tract, the pulmonary, renal and ocular systems are usually affected. In absence of diagnostic criteria, biopsy of the affected organ can only confirm diagnosis. Induction treatment usually consists of high doses of steroids along with cyclophosphamide. In cases without severe organ, especially renal or pulmonary, dysfunction on presentation, methotrexate could be administered as an alternative. Maintaining remission with azathioprine or mycophenolate mofetyl is essential in addition to regular monitoring with BVAS and laboratory parameters to prevent disease relapses and treat grumbling disease activity.

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New Orleans 2004. And then... (hurricane) Katrina hit *Liana Alexopoulou*