

## REVIEW

# Wegener's Granulomatosis: A comprehensive review

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**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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**ABSTRACT**

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.

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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.

<b>CHCC definition of Wegener's granulomatosis</b>
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.
<b>ACR Criteria for the classification of Wegener's granulomatosis</b>
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 naive 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 (TNF $\alpha$ ) 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  $\alpha$ 1-antitrypsin [32]. Further on in the molecular pathway both F(ab)<sub>2</sub> 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<sup>-/-</sup> 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 naive 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].

WEGENER'S GRANULOMATOSIS

TABLE 2. Birmingham Vasculitis Activity Score (BVAS)

VASCULITIS ACTIVITY SCORE			DEMOGRAPHY	
<input type="checkbox"/> Tick box <b>only</b> if abnormality is <b>newly present</b> since last assessment or <b>worse</b> in the last <b>few weeks</b> (use the Vasculitis Damage Index, VDI to score items of damage) <input type="checkbox"/> Tick box <b>only</b> if abnormality is due to <b>active</b> (but not new or worse) vasculitis <input type="checkbox"/> Tick box if more information (specialist opinion/tests) is requested @ oral/axillary temperatures; rectal temperatures are 0.5°C higher			<b>Trial Number</b> / / <b>Visit Date</b> / / <b>Investigator</b>	
PERSISTENT	NEW/WORSE		PERSISTENT	NEW/WORSE
<b>1. GENERAL</b> <input type="checkbox"/> (none)				
	<input type="checkbox"/>	<input type="radio"/>		
malaise	<input type="checkbox"/>	<input type="radio"/>		
myalgia	<input type="checkbox"/>	<input type="radio"/>		
arthralgia/arthritis	<input type="checkbox"/>	<input type="radio"/>		
headache	<input type="checkbox"/>	<input type="radio"/>		
fever (< 38.5°C) @	<input type="checkbox"/>	<input type="radio"/>		
fever (≥ 38.5°C) @	<input type="checkbox"/>	<input type="radio"/>		
wt loss (≥ 2kg)	<input type="checkbox"/>	<input type="radio"/>		
<b>2. CUTANEOUS</b> <input type="checkbox"/> (none)				
	<input type="checkbox"/>	<input type="radio"/>		
Infarct	<input type="checkbox"/>	<input type="radio"/>		
purpura	<input type="checkbox"/>	<input type="radio"/>		
other skin vasculitis	<input type="checkbox"/>	<input type="radio"/>		
ulcer	<input type="checkbox"/>	<input type="radio"/>		
gangrene	<input type="checkbox"/>	<input type="radio"/>		
multiple digit gangrene	<input type="checkbox"/>	<input type="radio"/>		
<b>3. MUCOUS MEMBRANES/EYES</b> <input type="checkbox"/> (none)				
	<input type="checkbox"/>	<input type="radio"/>		
mouth ulcers	<input type="checkbox"/>	<input type="radio"/>		
genital ulcers	<input type="checkbox"/>	<input type="radio"/>		
significant proptosis	<input type="checkbox"/>	<input type="radio"/>		
red eye- conjunctivitis	<input type="checkbox"/>	<input type="radio"/>		
red eye- episcleritis	<input type="checkbox"/>	<input type="radio"/>		
blurred vision	<input type="checkbox"/>	<input type="radio"/>		
sudden visual loss	<input type="checkbox"/>	<input type="radio"/>		
ophthalmic opinion	<input type="checkbox"/>	<input type="radio"/>		
no active vasculitis	<input type="checkbox"/>	<input type="radio"/>		
uveitis	<input type="checkbox"/>	<input type="radio"/>		
retinal exudates	<input type="checkbox"/>	<input type="radio"/>		
retinal haemorrhage	<input type="checkbox"/>	<input type="radio"/>		
<b>4. ENT</b> <input type="checkbox"/> (none)				
	<input type="checkbox"/>	<input type="radio"/>		
Nasal obstruction	<input type="checkbox"/>	<input type="radio"/>		
Bloody nasal discharge	<input type="checkbox"/>	<input type="radio"/>		
Nasal crusting	<input type="checkbox"/>	<input type="radio"/>		
Sinus involvement	<input type="checkbox"/>	<input type="radio"/>		
Hearing loss	<input type="checkbox"/>	<input type="radio"/>		
Hoarseness/stridor	<input type="checkbox"/>	<input type="radio"/>		
ENT opinion	<input type="checkbox"/>	<input type="radio"/>		
no active vasculitis	<input type="checkbox"/>	<input type="radio"/>		
Granulomatous sinusitis	<input type="checkbox"/>	<input type="radio"/>		
Conductive hearing loss	<input type="checkbox"/>	<input type="radio"/>		
Sensorineural hearing loss	<input type="checkbox"/>	<input type="radio"/>		
Significant Subglottic inflammation	<input type="checkbox"/>	<input type="radio"/>		
<b>5. CHEST</b> <input type="checkbox"/> (none)				
	<input type="checkbox"/>	<input type="radio"/>		
persistent cough	<input type="checkbox"/>	<input type="radio"/>		
dyspnoea or wheeze	<input type="checkbox"/>	<input type="radio"/>		
Haemoptysis/haemorrhage	<input type="checkbox"/>	<input type="radio"/>		
chest radiology performed	<input type="checkbox"/>	<input type="radio"/>		
no active vasculitis	<input type="checkbox"/>	<input type="radio"/>		
nodules or cavities	<input type="checkbox"/>	<input type="radio"/>		
pleural effusion/pleurisy	<input type="checkbox"/>	<input type="radio"/>		
Infiltrate	<input type="checkbox"/>	<input type="radio"/>		
massive haemoptysis or alveolar haemorrhage	<input type="checkbox"/>	<input type="radio"/>		
respiratory failure	<input type="checkbox"/>	<input type="radio"/>		
<b>6. CARDIOVASCULAR</b> <input type="checkbox"/> (none)				
	<input type="checkbox"/>	<input type="radio"/>		
aortic incompetence	<input type="checkbox"/>	<input type="radio"/>		
pericardial pain/rub	<input type="checkbox"/>	<input type="radio"/>		
ischaemic cardiac pain	<input type="checkbox"/>	<input type="radio"/>		
congestive cardiac failure	<input type="checkbox"/>	<input type="radio"/>		
cardiology opinion/tests	<input type="checkbox"/>	<input type="radio"/>		
no active vasculitis	<input type="checkbox"/>	<input type="radio"/>		
pericarditis	<input type="checkbox"/>	<input type="radio"/>		
myocardial infarct/angina	<input type="checkbox"/>	<input type="radio"/>		
cardiomyopathy	<input type="checkbox"/>	<input type="radio"/>		
<b>7. ABDOMINAL</b> <input type="checkbox"/> (none)				
	<input type="checkbox"/>	<input type="radio"/>		
severe abdominal pain	<input type="checkbox"/>	<input type="radio"/>		
bloody diarrhoea	<input type="checkbox"/>	<input type="radio"/>		
surgical opinion/tests	<input type="checkbox"/>	<input type="radio"/>		
no active vasculitis	<input type="checkbox"/>	<input type="radio"/>		
gut perforation/infarct	<input type="checkbox"/>	<input type="radio"/>		
acute pancreatitis	<input type="checkbox"/>	<input type="radio"/>		
<b>8. RENAL</b> <input type="checkbox"/> (none)				
	<input type="checkbox"/>	<input type="radio"/>		
hypertension (diastole>95)	<input type="checkbox"/>	<input type="radio"/>		
proteinuria >1+/-0.2g/24h)	<input type="checkbox"/>	<input type="radio"/>		
haematuria>1+/-10rbc/ml)	<input type="checkbox"/>	<input type="radio"/>		
creatinine 125-249 umol/l	<input type="checkbox"/>	<input type="radio"/>		
creatinine 250-499 umol/l	<input type="checkbox"/>	<input type="radio"/>		
creatinine >500 umol/l	<input type="checkbox"/>	<input type="radio"/>		
rise in creatinine >30% or fall in creatinine clearance>25%	<input type="checkbox"/>	<input type="radio"/>		
<b>9. NERVOUS SYSTEM</b> <input type="checkbox"/> (none)				
	<input type="checkbox"/>	<input type="radio"/>		
organic confusion/dementia	<input type="checkbox"/>	<input type="radio"/>		
seizures(not hypertensive)	<input type="checkbox"/>	<input type="radio"/>		
stroke	<input type="checkbox"/>	<input type="radio"/>		
cord lesion	<input type="checkbox"/>	<input type="radio"/>		
sensory peripheral neuropathy	<input type="checkbox"/>	<input type="radio"/>		
cranial nerve palsy	<input type="checkbox"/>	<input type="radio"/>		
motor mononeuritis multiplex	<input type="checkbox"/>	<input type="radio"/>		
<b>10. OTHER</b>				
	<input type="checkbox"/>	<input type="radio"/>		

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 persistent	BVAS new/worse
<b>1. General</b>			
<b>Maximum scores</b>			
Malaise	A general feeling of tiredness, illness & discomfort.	2	3
Myalgia	Pain in the muscles	1	1
Arthralgia or arthritis	Pain in the joints or joint inflammation.	1	1
Headache	New, unaccommodated & 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

<b>2. Cutaneous</b>			
<b>Maximum scores</b>			
Infect	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	5
Multiple digit gangrene	Extensive tissue necrosis occurring in more than one digit or limb.	2	5

<b>3. Mucous membranes/eyes</b>			
<b>Maximum score</b>			
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 conjunctivae (exclude infectious causes); (specialist opinion not usually required).	1	1
Red eye (Ipsilateral)	Inflammation of the sclera (specialist opinion not usually required)	1	2
Blurred vision	Significant impairment of vision.	2	3
Sudden visual loss	Sudden loss of vision requiring ophthalmological assessment.	2	5
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.	-	5
Retinal exudates*	Any area of soft retinal exudates (exclude hard exudates) seen on ophthalmoscopic examination.	-	5
Retinal haemorrhages*	Any area of retinal haemorrhage seen on ophthalmoscopic examination.	-	5

<b>4. ENT</b>			
<b>Maximum scores</b>			
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 diagnostic 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*	Ary hearing loss due to middle ear involvement preferably confirmed by audiometry.	-	3
Sensorineural hearing loss*	Deafness attributable to auditory nerve or cochlear damage.	-	5
Significant subglottic inflammation*	Inspiratory stridor with significant narrowing of subglottic space confirmed by further examination (usually by an ENT specialist) or by radiological assessment	-	5

<b>5. Chest</b>			
<b>Maximum scores</b>			
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.	-	5
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

<b>6. Cardiovascular</b>			
<b>Maximum scores</b>			
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.	-	5
Cardiomyopathy*	Heart failure by history or clinical examination	-	5

<b>7. Abdominal</b>			
<b>Maximum scores</b>			
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/infection*	Typical pain & peritonism includes gall bladder or appendix. Confirmed by X-ray or at surgery.	-	5
Acute pancreatitis*	Typical history & clinical examination findings of acute abdominal pain & tenderness with guarding. Confirmed by elevated serum amylase & a surgical opinion	-	5

<b>8. Renal</b>			
<b>Maximum scores</b>			
Hypertension	Diastolic BP >95, accelerated or not, with or without retinal changes.	1	4
Proteinuria	>1+ on urinalysis; >3g/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	5
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	5
Creatinine >=500	Serum creatinine values 500 umol/l or greater at first assessment only.	4	5
Rise in creatinine > 30% or creatinine clearance fall > 25%	Significant deterioration in renal function attributable to active vasculitis.	-	5

<b>9. Nervous system</b>			
<b>Maximum scores</b>			
Organic confusory	Impaired orientation, memory or other intellectual function in the absence of metabolic, psychiatric, pharmacological or toxic causes.	1	3
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	5
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	5
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	5
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	5
Cranial nerve palsy	Isolated acute cranial nerve palsy, excluding sensorineural hearing loss, or optic nerve lesion secondary to retro-orbital mass.	3	5
Motor mononeuritis multiplex	Simultaneous neuritis of many peripheral nerves, only scored if motor involvement. Other causes should be excluded (diabetes, sarcoidosis, carcinoma, amyloidosis).	3	5

<b>10. Other</b>			
<b>Significant features attributable to active vasculitis not listed above.</b>			
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

	No	Yes		No	Yes
<b>1. Musculoskeletal</b>			<b>Name</b>		
None	<input type="checkbox"/>		<b>Trial Number</b>		
Significant muscle atrophy or weakness		<input type="radio"/>	<b>Date</b>		
Deforming/erosive arthritis		<input type="radio"/>	<b>Centre</b>		
Osteoporosis/vertebral collapse		<input type="radio"/>	<b>7. Peripheral vascular disease</b>		
Avascular necrosis		<input type="radio"/>	None	<input type="checkbox"/>	
Osteomyelitis		<input type="radio"/>	Absent pulses in one limb		<input type="radio"/>
<b>2. Skin/Mucous membranes</b>			2 <sup>nd</sup> episode of absent pulses in one limb		<input type="radio"/>
None	<input type="checkbox"/>		Major vessel stenosis		<input type="radio"/>
Alopecia		<input type="radio"/>	Claudication >3 mths		<input type="radio"/>
Cutaneous ulcers		<input type="radio"/>	Minor tissue loss		<input type="radio"/>
Mouth ulcers		<input type="radio"/>	Major tissue loss		<input type="radio"/>
<b>3. Ocular</b>			Subsequent major tissue loss		<input type="radio"/>
None	<input type="checkbox"/>		Complicated venous thrombosis		<input type="radio"/>
Cataract		<input type="radio"/>	<b>8. Gastrointestinal</b>		
Retinal change		<input type="radio"/>	None	<input type="checkbox"/>	
Optic atrophy		<input type="radio"/>	Gut infarction/resection		<input type="radio"/>
Visual impairment/diplopia		<input type="radio"/>	Mesenteric insufficiency/pancreatitis		<input type="radio"/>
Blindness in one eye		<input type="radio"/>	Chronic peritonitis		<input type="radio"/>
Blindness in second eye		<input type="radio"/>	Oesophageal stricture/surgery		<input type="radio"/>
Orbital wall destruction		<input type="radio"/>	<b>9. Renal</b>		
<b>4. ENT</b>			None	<input type="checkbox"/>	
None	<input type="checkbox"/>		Estimated/measured GFR ≤ 50%		<input type="radio"/>
Hearing loss		<input type="radio"/>	Proteinuria ≥ 0.5g/24hr		<input type="radio"/>
Nasal blockage/chronic discharge/crusting		<input type="radio"/>	End stage renal disease		<input type="radio"/>
Nasal bridge collapse/septal perforation		<input type="radio"/>	<b>10. Neuropsychiatric</b>		
Chronic sinusitis/radiological damage		<input type="radio"/>	None	<input type="checkbox"/>	
Subglottic stenosis (no surgery)		<input type="radio"/>	Cognitive impairment		<input type="radio"/>
Subglottic stenosis (with surgery)		<input type="radio"/>	Major psychosis		<input type="radio"/>
<b>5. Pulmonary</b>			Seizures		<input type="radio"/>
None	<input type="checkbox"/>		Cerebrovascular accident		<input type="radio"/>
Pulmonary hypertension		<input type="radio"/>	2 <sup>nd</sup> cerebrovascular accident		<input type="radio"/>
Pulmonary fibrosis		<input type="radio"/>	Cranial nerve lesion		<input type="radio"/>
Pulmonary infarction		<input type="radio"/>	Peripheral neuropathy		<input type="radio"/>
Pleural fibrosis		<input type="radio"/>	Transverse myelitis		<input type="radio"/>
Chronic asthma		<input type="radio"/>	<b>11. Other</b>		
Chronic breathlessness		<input type="radio"/>	None	<input type="checkbox"/>	
Impaired lung function		<input type="radio"/>	Gonadal failure		<input type="radio"/>
<b>6. Cardiovascular</b>			Marrow failure		<input type="radio"/>
None	<input type="checkbox"/>		Diabetes		<input type="radio"/>
Angina/angioplasty		<input type="radio"/>	Chemical cystitis		<input type="radio"/>
Myocardial infarction		<input type="radio"/>	Malignancy		<input type="radio"/>
Subsequent myocardial infarction		<input type="radio"/>	Other		<input type="radio"/>
Cardiomyopathy		<input type="radio"/>	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.		
Valvular disease		<input type="radio"/>			
Pericarditis ≥ 3 mths or pericardectomy		<input type="radio"/>			
Diastolic BP ≥ 95 or requiring antihypertensives		<input type="radio"/>			

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 MTX 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-mercaptopurine 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 than 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 (TNF $\alpha$ ) is considered an important component in the pathophysiology of vasculitis and, as a result, treatment with anti-TNF $\alpha$  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 adminis-

tered 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 tracheo-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].

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## SUMMARY

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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

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