Vasculitis

Carol A. Langford, MD, MHS *Cleveland, Ohio*

Vasculitis is defined by the presence of blood vessel inflammation. It can be observed in a wide variety of settings, which can be broadly grouped as secondary vasculitides, which occur in association with an underlying disease or trigger, or primary vasculitides, in which vasculitis is occurring for as-yet unknown causes. The primary systemic vasculitides comprise a range of disease entities that are uniquely identified by their clinical, histopathologic, and therapeutic characteristics. Individual diseases predominantly affect blood vessels of a particular size, which influences their clinical manifestations and has been used in their classification. The vasculitides can also differ in their severity, extending from self-limited illnesses to those that can be life-threatening in the absence of prompt initiation of treatment. Immunosuppressive agents are used to treat many vasculitic diseases. Although such approaches can be effective, the patient's long-term course can be influenced by organ damage from their initial presentation, disease relapses, and medication toxicity. Recent investigations have focused on understanding disease pathophysiology and the exploration of novel therapeutic approaches. (J Allergy Clin Immunol 2010;125:S216-25.)

Key words: *Vasculitis, arteritis, antineutrophil cytoplasmic antibody, granuloma, glucocorticoid, cyclophosphamide*

Abbreviations used

ANCA:	Antineutrophil cytoplasmic antibodies
AZA:	Azathioprine
CHCC:	Chapel Hill Consensus Conference
CNS:	Central nervous system
CSS:	Churg-Strauss syndrome
CYC:	Cyclophosphamide
GACNS:	Granulomatous angiitis of the central nervous system
GCA:	Giant cell arteritis
HCV:	Hepatitis C virus
HSP:	Henoch-Schönlein purpura
MPA:	Microscopic polyangiitis
MPO:	Myeloperoxidase
MTX:	Methotrexate
PACNS:	Primary angiitis of the central nervous system
PAN:	Polyarteritis nodosa
PMR:	Polymyalgia rheumatica
PR3:	Proteinase 3
TAK:	Takayasu arteritis
WG:	Wegener granulomatosis

Vasculitis is characterized by histologic evidence of blood vessel inflammation. When vasculitis occurs, it can lead to blood vessel stenosis/occlusion, causing organ ischemia or thinning of the blood vessel and resulting in aneurysm formation or hemorrhage. Vasculitis can be thought of in 2 broad categories: secondary vasculitides, in which blood vessel inflammation occurs in association with an underlying disease or exposure, or primary vasculitides, which are entities of unknown cause in which vasculitis is the pathologic basis of tissue injury. This review will focus on the clinical features, diagnosis, and treatment of the primary vasculitic diseases.

CLASSIFICATION

The first account of a patient who had a noninfectious vasculitis was made in 1866, when Kussmaul and Maier published a detailed report of a disorder characterized by nodular inflammation of the muscular arteries. They named this disease periarteritis nodosa, which later also became referred to as polyarteritis nodosa (PAN). The description of other necrotizing vasculitides followed, and in 1952, Zeek proposed the first classification system. The nomenclature and classification of the vasculitides has remained an evolving process as our knowledge about these diseases has grown. In 1990, the American College of Rheumatology introduced classification criteria for 7 forms of vasculitis to provide a standard way to describe groups of patients in therapeutic, epidemiologic, or other studies.[1] This was followed in 1994 by a proposal of uniform terms and definitions for the most common forms of vasculitis at the Chapel Hill Consensus Conference (CHCC; Table I).[2] Although these both represented advancements in standardization for the vasculitic diseases, they were not intended and should not be used for the purposes of diagnosing the individual patient.

PATHOPHYSIOLOGY AND ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

The pathophysiology of the vasculitides remains poorly understood and can vary between different diseases.[3,4] Clinical and laboratory-based evidence has supported the hypothesis that immunologic mechanisms appear to play an active role in mediating the necrotizing inflammation of blood vessels. Although the primary events that initiate this process remain largely unknown, recent investigators have brought us closer to understanding some of the critical pathways involved in disease and provided a rationale for the study of novel therapeutic agents (Table II).

Antineutrophil cytoplasmic antibodies (ANCA) have been a prominent focus of study in the vasculitides, not only for their possible influence in disease pathogenesis but also for their clinical applications. Two types of ANCA have been identified in patients with vasculitis: ANCA directed against the neutrophil serine protease proteinase 3 (PR3), which cause a

From the Center for Vasculitis Care and Research, Department of Rheumatic and Immunologic Diseases, Cleveland Clinic.

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Reprint requests: Carol A. Langford, MD, MHS, Center for Vasculitis Care and Research, Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, 9500 Euclid Ave, A50, Cleveland OH 44195. E-mail: langfoc@ccf.org.

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TABLE I. Names and definitions of vasculitides adopted by the CHCC on the Nomenclature of Systemic Vasculitis

Large-vessel vasculitis	
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches with a predilection for the extracranial branches of the carotid artery: often involves the temporal artery, usually occurs in patients older than 50 y, and often is associated with PMR.
TAK	Granulomatous inflammation of the aorta and its major branches: usually occurs in patients younger than 50 y.
Medium-sized vessel vasculitis	
PAN	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or (classic PAN) vasculitis in arterioles, capillaries, or venules.
Kawasaki disease	Arteritis involving large, medium, and small arteries, and associated with mucocutaneous lymph node syndrome: coronary arteries are often involved, aorta and veins might be involved, and usually occurs in children.
Small-vessel vasculitis	
WG	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels (eg, capillaries, venules, arterioles, and arteries): necrotizing glomerulonephritis is common.
CSS	Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels often associated with asthma and eosinophilia.
MPA	Necrotizing vasculitis with few or no immune deposits affecting small vessels (ie, capillaries, [microscopic polyarteritis] venules, or arterioles): necrotizing arteritis involving small- and medium-sized arteries might be present, necrotizing glomerulonephritis is very common, and pulmonary capillaritis often occurs.
HSP	Vasculitis with IgA-dominant immune deposits affecting small vessels (ie, capillaries, venules, or arterioles): typically involves skin, gut, and glomeruli and is associated with arthralgias or arthritis.
Essential cryoglobulinemic vasculitis	Vasculitis with cryoglobulin immune deposits affecting small vessels (ie, capillaries, venules, or arterioles) and associated with cryoglobulins in serum: skin and glomeruli are often involved.
Cutaneous leukocytoclastic vasculitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

Adapted from Jennette et al.[2]

cytoplasmic immunofluorescence pattern (cANCA) on ethanol-fixed neutrophils, and ANCA directed against the neutrophil enzyme myeloperoxidase (MPO), which result in a perinuclear immunofluorescence pattern (pANCA).[5] Because the methodology of testing can influence the interpretation, ANCA positivity determined by means of indirect immunofluorescence should be corroborated with antigen-specific testing for PR3 and MPO.

The strongest association of a disease with ANCA has been that between Wegener granulomatosis (WG) and PR3-cANCA. Although ANCA have also been described with variable frequency in other vasculitic diseases, in particular microscopic polyangiitis (MPA) and, to a lesser degree, Churg-Strauss syndrome (CSS) (Table III), many forms of vasculitis are not associated with circulating ANCA. ANCA can also be seen in association with other entities, including infection, inflammatory bowel disease, and other connective tissue diseases. In these settings ANCA are typically positive, as determined by means of indirect immunofluorescence, but negative for PR3, MPO, or both, as determined by means of antigen-specific testing, which emphasizes the importance of testing with both methodologies.

In patients with WG, the sensitivity of PR3-cANCA has been reported to be 28% to 92%, whereas specificity has been reproducibly high, ranging from 80% to 100%.[5] This raised the question as to whether ANCA measurement can be used in place of tissue biopsy for diagnosing WG. In patients with sinusitis, an active urine sediment, and pulmonary disease in which infection has been excluded, the predictive value of PR3-cANCA for WG can exceed 90%.[6] However, for other clinical presentations in which the prevalence of WG would be low, the predictive value of ANCAs is insufficient to justify the initiation of toxic therapy in the absence of a tissue diagnosis.

ANCA levels will vary during the course of WG, and from cohort studies, it was observed that patients with active disease had higher levels of ANCA compared with those who were in remission. However, changes in sequential ANCA measurements in an individual patient have not been found to be a reliable disease biomarker. In the largest prospective study published to date, increases in ANCA levels were not associated with relapse, and only 43% relapsed within 1 year of an increase in ANCA levels.[7] Given the toxicity of therapy, an increasing ANCA titer should not be used as the sole basis to start or increase immunosuppressive therapy.

TABLE II. Potential mechanisms of vessel damage in selected primary vasculitis syndromes

Immune complex formation
PAN-like vasculitis associated with hepatitis B
HSP
Cryoglobulinemic vasculitis
Production of ANCA
WG
MPA
CSS
Pathogenic T-lymphocyte responses and granuloma formation
GCA
TAK
WG
CSS

INDIVIDUAL VASCULITIC DISEASES

Giant cell arteritis

Giant cell arteritis (GCA), which has also been known as *temporal arteritis*, is a granulomatous, large-vessel vasculitis that preferentially affects the extracranial branches of the carotid artery.[8] It is the most common form of systemic vasculitis that

TABLE III. Clinical comparison of 4 forms of systemic vasculitis affecting small-sized vessels, medium-sized vessels, or both

Characteristic	WG	MPA	PAN	CSS
Upper airways disease	95%	No	No	50% to 60%
Pulmonary disease				
Asthma	No	No	No	90% to 100%
Radiographic nodule/infiltrates	70% to 85%	15% to 70%	No	40% to 70%
Alveolar hemorrhage	5% to 15%	10% to 50%	No	<5%
Glomerulonephritis	70% to 80%	75% to 90%	No	10% to 40%
Gastrointestinal	<5%	30%	14% to 53%	30% to 50%
Nervous system				
Peripheral	40% to 50%	60% to 70%	38% to 72%	70% to 80%
Central	5% to 10%	10% to 15%	3% to 30%	5% to 30%
Cardiac	10% to 25%	10% to 15%	5% to 30%	10% to 40%
Ocular	50% to 60%	<5%	<5%	<5%
Arthralgia/arthritis	60% to 70%	40% to 60%	50% to 75%	40% to 50%
Genitourinary	<2%	<5%	5% to 10%	<2%
Skin	40% to 50%	50% to 65%	28% to 60%	50% to 55%
ANCA				
PR3-cANCA	75% to 90%	10% to 50%	Rare	3% to 35%
MPO-pANCA	5% to 20%	50% to 80%	Rare	2% to 50%

affects human subjects, with an incidence of 18.8 cases per 100,000 persons in Olmsted County, Minnesota. GCA occurs almost exclusively in persons older than 50 years at a female/male ratio of up to 2:1 and is observed predominantly in persons of European ancestry.

GCA can be thought of as having 4 phenotypes that can occur alone, together, or sequentially and include cranial disease, polymyalgia rheumatica (PMR), systemic inflammatory disease, and large-vessel involvement. The most common presenting symptoms of GCA include headache, jaw or tongue claudication, scalp tenderness, weight loss, or fever (Table IV).[9] PMR, which is characterized by aching and morning stiffness in the proximal muscles of the shoulder and hip girdles, can occur in isolation but is also seen in 40% to 60% of patients with GCA. Cranial ischemic complications can occur as a result of vascular occlusion causing tissue infarction. Of these, the most dreaded complication is vision loss, which can occur in 14% of patients and is caused by optic nerve ischemia from arteritis involving vessels of the ocular circulation. Large-vessel involvement of the aorta or its primary branches occurs in 27% of cases and can present with limb claudication or complications related to an aortic aneurysm.[10]

The suspicion of GCA is raised by clinical features together with an increased erythrocyte sedimentation rate, which occurs in more than 80% of patients. The diagnosis is confirmed by means of temporal artery biopsy, which demonstrates a panmural mononuclear cell infiltration that can be granulomatous with histiocytes and giant cells. To increase yield, the length of the biopsy specimen should be at least 3 to 5 cm and sampled at multiple levels. Temporal artery biopsy specimens are positive in 50% to 80% of cases, and if the first biopsy specimen is negative, consideration should be given to a biopsy of the contralateral artery. In patients strongly suspected of having GCA, treatment should be instituted immediately to protect vision while a prompt temporal artery biopsy is being arranged. Although histologic changes can persist, a temporal artery biopsy should be performed as soon as possible after starting prednisone to obtain the best possible yield.

Glucocorticoids bring about a rapid improvement in cranial and systemic symptoms and prevent visual complications in patients with GCA. In one study the probability of loss of vision was only 1% after starting glucocorticoids.[11] Prednisone is usually initiated at a dose of 40 to 60 mg/d. After an initial dose of 60 mg/d, this can usually be reduced to 50 mg/d after 2 weeks and to 40 mg/d after 4 weeks. After that time, the dose is decreased by approximately 10% of the total daily dose every 1 to 2 weeks.[8] In patients with acute visual loss, 1 g/d methylprednisolone sodium succinate for 3 to 5 days is frequently given to protect remaining vision.[11] Isolated PMR can be effectively treated with 10 to 20 mg/d prednisone, with a rapid response to glucocorticoids being one of the diagnostic hallmarks of this disease.

The desire to identify effective treatment beyond prednisone has come from the recognition that 36% to 85% of patients have 1 or more side effects from this therapy.[12] Aspirin, 81 mg/d, has been found to reduce the risk of cranial ischemic complications and should be given together with prednisone in all patients who do not have a contraindication.[13,14] The ability of methotrexate (MTX) to decrease relapses and lessen glucocorticoids was examined in 2 randomized studies that yielded conflicting results.[15-17] At this time, neither the addition of MTX nor any other cytotoxic agent has been found to be uniformly effective in

TABLE IV. Clinical manifestations of GCA

Manifestation	Patients affected (%)
Headache	68
Weight loss/anorexia	50
Jaw claudication	45
Fever	42
Malaise/fatigue/weakness	40
PMR	39
Other musculoskeletal pain	30
Transient visual symptoms	16
Synovitis	15
CNS abnormalities	15
Fixed visual symptoms	14
Sore throat	9
Swallowing claudication/dysphagia	8
Tongue claudication	6

Adapted from Calamia and Hunder.[9]

FIG 1. Magnetic resonance arteriogram in a patient with Takayasu arteritis demonstrating occlusion of the left subclavian artery coming off the aortic arch and severe stenosis of the left common carotid shortly after its origin from the arch.

reducing the use of prednisone sufficiently to decrease its risk of side effects. Randomized trials in patients with GCA and PMR did not find infliximab to provide benefit, and it is not recommended for use in these diseases.[18,19]

Acute mortality from GCA caused by stroke or myocardial infarction is uncommon, and overall, patients with GCA have a survival rate similar to that of the general population. However, thoracic aortic aneurysms might occur as a late complication of disease and can be associated with rupture and death.[10] Symptomatic relapses requiring increase or reinstitution of prednisone occur in at least 75% of patients.[16] Most patients require glucocorticoids for more than 2 years, with many receiving more than 4 years of treatment.

Takayasu arteritis

Takayasu arteritis (TAK) is a disease that affects the aorta, its main branches, and the pulmonary arteries in which granulomatous vasculitis results in stenosis, occlusion, or aneurysms of affected vessels.[20,21] Although it has been characterized as a disease affecting young women of eastern ethnicity, TAK has been observed throughout the world and can have varying clinical spectrums in different populations.

Patients with TAK can have systemic symptoms, features, or both of vascular injury. Systemic symptoms might be absent in 13% to 80% of patients and include fatigue, malaise, weight loss, night sweats, fever, arthralgias, or myalgias. Vascular symptoms are related to the location and nature of the lesion or lesions and the collateral blood flow. Hypertension occurs in 32% to 93% of patients and contributes to renal, cardiac, and cerebral injury.

A complete aortic arteriogram with visualization of all major branches is important in all patients in whom TAK is being considered as a means of diagnosis and determination of disease extent (Fig 1). The noninvasive nature of magnetic resonance and computed tomographic arteriography has made these modalities useful for serial vascular monitoring in patients with TAK, although catheter-directed dye arteriography remains valuable in providing central blood pressure measurements and precise assessment of luminal dimensions.

Disease activity is typically assessed based on clinical symptoms and signs, the erythrocyte sedimentation rate, and the presence of new arteriographic changes. However, these are not always reliable, and in one surgical series active arteritis was observed in 44% of patients who had been judged quiescent.[20]

Initial treatment of TAK usually consists of 1 mg/kg per day prednisone given for the first 1 to 3 months and then tapered to discontinuation over a 6- to 12-month period. Glucocorticoids relieve systemic symptoms in 25% to 100% of patients and might bring about an improvement in blood flow. Cytotoxic therapy is primarily used in patients who have persistent disease activity despite glucocorticoid treatment or in whom glucocorticoids cannot be tapered. MTX at 15 to 25 mg/wk in combination with glucocorticoids has been found to induce remission and minimize

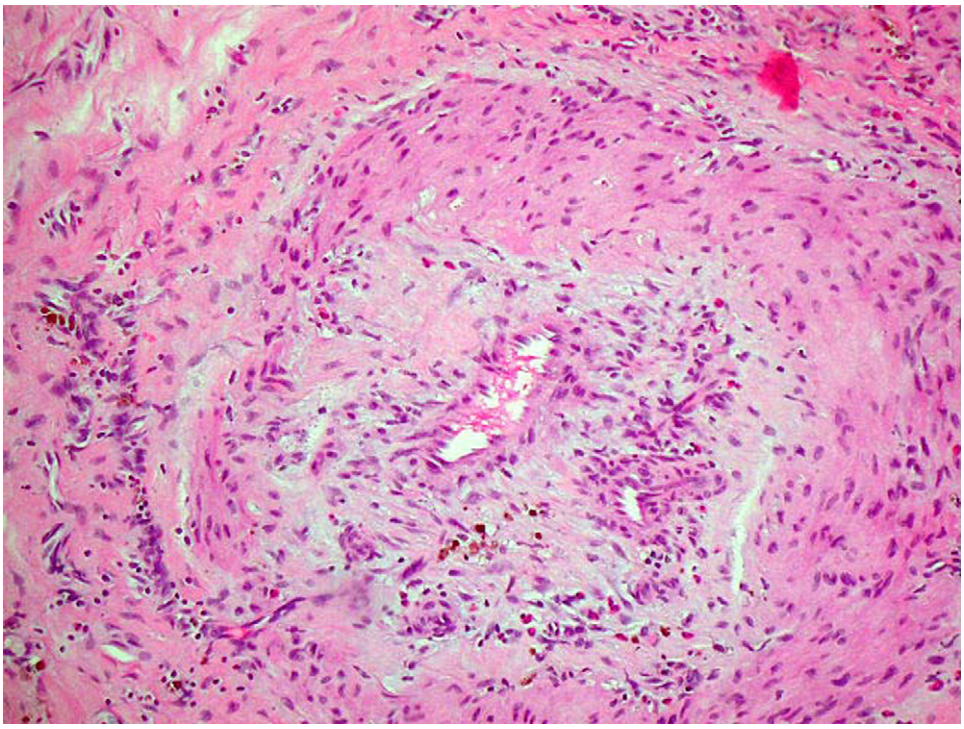

FIG 2. Medium-vessel vasculitis in a patient with PAN.

glucocorticoid therapy and toxicity.[22] Cyclophosphamide (CYC) should be reserved for patients with severe disease who cannot taper glucocorticoids and are unresponsive, intolerant, or unable to take MTX. Pilot studies have demonstrated favorable results with infliximab, but the efficacy of this therapy has not been proved from randomized trials.[23]

Nonmedical interventions have an important role in TAK in treating fixed vascular lesions that produce significant ischemia or aneurysms. The most frequent indications for surgical intervention include cerebral hypoperfusion, renovascular hypertension, limb claudication, repair of aneurysms, or valvular insufficiency. Surgical bypass has had the highest long-term patency rate, with vascular stents and angioplasty often occluding over time.[21] Nonmedical interventions should be performed in the setting of quiescent disease when possible to optimize outcome.

Patients with TAK have a low frequency of acute mortality, with the estimated 15-year survival rate being 83%. Relapses have been observed in 70% to 96% of patients, with sustained remission seen in only 28% of patients.[21]

PAN

Although PAN was the first described form of systemic vasculitis, changes in nomenclature have affected our interpretation of past literature, which included many patients who would now be considered to have MPA under the definitions of the CHCC. PAN, as it is currently defined, is estimated to be an extremely uncommon disease.

The most common clinical manifestations of PAN include hypertension, fever, musculoskeletal symptoms, and vasculitis involving the nerves, gastrointestinal tract, skin, heart, and nonglomerular renal vessels (Table III).[24] PAN is diagnosed by means of biopsy or arteriography. Biopsy specimens reveal necrotizing inflammation involving the medium-sized or small arteries, with abundant neutrophils, fibrinoid changes, and disruption of the internal elastic lamina (Fig 2). Dye arteriography is most often performed to examine the visceral and renal circulation, in which PAN would be suggested by the presence of microaneurysms, stenoses, or a beaded pattern brought about by sequential areas of arterial narrowing and dilation.

Patients with immediately life-threatening PAN affecting the gastrointestinal system, heart, or central nervous system (CNS) should be treated with 2 mg/kg per day CYC and glucocorticoids.[25] In patients in whom the disease manifestations do not pose an immediate threat to life or major organ function, glucocorticoids alone can be considered as initial therapy, with CYC being added in patients who continue to have evidence of active disease or who are unable to taper prednisone. The estimated 5-year survival rate of treated patients with PAN is 80%, with death being influenced by disease severity.[25] Relapses occur in 10% to 20% of patients.[25]

A PAN-like vasculitis can also be seen in patients infected with hepatitis B, hepatitis C, or HIV.[26] In the setting of hepatitis B or C, an antiviral agent should be part of the treatment regimen, with the goal being to contain viral replication and favor seroconversion. Patients might require glucocorticoids, alone or combined with CYC, together with plasmapheresis to initially gain control of the active vasculitis.[26]

WG

WG is a multisystem disease characterized by clinical disease involving the upper and lower respiratory tracts and kidneys with histologic evidence of granulomatous inflammation, vasculitis of the small- to medium-sized vessels, and a

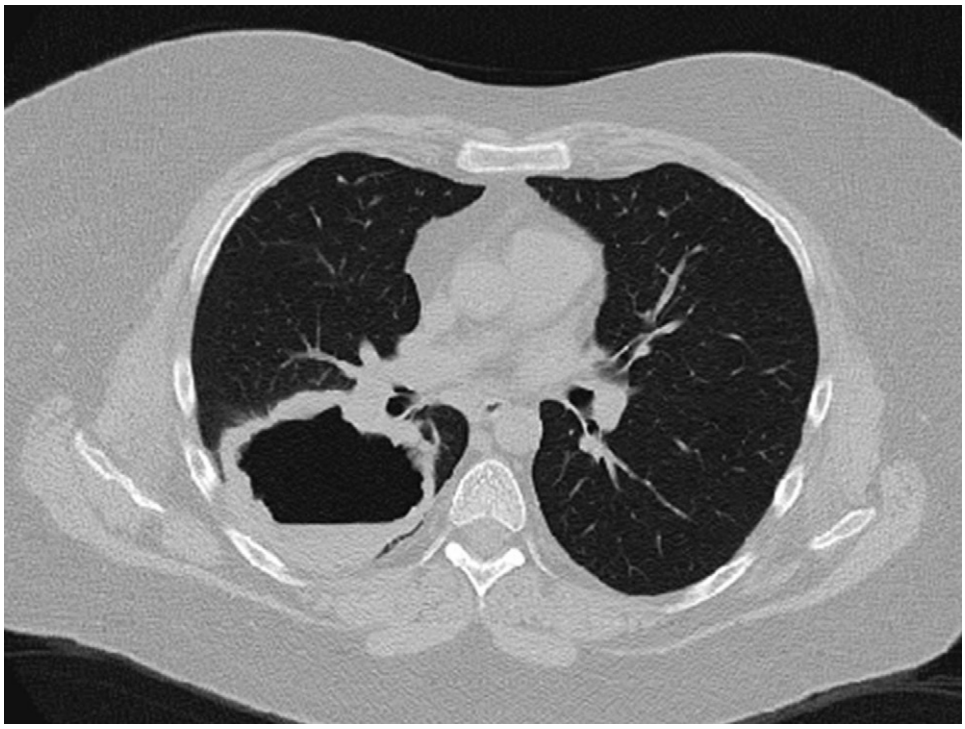

FIG 3. A large cavitary lung nodule seen on a computed tomographic scan in a patient with WG.

pauci-immune glomerulonephritis (Table III).[27] The disease can occur at any age and appears to affect men and women in equal proportions.

More than 90% of patients with WG first seek medical attention for upper airways symptoms, lower airways symptoms, or both. Nasal and sinus mucosal inflammation might result in cartilaginous ischemia with perforation of the nasal septum, saddlenose deformity, or both. Pulmonary radiographic abnormalities can include single or multiple nodules or infiltrates, cavities (Fig 3), and ground-glass infiltrates (Fig 4). Glomerulonephritis is present in 20% of patients at the time of diagnosis but develops in 80% at some point during the disease course. Renal involvement has the potential to be rapidly progressive but is asymptomatic, being detected by the presence of an active urine sediment with dysmorphic red blood cells and red blood cell casts.

The diagnosis of WG is usually based on biopsy results, with nonrenal tissues demonstrating the presence of granulomatous inflammation and necrosis, with necrotizing or granulomatous vasculitis.[27] Surgically obtained biopsy specimens of abnormal pulmonary parenchyma demonstrate diagnostic changes in 91% of cases. Biopsy of the upper airways is less invasive but demonstrates diagnostic features only 21% of the time. The characteristic renal histology is that of a focal, segmental, necrotizing, crescentic glomerulonephritis with few to no immune complexes. The clinical utility of ANCA in patients with WG is discussed in a separate section of this review.

Active WG is potentially life-threatening, and initial treatment requires glucocorticoids combined with a cytotoxic agent. Patients who have active severe WG should initially be treated with 2 mg/kg per day CYC in combination with prednisone at 1 mg/kg per day. After 4 weeks of treatment, if there is improvement, the prednisone is tapered and discontinued by 6 to 12 months. CYC is given for 3 to 6 months, after which time it is stopped and switched to a less toxic medication for remission maintenance. The 2 maintenance agents with which there has been the greatest body of data have been 20 to 25 mg/wk MTX[28] or 2 mg/kg per day azathioprine (AZA),[29,30] with a smaller experience existing with mycophenolate mofetil. In patients who have active but nonsevere disease, prednisone given together with 20 to 25 mg/wk MTX has been found to be effective at inducing and then maintaining remission.[31] In the absence of side effects, maintenance therapy is continued for at least 2 years, after which, if patients remain in remission, consideration can be made on an individual basis for tapering and discontinuation of therapy. In the setting of fulminant disease immediately threatening to life, 1 g/d methylprednisolone sodium succinate can be given in divided doses over a period of 3 days in combination with 3 to 4 mg/kg per day CYC for 3 days, after which time it is reduced to 2 mg/kg per day. Plasmapheresis has also been found to offer benefit in patients with rapidly progressive glomerulonephritis.[32]

Recognition of medication toxicity with strategies for monitoring and prevention play an important role in patient care (Table V).[33] CYC is associated with substantial toxicity, including bone marrow suppression, bladder injury, infertility, myeloproliferative disease, and transitional cell carcinoma of the bladder. Daily CYC should be taken all at once in the morning with a large amount of fluid, with monitoring of complete blood counts every 1 to 2 weeks. MTX should not be given to patients with impaired renal function (creatinine clearance, <35 mL/min) or chronic liver disease. Screening for the thiopurine methyltransferase genotype to detect patients at risk of severe neutropenia has become widely used before AZA initiation.

Recent investigations have explored the role of biologic agents. A randomized trial did not find etanercept to have any beneficial role in the induction or maintenance of WG.[34] A promising preliminary experience has been seen with rituximab (anti-CD20)

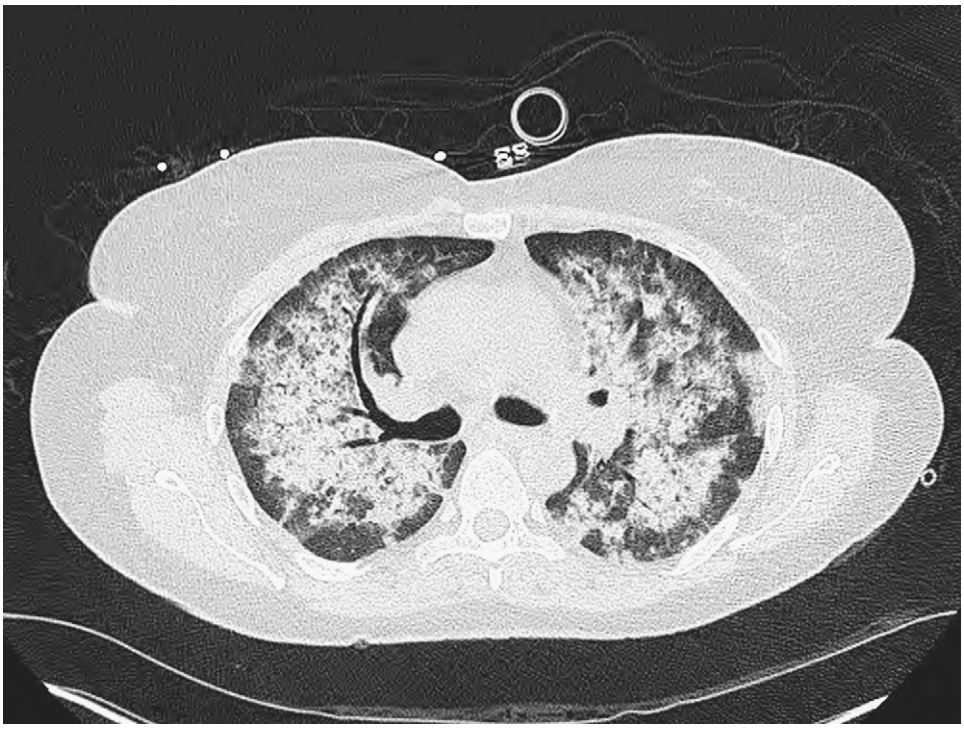

FIG 4. Computed tomographic scan demonstrating bilateral ground-glass infiltrates from alveolar hemorrhage as can occur in WG or MPA.

in patients with active severe WG or MPA.[35] This agent is currently being compared against CYC in a randomized, double-blind, placebo-controlled trial.

Before the development of treatment, patients with WG had a mean survival time of 5 months, with death occurring from pulmonary or renal failure. Current treatment regimens induce remission in 75% to 100% of patients with WG and result in the potential for long-term survival. However, relapse occurs in 50% to 70% of patients,[27] and disease-related organ damage is common.

MPA

As defined by the CHCC, MPA is characterized by necrotizing vasculitis with few or no immune deposits affecting small vessels. MPA has many similarities to WG, which has provided useful insights regarding diagnosis and management.

The cardinal features of MPA include glomerulonephritis, pulmonary hemorrhage (Fig 4), mononeuritis multiplex, and fever (Table III).[36] Approximately 75% to 85% of patients with MPA have circulating MPO-pANCA. The diagnosis of MPA is made by means of biopsy demonstration of necrotizing vasculitis of the small vessels or small- to medium-sized arteries in which granulomatous inflammation is absent. Biopsy specimens of lung tissue in the setting of pulmonary hemorrhage reveal capillaritis, hemorrhage into the alveolar space, and the absence of linear immunofluorescence, as would be seen in antiglomerular basement membrane antibody disease (Goodpasture syndrome). The renal histology is similar to that observed in WG in being a focal segmental necrotizing glomerulonephritis with few to no immune complexes.

Patients with life-threatening disease involving the lung, kidney, or nerve should initially be treated with 2 mg/kg per day CYC and 1 mg/kg per day prednisone, according to the schedule outlined for WG, followed by AZA or MTX for remission maintenance.[29,30] Patients with active nonsevere disease can be treated with MTX for remission and maintenance.[31]

In one series the estimated 5-year survival rate of MPA was 74%.[36] Like WG, MPA is a relapsing disease, with recurrences developing in at least 38% of patients.

CSS

CSS is a rare disease characterized by asthma, fever, hypereosinophilia, and systemic vasculitis.[37,38] It has been estimated to affect about 3 persons per million and has been observed in all ages equally between sexes.

CSS has been thought of as having 3 phases: a prodromal phase with allergic rhinitis and asthma, a phase characterized by peripheral eosinophilia and eosinophilic tissue infiltrates, and, ultimately, vasculitic disease that can involve the nerve, lung, heart, gastrointestinal tract, and kidney (Table III).[37] Although these phases are conceptually helpful, they might not be clinically identifiable in all patients, and they often do not occur in sequence. The histologic features of CSS include eosinophilic tissue infiltrates, extravascular "allergic" granuloma, and small-vessel necrotizing vasculitis. Vasculitis can be difficult to definitively establish, making clinical manifestations of particular importance in the diagnosis of CSS.

Prednisone, 1 mg/kg per day, is effective for many manifestations of CSS.[39] Asthma often persists after remission of the vasculitis and might limit the ability for pred to be tapered to complete discontinuation. Patients with life-threatening disease should be treated with glucocorticoids and 2 mg/kg per day CYC, as would be given for WG.[25]

Prognosis is influenced by the presence of severe disease involving sites such as the heart, gastrointestinal tract, CNS, and kidney.[37] CSS is characterized by frequent exacerbations of asthma, and relapses of vasculitic disease occur in at least 26%.[37]

Cutaneous vasculitis

Cutaneous vasculitis is the most commonly encountered vasculitic manifestation in clinical practice. Lesions most commonly consist of palpable purpura, although nodules and ulcerative lesions are also seen. Cutaneous vasculitis is histologically characterized by the presence of small-vessel inflammation within the dermis, often with leukocytoclasis.[40,41] Involvement of medium-sized vessels might be seen in cutaneous PAN.

In more than 70% of cases, cutaneous vasculitis occurs in the setting of an underlying process, such as a medication exposure, infection, malignancy, or connective tissue disease, or as a manifestation of a primary systemic vasculitis. A diagnosis of idiopathic cutaneous vasculitis should only be made after other causes have been ruled out. The course of idiopathic cutaneous vasculitis ranges from a single episode to multiple protracted recurrences. Progression to systemic vasculitis occurs infrequently.

If an underlying disease or exposure is identified, management of this process forms the primary basis for treating the cutaneous vasculitis. The therapeutic principle for idiopathic cutaneous vasculitis should be to use the least toxic yet effective regimen because there have been no standardized trials in this disease setting. Glucocorticoids are frequently used, but there remains no optimal dosage schedule. Other agents with which there has been anecdotal experience include nonsteroidal anti-inflammatory agents, antihistamines, dapsone, hydroxychloroquine, and colchicine. Cytotoxic agents should be reserved for select cases in which patients have severe disease that is unresponsive to other measures or when glucocorticoids cannot be tapered. CYC should rarely, if ever, be used to treat isolated cutaneous vasculitis.

Cryoglobulinemic vasculitis

Cryoglobulins are cold-precipitable monoclonal or polyclonal immunoglobulins that can occur in conjunction with a variety of diseases, including plasma cell or lymphoid neoplasms, chronic infection, and inflammatory diseases.[42] With the discovery of the hepatitis C virus (HCV), it became established that the majority of cases of cryoglobulinemia are related to HCV infection.[43] Cryoglobulinemia can be associated with a vasculitic illness characterized by palpable purpura, arthritis, weakness, neuropathy, and glomerulonephritis.[42] Although the presence of glomerulonephritis is associated with an overall poor prognosis, progression to end-stage renal failure is uncommon.

Combined therapy with IFN-α and ribavirin provide the best opportunity for improvement of HCV-associated cryoglobulinemic vasculitis, but long-term resolution is confined to patients who have a sustained virologic response.[44] Plasmapheresis has been used with brief responses but is not practical for long-term management. Glucocorticoids, CYC, AZA, and MTX have been applied, particularly in the case of severe disease.[44,45] Treatment with immunosuppressive drugs might transiently improve the inflammatory manifestations of cryoglobulinemic vasculitis but might also lead to an increase in HCV viremia. Although favorable results have been seen in case series with the use of rituximab, randomized controlled trials are needed to determine its efficacy.

TABLE V. Suggested toxicity laboratory monitoring schedule for prominent medications that are used in the treatment of certain vasculitides

Agent	Frequency	Investigation
Cyclophosphamide	Every 1-2 wk	CBC with differential Serum creatinine ESR Urinalysis
	Every 6-12 mo (even after treatment has been discontinued)	Urine cytology
Methotrexate	Every week during dose escalation and every 4 wk thereafter	CBC with differential Serum creatinine LFTs ESR Urinalysis
Azathioprine or mycophenolate mofetil	Every week for the first month, every 2 wk for the second month, and every 4 wk thereafter	CBC with differential Serum creatinine LFTs ESR Urinalysis

CBC, Complete blood count; *ESR*, erythrocyte sedimentation rate; *LFTs*, liver function tests.

Henoch-Schönlein purpura

Henoch-Schönlein purpura (HSP) is a small-vessel vasculitis that predominantly affects children.[46] Although adults can have HSP, 75% of cases occur before the age of 8 years. Two thirds of patients report an antecedent upper respiratory tract infection, although no predominant organism has been identified.

The 4 cardinal features of HSP are palpable purpura, arthritis, gastrointestinal involvement, and glomerulonephritis. Gastrointestinal manifestations include colicky abdominal pain, vomiting, and potentially intussusception. Renal disease, most often characterized by hematuria and proteinuria, is seen in 20% to 50% of affected children, with 2% to 5% progressing to end-stage renal failure. Less is known about HSP in adults, although several studies suggest that glomerulonephritis might be more severe and lead to renal insufficiency in up to 13% of cases.

The diagnosis of HSP is established by the pattern of clinical manifestations but can be less certain when other features precede the skin lesions. Skin biopsy reveals leukocytoclastic vasculitis with IgA deposition in blood vessel walls but is not required in most instances. Renal biopsy is rarely necessary for diagnosis but might have prognostic utility.

HSP is typically a self-limited condition that often does not require treatment. Glucocorticoids can lessen tissue edema, arthritis, and abdominal discomfort and decrease the rate of intussusception. However, they are of no proved benefit in skin or renal disease and do not appear to shorten the duration or lessen the likelihood of relapse.[47] Uncontrolled studies suggest that glucocorticoids in combination with a cytotoxic agent might be beneficial in patients with active glomerulonephritis and progressive renal insufficiency.

Outcome in patients with HSP is excellent, with disease-related death occurring in 1% to 3% of cases. Relapse occurs in up to 40% of cases, often within the first 3 months after the initial episode.

Kawasaki disease

Kawasaki disease is an acute vasculitis of childhood and represents the primary cause of acquired heart disease in children from the United States and Japan.[48] Eighty percent of children with Kawasaki disease are less than 5 years old, and boys are affected 1.5 times more often than girls.

Kawasaki disease begins as an acute febrile illness that is followed within 1 to 3 days by rash, conjunctival injection, and oral mucosal changes. Extremity changes characterized by brawny induration occur early in the disease, and 50% to 75% have cervical adenopathy. Together with fever, these 5 features constitute the criteria on which the diagnosis is based. Coronary artery lesions are responsible for most of the disease-related morbidity and mortality that occurs in patients with Kawasaki disease. Aneurysms appear 1 to 4 weeks after the onset of fever and develop in up to 25% of affected children who do not receive intravenous immunoglobulin.

Intravenous immunoglobulin, 2 g/kg, has been shown to prevent coronary aneurysm formation, lessen fever, and reduce myocardial inflammation.[49] Aspirin, 80 to 100 mg/kg per day, is given concurrently. An echocardiogram should be obtained at diagnosis and then at 2, 6, and 8 weeks to monitor for the development of coronary aneurysms. Children with multiple aneurysms, giant aneurysms, or coronary artery obstruction require close follow-up with serial ultrasonographic monitoring into adulthood and possible long-term anticoagulation.

Kawasaki disease has been reported to have a 3% mortality rate. Recurrences can develop in 1% to 3% of patients.

Behçet disease

Behçet disease is a multisystem inflammatory disease with manifestations that can affect arteries and veins of all sizes.[50,51] It occurs most commonly in 20- to 35-year-old persons of Asian and Eastern Mediterranean descent, with a male predominance in some ethnic populations.

Behçet disease is characterized by recurrent aphthous oral ulcers and at least 2 or more of the following: recurrent genital ulceration, eye lesions, cutaneous lesions, or a positive pathergy test result.[52] Among the most severe manifestations are gastrointestinal inflammation and ulceration, ocular inflammation that can lead to blindness, CNS disease with meningoencephalitis, and vascular involvement. Large venous or arterial lesions occur in 7% to 38% of patients and might include vessel thrombosis and occlusion, as well as pulmonary or peripheral artery aneurysms.

Treatment of Behçet disease is based on the disease manifestations. Aphthous lesions and mucocutaneous disease can be treated with topical or intralesional glucocorticoids, dapsone, or colchicine. Ocular and CNS disease require aggressive immunosuppression, with cyclosporine, AZA, and chlorambucil being the most commonly used agents. Preliminary studies have suggested favorable results with anti-TNF agents in patients with severe ocular inflammation.

Death occurs in 4% of patients with Behçet disease, generally as the result of gastrointestinal perforation, vascular rupture, and CNS disease. Behçet disease has the ability to remit and relapse frequently.

Primary angiitis of the CNS

Primary angiitis of the CNS (PACNS) is an uncommon disease in which patients have vasculitis isolated to the CNS without evidence of systemic vasculitis.[53,54] Granulomatous angiitis of the CNS (GACNS) represents about 50% of cases of PACNS and is a progressive disease that clinically presents with focal neurological deficits, chronic headache, or alterations in higher cortical function. More than 90% of patients with GACNS will have abnormal cerebrospinal fluid with mononuclear pleocytosis and increased protein with normal glucose levels. Results of magnetic resonance imaging are almost always abnormal, reflecting multifocal vascular insults of different ages. A cerebral arteriogram can reveal stenoses and ectasia in up to 40% of patients. Biopsy of tissue from the CNS is the diagnostic modality of choice, but results can be falsely negative in up to one fifth of patients. The diagnostic yield might be increased by taking biopsy specimens of both the leptomeninges and the underlying cortex.

In all instances a careful search must be made for processes of similar appearance, including atherosclerosis, infection, neoplasms, and drug-induced changes. An important diagnosis to distinguish from PACNS is reversible cerebral vasoconstrictive syndrome, which is characterized by a sudden onset of severe headache (thunderclap headache) with arteriographic cerebrovascular changes that have a similar appearance to vasculitis but that normalize within 12 months.[55]

GANCS is characteristically a fatal and progressive disorder but can respond to 1 mg/kg per day prednisone and 2 mg/kg per day CYC. For the 50% of patients with PACNS who do not have GACNS, treatment is based on the severity of disease manifestations and the rate of progression.

REFERENCES

1. Hunder GG, Arend WP, Bloch DA, Calabrese LH, Fauci AS, Fries JF, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. Arthritis Rheum 1990;33:1065-7.
2. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994;37:187-92.
3. Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. N Engl J Med 2003;349:160-9.
4. Kallenberg CG. Pathogenesis of PR3-ANCA associated vasculitis. J Autoimmun 2008;30:29-36.
5. Bosch X, Guilabert A, Font J. Antineutrophil cytoplasmic antibodies. Lancet 2006; 368:404-18.
6. Langford CA. The diagnostic utility of c-ANCA in Wegener's granulomatosis. Cleve Clin J Med 1998;65:135-40.
7. Finkielman JD, Merkel PA, Schroeder D, Hoffman GS, Spiera R, St Clair EW, et al. Antiproteinase 3 antineutrophil cytoplasmic antibodies and disease activity in Wegener granulomatosis. Ann Intern Med 2007;147:611-9.
8. Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med 2002;347:261-71.
9. Calamia KT, Hunder GG. Clinical manifestations of giant cell (temporal) arteritis. Clin Rheum Dis 1980;6:389-403.
10. Nuenninghoff DM, Hunder GG, Christianson TJ, McClelland RL, Matteson EL. Mortality of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum 2003;48:3532-7.
11. Aiello PD, Trautmann JC, McPhee TJ, Kunselman AR, Hunder GG. Visual prognosis in giant cell arteritis. Ophthalmology 1993;100:550-5.
12. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. Arthritis Rheum 2003; 49:703-8.
13. Nesher G, Berkun Y, Mates M, Baras M, Rubinow A, Sonnenblick M. Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. Arthritis Rheum 2004;50:1332-7.
14. Lee MS, Smith SD, Galor A, Hoffman GS. Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. Arthritis Rheum 2006;54:3306-9.
15. Jover JA, Hernandez-Garcia C, Morado IC, Vargas E, Banares A, Fernandez-Gutierrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2001;134:106-14.

16. Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum 2002;46:1309-18.
17. Mahr AD, Jover JA, Spiera RF, Hernandez-Garcia C, Fernandez-Gutierrez B, Lavalley MP, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. Arthritis Rheum 2007;56: 2789-97.
18. Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. Ann Intern Med 2007;146:621-30.
19. Salvarani C, Macchioni P, Manzini C, Paolazzi G, Trotta A, Manganelli P, et al. Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized trial. Ann Intern Med 2007;146:631-9.
20. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. Ann Intern Med 1994;120:919-29.
21. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum 2007;56:1000-9.
22. Hoffman GS, Leavitt RY, Kerr GS, Rottem M, Sneller MC, Fauci AS. Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with methotrexate. Arthritis Rheum 1994;37:578-82.
23. Molloy ES, Langford CA, Clark TM, Gota CE, Hoffman GS. Anti-tumour necrosis factor therapy in patients with refractory Takayasu arteritis: long-term follow-up. Ann Rheum Dis 2008;67:1567-9.
24. Mouthon L, Le Toumelin P, Andre MH, Gayraud M, Casassus P, Guillevin L. Polyarteritis nodosa and Churg-Strauss angiitis: characteristics and outcome in 38 patients over 65 years. Medicine (Baltimore) 2002;81:27-40.
25. Gayraud M, Guillevin L, le Toumelin P, Cohen P, Lhote F, Casassus P, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum 2001;44:666-75.
26. Guillevin L, Mahr A, Callard P, Godmer P, Pagnoux C, Leray E, et al. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. Medicine (Baltimore) 2005;84:313-22.
27. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116: 488-98.
28. Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's granulomatosis: extended follow-up and rate of relapse. Am J Med 2003;114: 463-9.
29. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36-44.
30. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008;359:2790-803.
31. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461-9.
32. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007;18:2180-8.
33. Nataraja A, Mukhtyar C, Hellmich B, Langford C, Luqmani R. Outpatient assessment of systemic vasculitis. Best Pract Res Clin Rheumatol 2007;21:713-32.
34. Wegener's Granulomatosis Etanercept Trial Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352:351-61.
35. Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:262-8.
36. Guillevin L, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Callard P, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum 1999;42:421-30.
37. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore) 1999;78:26-37.
38. Keogh KA, Specks U. Churg-Strauss syndrome. Semin Respir Crit Care Med 2006; 27:148-57.
39. Ribi C, Cohen P, Pagnoux C, Mahr A, Arene JP, Lauque D, et al. Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients. Arthritis Rheum 2008;58:586-94.
40. Chen KR, Carlson JA. Clinical approach to cutaneous vasculitis. Am J Clin Dermatol 2008;9:71-92.
41. Gibson LE. Cutaneous vasculitis update. Dermatol Clin 2001;19:603-15, vii.
42. Lamprecht P, Gause A, Gross WL. Cryoglobulinemic vasculitis. Arthritis Rheum 1999;42:2507-16.
43. Cacoub P, Saadoun D. Hepatitis C virus infection induced vasculitis. Clin Rev Allergy Immunol 2008;35:30-9.
44. Saadoun D, Delluc A, Piette JC, Cacoub P. Treatment of hepatitis C-associated mixed cryoglobulinemia vasculitis. Curr Opin Rheumatol 2008;20:23-8.
45. Vassilopoulos D, Calabrese LH. Hepatitis C virus infection and vasculitis: implications of antiviral and immunosuppressive therapies. Arthritis Rheum 2002;46: 585-97.
46. Saulsbury FT. Henoch-Schonlein purpura in children. Report of 100 patients and review of the literature. Medicine (Baltimore) 1999;78:395-409.
47. Meadow SR, Glasgow EF, White RHR, Moncrieff MW, Cameron JS, Ogg CS. Schonlein-Henoch nephritis. QJM 1972;41:241-58.
48. Barron KS, Shulman ST, Rowley A, Taubert K, Myones BL, Meissner HC, et al. Report of the National Institutes of Health Workshop on Kawasaki Disease. J Rheumatol 1999;26:170-90.
49. Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N Engl J Med 1991;324:1633-9.
50. Calamia KT, Kaklamanis PG. Behcet's disease: recent advances in early diagnosis and effective treatment. Curr Rheumatol Rep 2008;10:349-55.
51. Yurdakul S, Yazici H. Behcet's syndrome. Best Pract Res Clin Rheumatol 2008;22: 793-809.
52. International Study Group for Behcet's Disease. Criteria for diagnosis of Behcet's disease. Lancet 1990;335:1078-80.
53. Hajj-Ali RA, Calabrese LH. Central nervous system vasculitis. Curr Opin Rheumatol 2009;21:10-8.
54. Salvarani C, Brown RD Jr, Calamia KT, Christianson TJ, Weigand SD, Miller DV, et al. Primary central nervous system vasculitis: analysis of 101 patients. Ann Neurol 2007;62:442-51.
55. Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative review: reversible cerebral vasoconstriction syndromes. Ann Intern Med 2007;146:34-44.