Concise Clinical Review

The Pulmonary Vasculitides

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The pulmonary vasculitides are a rare group of heterogeneous disorders unified by the histopathologic finding of inflammation and destruction of the blood vessel wall. Diagnosis of these disorders is exceptionally challenging, given their highly variable clinical presentation, their relative rarity, and the overlap of the signs and symptoms of vasculitis with much more common entities. However, advances in the management of vasculitis allow for accurate diagnosis, risk stratification in the individual patient, and the implementation of evidence-based, effective pharmacologic therapies. This concise clinical review addresses the diagnosis and management of the patient with pulmonary vasculitis and provides an up-to-date review of the state of the field.

Keywords: vasculitis; Churg-Strauss; granulomatosis with polyangiitis (Wegener's); alveolar hemorrhage

The vasculitides are a heterogeneous group of disorders unified by the histopathologic finding of "vasculitis," or inflammation and necrosis of the blood vessel wall. Clinically, pulmonary vasculitis may present in a variety of ways including alveolar hemorrhage, pulmonary nodules, cavitating lesions, or airway disease depending on both the specific underlying disorder and the particular manifestations that develop in the individual patient. The pulmonary vasculitides may be organized by the size of vessel predominantly affected (e.g., small, medium, and large vessel vasculitis) as well as by the pathophysiologic mechanism of the disorder (e.g., pauci-immune or immune complex–mediated disease). Ultimately, it is the small vessel anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitides that most commonly affect the lung, and hence, it is the ANCA-associated vasculitides (AAVs) of granulomatosis with polyangiitis (GPA) (the entity formerly known as Wegener's granulomatosis), Churg-Strauss syndrome (CSS), microscopic polyangiitis (MPA), and idiopathic pauci-immune pulmonary capillaritis (IPIPC) that are the main focus of this review.

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EPIDEMIOLOGY

Pulmonary vasculitis is rare. The incidence of AAV is only 15–20 cases per million per year, which translates into a prevalence of 90–300 cases per million (1–4). GPA is more common than either MPA or CSS in European and North American populations, with an incidence of 8–10 cases per million per year, but data from Japan and China suggest a relatively higher rate of MPA and lower rate of GPA in Asian populations (5–9). CSS is even less frequent, with an incidence of 1–3 cases per million per year and a prevalence of 10–15 cases per million (3, 7, 10, 11). The increased incidence of vasculitis among family members of affected patients and its associations with HLA and other immune response genes suggest a genetic component to the disease (12). Long-term follow-up from patients enrolled in European Vasculitis Study Group (EUVAS) clinical trials has shown that the 1-, 2-, and 5-year survival rates of patients with AAV are 88, 85, and 78%, respectively, which translates into a mortality risk of 2.6 when compared with the general population (13). Poor prognostic factors for long-term survival include advanced age, higher degrees of disease activity, alveolar hemorrhage, cardiac involvement, and proteinase-3 positivity.

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of the patient with vasculitis is highly variable and the diagnosis of vasculitis is exceptionally challenging. Although the 1990 American College of Rheumatology and 1994 Chapel Hill Consensus Conference criteria for the classification of the vasculitis have been validated and widely accepted, they are not intended to be used as diagnostic criteria and perform poorly when used as such (14–17). The diagnosis of vasculitis is a clinical diagnosis that requires the clinician caring for the patient to integrate clinical, laboratory, radiographic, and histopathologic data and make a determination that the preponderance of the data supports or does not support a diagnosis of vasculitis. Hence, it is important that the clinician making this determination be familiar with the common clinical features of each of the pulmonary vasculitides as well as the competing diagnostic considerations (Table 1).

Clinical scenarios that may prompt consideration of small vessel vasculitis, especially GPA or MPA, include (*1*) alveolar hemorrhage, (*2*) tracheal or subglottic stenosis, (*3*) pulmonary nodules or cavities (especially once malignancy and infection have been excluded), (*4*) glomerulonephritis, (*5*) destructive or ulcerating upper airway disease, (*6*) mononeuritis multiplex, (*7*) retro-orbital mass, and (*8*) palpable purpura (18, 19). Consideration of CSS may also be prompted by the development of severe or refractory maturity-onset asthma with or without peripheral eosinophilia or the identification of eosinophilic parenchymal infiltrates.

Granulomatosis with polyangiitis (the entity previously known as Wegener's granulomatosis) (20) commonly affects the upper airways, tracheobronchial tree, and pulmonary parenchyma.

TABLE 1. CLINICAL MANIFESTATIONS OF PULMONARY VASCULITIS

Manifestations	GPA	MPA	CSS	IPIPC
Upper airway	⩾85%. May include epistaxis, destructive and ulcerating lesions, otitis, sinusitis, and mastoiditis	⩽15%	70–90%. Commonly manifests as rhinitis and sinusitis	Not characteristic
Asthma and airways	Approximately 60%. Manifestations include subglottic or tracheal stenosis, airway narrowing, ulcerations, endobronchial lesions, stenosis, or occlusion	Not characteristic	>95% present with asthma. Variable severity, but commonly steroid-requiring	Not characteristic
Nodules, cavities, and infiltrates	>80% will have focal consolidation, infiltrates, atelectasis, nodules, cavities, or other abnormalities. 40–70% will have nodules and/or cavities. Easily confused with infection or malignancy	Up to 30% will have infiltrates, often reflecting the presence of alveolar hemorrhage	70% by plain film and up to 90% by HRCT. Commonly appears as patchy, bilateral, heterogeneous disease with areas of ground-glass appearance and consolidation	Infiltrates seen in association with alveolar hemorrhage
Alveolar hemorrhage	5–10%	10–30%	Rare	100%
Thromboembolic disease	7 cases per 100 person-years. Comparable to patients with a known history of VTE	Unknown incidence	Unknown incidence	Unknown incidence
Infection	Common cause of morbidity and mortality	*See* GPA	*See* GPA	*See* GPA
Drug toxicity	Pulmonary toxicity most commonly with methotrexate but may also be seen with other immunosuppressive agents	*See* GPA	*See* GPA	*See* GPA
Extrapulmonary disease	Constitutional symptoms 50–90% GN 40–90% Cutaneous disease 45–60% Musculoskeletal disease 30–70% Ocular involvement 25–50% Cardiac involvement 5–15%	Constitutional symptoms > 90% GN 100% Musculoskeletal disease > 50% PNS 10–50% GI disease 35–45% Cardiac involvement 10–20%	Constitutional symptoms 50–90% Musculoskeletal disease > 50% Cutaneous disease 40–70% PNS > 50% GI disease 30–50% Cardiac involvement 30–50%	Generally considered a lung-limited disorder, but constitutional symptoms and other nonspecific findings may be seen

Definition of abbreviations: CSS = Churg-Strauss syndrome; GI = gastrointestinal; GN = glomerulonephritis; GPA = granulomatosis with polyangiitis; IPIPC = idiopathic pauci-immune pulmonary capillaritis; MPA = microscopic polyangiitis; PNS = peripheral nervous system; VTE = venous thromboembolic disease.
Sources: References 22–25, 30, 31, 33, and 72–77.

Upper respiratory tract involvement is quite common (>85%) and presents as otitis, hearing loss, sinusitis, epistaxis, septal perforation, mastoiditis, or the "classic" saddle nose deformity. The lower respiratory tract is similarly involved in a majority of patients (>80%) and will frequently manifest with cough, dyspnea, chest discomfort, hemoptysis, alveolar hemorrhage, pulmonary nodules, cavities, or infiltrates (Figure 1). Tracheobronchial disease, although less common than parenchymal disease, still occurs in 50–60% of patients. Constitutional symptoms frequently accompany or precede disease onset. Common target organs outside the lung include the kidney, skin, eyes, joints, muscles, nervous system, and heart (21–25).

MPA is characterized by profound constitutional symptoms and glomerulonephritis. Pulmonary involvement is less frequent than in GPA and CSS; however, 10–30% of patients will develop diffuse alveolar hemorrhage, and as such, will have life-threatening pulmonary disease (Figure 2) (26, 27). Other pulmonary complications of MPA may include radiographic infiltrates, pulmonary artery aneurysms, fibrotic changes, and airway disease.

Churg-Strauss syndrome (CSS) is typically characterized by the triad of asthma, eosinophilia, and vasculitis. Alternatively, CSS is described as having three progressive phases, namely, (*1*) a prodromal "allergic/atopic" phase of asthma and rhinosinusitis, (*2*) an eosinophilic phase in which eosinophil-rich inflammatory tissue infiltrates develop, and (*3*) a vasculitic phase that presents with manifestations common to AAV such as palpable purpura or mononeuritis multiplex (28–33). Asthma in CSS commonly precedes the onset of the vasculitis phase (7–8 yr on average) and is often severe, frequently requiring oral corticosteroids. Upper airway involvement occurs in 70–90% of patients and is generally characterized by chronic rhinosinusitis, with or without nasal polyposis, often lacking the destructive features found in patients with GPA. Chest imaging demonstrates abnormalities in 70–90% of patients with CSS, most commonly patchy, bilateral, heterogeneous, migratory infiltrates combined with features of airway disease (34). Extrapulmonary manifestations of CSS may include constitutional symptoms, mononeuritis multiplex, cutaneous lesions, glomerulonephritis, and cardiac involvement. The cardiac involvement is of particular importance as roughly half of the attributable mortality in CSS is due to cardiac complications that include cardiomyopathy, myocarditis, coronary arteritis, conduction delays, and sudden death.

Idiopathic pauci-immune pulmonary capillaritis (IPIPC) is an isolated small vessel vasculitis that by definition is isolated to the lungs and, hence, presents with diffuse alveolar hemorrhage as its primary clinical manifestation (35, 36). In a case series of 29 patients who presented with diffuse alveolar hemorrhage, 8 of these patients (28%) were found to have IPIPC (35). Clinically, the entity appears to behave as a "lung-limited MPA," and as such, decisions regarding the management of IPIPC are extrapolated from the AAV experience and data.

As with all complex diseases, the evaluation of the patient with suspected vasculitis begins with a comprehensive history and physical examination to identify all the potential signs and symptoms that the patient may be experiencing and that may contribute to the final diagnosis. Competing diagnostic considerations often include complex systemic illnesses including infections (or postinfection complications), malignancy, drug reactions, and primary rheumatologic diseases. The review of systems is exceptionally important, as patients will not necessarily draw connections to seemingly unrelated problems. Laboratory testing generally includes a complete blood count, renal function, liver function, urinalysis with sediment examination,

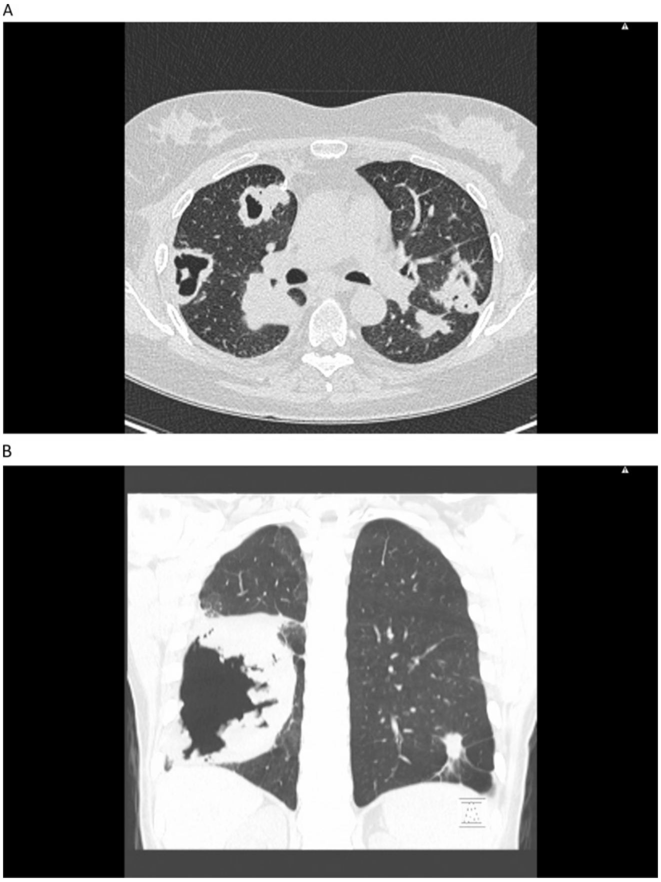

Figure 1. (*A*) High-resolution computed tomography (HRCT) demonstrating multiple pulmonary cavitary lesions in a patient with granulomatosis with polyangiitis (GPA). (*B*) HRCT demonstrating right lower lobe consolidation, necrosis, and cavitation in a patient with GPA. Also note the nodule in the left lower lobe with traction on the surrounding lung.

electrocardiogram, connective tissue disease serologies, and anti-neutrophil cytoplasmic antibody (ANCA) testing.

ANCAs are neutrophil-specific autoantibodies that play a critical role in the pathogenesis of ANCA-associated vasculitis. ANCAs promote neutrophil migration to and degranulation in the vessel wall, resulting in the release of reactive oxygen species, proteases, and other toxic metabolites (37–39). Animal models have further demonstrated that these antibodies are capable of producing disease characterized by glomerulonephritis and pulmonary vasculitis (40, 41). Clinically, ANCA titers have been shown to correlate with disease activity (although a rise in ANCA titers alone is not sensitive or specific for predicting impending relapse) (42). To date, three ANCA staining patterns have been characterized on indirect immunofluorescence: cytoplasmic, perinuclear, and atypical, designated as c-ANCA, p-ANCA, and a-ANCA, respectively. c-ANCAs are associated with specific autoantibodies directed against proteinase-3 (PR3), and autoantibodies against proteinase-3 may be measured via a separate ELISA. Both c-ANCA and PR-3 antibodies are closely associated with GPA with 85–90% sensitivity and 95% specificity for generalized active disease (43, 44). Patients with limited disease or who are in disease remission may still be ANCA positive, but at significantly lower rates (60 and 40%, respectively) (45).

p-ANCAs are associated with MPA and CSS, but are less specific than c-ANCA, and may be seen in a number of other

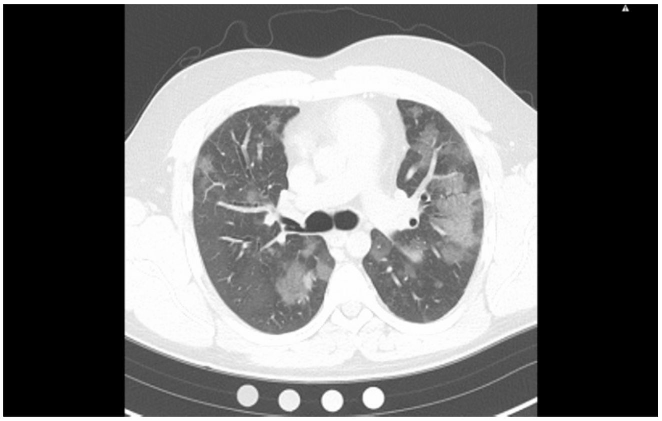

Figure 2. High-resolution computed tomography demonstrating heterogeneous, bilateral, ground-glass infiltrates suggestive of diffuse alveolar hemorrhage.

autoimmune diseases. Although p-ANCAs are commonly associated with autoantibodies directed against myeloperoxidase, which may also be measured directly via ELISA testing, they have also been associated with autoantibodies against other antigens. p-ANCA/myeloperoxidase positivity has a sensitivity of 50–75% for MPA and 35–50% for CSS (46, 47). Thus, a positive test is helpful, but a negative test does not exclude the disease. Indeed, ANCA-associated vasculitis need not be associated with a positive ANCA in any individual patient.

Imaging studies are useful in both the diagnosis of vasculitis and in fully characterizing disease manifestations in a given patient. Imaging studies are guided by the clinical manifestations identified in an individual patient and by the established patterns of target organ involvement specific to a given disease entity. As such, high-resolution computed tomography (HRCT) of the chest, CT of the sinuses, and echocardiography are central to the evaluation of most patients with pulmonary vasculitis. Additional imaging studies are dictated by the clinical scenario.

The role of bronchoscopy in the evaluation in pulmonary vasculitis is targeted to (*1*) the identification of diffuse alveolar hemorrhage, (*2*) the diagnosis of lower respiratory tract infections, and (*3*) assessment of the large airways for complications such as stenosis or endobronchial lesions. Transbronchial biopsies rarely provide a positive diagnosis of pulmonary vasculitis as diagnostic tissue is seldom obtained (48).

Although the presence of a compelling clinical, radiologic, and serologic profile may be sufficient to diagnosis vasculitis, histopathologic evidence of vasculitis is frequently required to confirm a suspected diagnosis. Biopsy of the skin or sinuses is relatively safe and straightforward, but is less likely to yield a definitive diagnosis than the more invasive renal biopsy or surgical lung biopsy (49). Surgical lung biopsy (video assisted) is a high-yield procedure that permits accurate diagnosis in the majority of cases. Close coordination between providers is required to ensure that the sample is processed to obtain as much information as possible including frozen sections for immunofluorescence studies, samples in saline for microbiological culture, and formalin-fixed tissue for histology.

TREATMENT

The pharmacologic treatment of vasculitis necessitates the use of cytotoxic medications and systemic corticosteroids. As such, the pharmacologic therapies for vasculitis carry significant risk for drug-associated adverse effects. Thus, the intensity of the immunosuppressive regimen should be based on disease activity. To this end, management is commonly divided into two phases: (*1*) an induction of remission phase, in which more aggressive therapies are used to induce remission of an active vasculitis, and (*2*) a maintenance of remission phase in which therapy is deescalated to reduce the potential for adverse side effects but is still sufficient to keep the disease in remission. Induction therapies are further tailored to disease severity with more aggressive pharmacologic regimens for organ- and life-threatening disease and less aggressive regimens for milder disease.

Grading Disease Severity

In order for the clinician to tailor pharmacologic therapy to disease activity, accurate and reproducible assessments of disease activity are required to inform management decisions. The best characterized system for risk stratification remains the EUVAS classification, which groups patients into the following categories: (*1*) limited, (*2*) early, generalized, (*3*) generalized active, (*4*) severe, (*5*) refractory, and (*6*) remission. Limited disease, by definition, is non–organ-threatening, isolated disease of the upper airway. Early generalized disease is characterized by constitutional symptoms plus the presence of end-organ involvement, but lacks a clear or immediate threat to organ function, whereas generalized active disease is defined by the presence of clearly impaired and threatened organ function. Severe disease includes those manifestations that represent an immediate threat of organ failure or death and include severe renal insufficiency (defined by a creatinine level > 5.7 mg/dl), alveolar hemorrhage, central nervous system disease, cardiomyopathy, and life-threatening gastrointestinal disease such as bowel ischemia or hemorrhage. Refractory disease is one that has failed to respond to conventional therapy (Table 2).

An alternative approach to assessing disease severity/risk stratification is the use of the Five Factor Score (FFS) developed by the French Vasculitis Study Group, originally validated for patients with MPA, polyarteritis nodosa, and CSS, but more recently validated in a cohort that included patients with GPA (50). The calculation of the score attributes +1 point for the presence of each of the following elements: (*1*) age 65 years or more, (*2*) renal insufficiency, (*3*) cardiac involvement, (*4*) gastrointestinal involvement, and (*5*) the absence of upper airway (i.e., ear, nose, and sinus) involvement. A score of 2 or higher carries a mortality of 40% and necessitates the use of more aggressive therapies, whereas a score of 0 is associated with a mortality of 9%, arguing for less aggressive therapies.

The use of an inventory, specifically the Birmingham Vasculitis Activity Score (BVAS, version 3.0) permits objective, reproducible, quantitative scoring of vasculitis disease activity (51). Similarly, the Vasculitis Damage Index permits a similar quantitative scoring of vasculitic damage (52–54). These instruments organize signs and symptoms commonly associated with vasculitis by organ system and offer the clinician or researcher a systematic way to capture the detailed, multisystem clinical assessment that is routinely performed by clinicians caring for these patients. These instruments are well validated and are useful in clinical trials.

Induction of Remission

Limited disease. There are few data to inform management concerning this subgroup of patients, but expert opinion suggests that limited, localized disease may be managed with topical therapies, oral corticosteroid monotherapy, and/or a single moderate potency cytotoxic agent such as methotrexate, azathioprine, or mycophenolate mofetil.

Early generalized disease. After the identification of cyclophosphamide and corticosteroids as effective therapy for the induction of disease remission, patients with early generalized disease were so treated (24). However, more recent studies suggest that patients with milder disease may be candidates for treatment with less potent agents. The Non-Renal Alternative with Methotrexate Trial (NORAM) directly compared cyclophosphamide with methotrexate for the induction of remission in this group of patients and found that whereas the time to remission was longer in the patients in the methotrexate arm (5.2 vs. 3.2 mo), by 6 months the rate of remission was identical (84 vs. 83%) (55). Moreover, methotrexate was better tolerated than cyclophosphamide and had a more favorable side effect profile. On the other hand, relapse rates were significantly higher with methotrexate (42 vs. 74%). As such, both methotrexate and cyclophosphamide may be considered as first-line therapy for the induction of remission in patients with early, generalized disease and the choice of therapy should be individualized to each patient.

In addition to methotrexate and cyclophosphamide, both mycophenolate mofetil (MMF) and azathioprine have been proposed as potential alternative, moderate-potency cytotoxic agents that may be considered in this patient population. To this end, Silva and colleagues evaluated MMF for patients with MPA with mild–moderate renal involvement in a prospective, open-label pilot study (56). In this small (17 patient) case series, 76% of patients achieved disease remission with corticosteroids plus MMF and 70% had sustained remission at 18 months. At present, the EUVAS study group is conducting a larger, randomized, controlled trial comparing MMF against cyclophosphamide for the induction of remission in AAV, but results are not yet available.

Generalized active disease. In 1983, Fauci and colleagues published their landmark study of 85 patients with GPA prospectively studied at the National Institutes of Health (Bethesda, MD) and definitely demonstrated that daily oral cyclophosphamide combined with oral corticosteroids was effective for the treatment of GPA (24). Remission was achieved in 93% of patients, and daily oral cyclophosphamide combined with oral corticosteroids became the yardstick by which all other pharmacologic regimens have been measured.

The Daily Oral versus Pulse Cyclophosphamide for Renal Vasculitis (CYCLOPS) trial compared pulse intravenous cyclophosphamide with daily oral cyclophosphamide and found that there was no difference in the rate of or time to disease remission between the groups (57). The pulsed intravenous cyclophosphamide group had a lower rate of leukopenia and received a lower cumulative dose of cyclophosphamide compared with the oral therapy group. However, retrospective data looking at long-term outcomes found that the risk of relapse was significantly lower in patients treated with daily oral therapy (20.8 vs. 39.5%) (58). No significant differences were noted in survival, renal function, or adverse events. Thus, arguments may be made supporting either pulse intravenous or daily oral cyclophosphamide and therapy should be tailored to individual circumstances. Interestingly, data from the Wegener's Granulomatosis-Entretien (WEGENT) trial suggest that patients who fail first-line induction with corticosteroids and intravenous cyclophosphamide may respond to oral daily cyclophosphamide therapy (59).

On the basis of the role of ANCA and B lymphocytes in the pathogenesis of AAV, a strong argument was made for the biological plausibility of rituximab, an anti-CD20 monoclonal antibody, as a possible therapeutic agent for the treatment of vasculitis. Indeed, a number of case series have been published suggesting that rituximab may be efficacious for the treatment of AAV. As such, two large, multicenter controlled trials evaluating the efficacy of rituximab for the treatment of generalized active and severe disease were conducted.

TABLE 2. FIRST-LINE TREATMENT OPTIONS STRATIFIED BY DISEASE SEVERITY

EUVAS Classification	Clinical Features	Five Factor Score	Treatment Options
Limited	Isolated upper airway disease	0	Corticosteroids *or* methotrexate *or* azathioprine
Early generalized	End-organ involvement that lacks a clear or immediate threat to organ function. Examples include glomerulonephritis with serum creatinine < 1.4 mg/dl or the presence of minimally symptomatic pulmonary nodules. Constitutional symptoms are common	0–1	Cyclophosphamide + corticosteroids *or* methotrexate + corticosteroids (for MPA may also consider mycophenolate + corticosteroids)
Generalized active	End-organ involvement with clinically significant impairment of organ function. Examples include glomerulonephritis with serum creatinine > 1.4 mg/dl but < 5.7 mg/dl or pulmonary infiltrates with cough, dyspnea, and impaired exercise tolerance	1–2	Rituximab + corticosteroids *or* cyclophosphamide + corticosteroids
Severe	Immediate threat of organ failure or death. Examples include severe renal disease with serum creatinine > 5.7 mg/dl, alveolar hemorrhage, and heart failure/cardiomyopathy	⩾2	Plasmapheresis + corticosteroids + cyclophosphamide (or rituximab)
Refractory	Disease that has failed to respond to conventional therapy	N/A	Referral to a center of specialized expertise. Consider investigational agents
Remission (maintenance)	No evidence of ongoing vasculitic activity (BVAS = 0)	N/A	If induced with cyclophosphamide then azathioprine ± low-dose oral corticosteroids *or* methotrexate ± low-dose oral corticosteroids If induced with rituximab no additional maintenance therapy may be required or may use low-dose oral corticosteroids alone

Definition of abbreviations: BVAS = Birmingham Vasculitis Activity Score; EUVAS = European Vasculitis Study Group; MPA = microscopic polyangiitis; N/A = not applicable.

Sources: References 24, 55–57, 59, 60, 62–67, and 78–80.

The Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis (RAVE) trial of 197 patients with either GPA or MPA compared rituximab (375 mg/m^2) given weekly for 4 weeks with daily oral cyclophosphamide at 2 mg/kg/day (adjusted for renal function) for induction of disease remission (60). Both groups received a standardized corticosteroid taper. The primary end point of the trial was a BVAS/WG of 0 and successful completion of the prednisone taper at 6 months. The rituximab arm reached the primary end point in 64% of subjects as compared with 53% in the cyclophosphamide group, consistent with noninferiority ($P < 0.001$) and, on the basis of these findings, rituximab received a label indication for induction of disease remission in AAV. No significant differences in total or serious adverse events were noted between the treatment groups. Subgroup analysis did suggest that rituximab may be more effective than cyclophosphamide for relapsing disease (67 vs. 42%; $P = 0.01$) and was equally effective for the management of alveolar hemorrhage.

The Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis (RITUXVAS) trial similarly compared rituximab with intravenous, pulsed cyclophosphamide as induction therapy for the treatment of AAV in 44 patients with generalized active or severe disease with renal involvement (61). Of note, the rituximab group received concomitant pulsed cyclophosphamide with the first and third rituximab infusions, and both groups received the same oral corticosteroid regimen. Rates of sustained remission were similar (76 vs. 82%; $P = 0.68$), as were median time to remission (90 vs. 94 d; $P = 0.87$) and adverse event rates ($P = 0.77$).

Although a number of investigators hypothesized that rituximab would prove to have either a more favorable side effect profile and/or greater efficacy than cyclophosphamide, this has not been borne out. On the other hand, in both trials, rituximab served as both the induction and maintenance agent, and no maintenance cytotoxic agent was deployed in the rituximab arm, whereas patients receiving cyclophosphamide required on-going maintenance therapy with azathioprine. Furthermore, the end points of the trials were at 6 and 12 months, respectively, such that the longer term toxicities known to be associated with cyclophosphamide use would not yet have been identified. Hence, the ultimate role of rituximab in the management of AAV remains to be fully elucidated, but clearly, the identification of rituximab as an efficacious agent is a major advance.

Severe disease. On the basis of data from the Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis (MEPEX) study, plasma exchange in addition to corticosteroids and cytotoxic therapy has been recommended for patients with severe disease (62). In MEPEX, patients with a new diagnosis of vasculitis and severe renal impairment were treated with oral corticosteroids and oral cyclophosphamide and simultaneously randomized to plasma exchange or high-dose intravenous methylprednisolone. Dialysis-independent survival at 3 months was 69% among the plasma exchange patients as opposed to 49% for the intravenous corticosteroid group. Furthermore, a 20-patient case series supports this strategy in alveolar hemorrhage as well (63). The RAVE and RITUXVAS trials suggest that rituximab may be used as a potential alternative to cyclophosphamide in this patient population. However, the optimal timing of cyclophosphamide or rituximab administration in critically ill patients remains an open question, as do the potential risks and benefits of intravenous versus oral cyclophosphamide, the optimal dose and route of administration of corticosteroids, and whether or not these principles of therapy apply equally to patients with other life-threatening disease manifestations (i.e., CNS disease or gastrointestinal disease.) Thus, referral of these patients to a center of expertise should be strongly considered in this circumstance.

Refractory disease. By definition, refractory disease is disease that failed to respond to conventional therapy, and hence, investigational or compassionate use therapies are then considered. Agents that have been considered for refractory disease include anti-thymocyte globulin, intravenous immunoglobulin, infliximab, and deoxyspergualin. Ultimately, patients with refractory disease are best served by referral to a center with specialized expertise in the management of vasculitis.

Maintenance of Remission

Throughout the 1980s and 1990s, patients would commonly receive defined courses of oral cyclophosphamide therapy for the management of active vasculitis as this represented the only proven effective therapy, and conceptually, the idea of "consolidating" disease remission appeared to be a conservative approach to management. However, in the landmark CYCAZAREM study (Cyclophosphamide versus Azathioprine for Remission in Generalized Vasculitis), transitioning patients from cyclophosphamide to azathioprine as soon as clinical remission was achieved did not increase the rate of disease relapse and reduced total cyclophosphamide exposure (64). In this trial, patients with a new diagnosis of generalized active vasculitis received oral cyclophosphamide plus a corticosteroid taper for the induction of disease remission. Patients who achieved disease remission within 3 to 6 months were then randomized to either azathioprine or cyclophosphamide therapy. At 12 months, all patients were transitioned to azathioprine. Analysis at 18 months demonstrated that the rate of relapse was similar in both groups (15.5% in the azathioprine group and 13.7% in the cyclophosphamide group; $P = 0.65$), as were the rates of serious adverse events (11 vs. 10%; $P = 0.94$).

Methotrexate has similarly been proposed as a safer alternative to cyclophosphamide for the maintenance of disease remission in AAV. The WEGENT trial compared the safety and efficacy of azathioprine versus methotrexate for the maintenance of disease remission (65). One hundred and eighty patients were randomized to daily oral azathioprine (2 mg/kg/d) or weekly methotrexate (progressively dose escalated to a goal dose of 25 mg/wk) after the induction of disease remission. Relapse-free survival rates were 71.8% in the azathioprine group and 74.5% in the methotrexate group, suggesting equivalent efficacy (relative risk of 0.92; $P = 0.78$), although 11% of the azathioprine group and 19% of the methotrexate group suffered an adverse event leading to death or study drug discontinuation for a hazard ratio of 1.65 ($P = 0.29$).

Mycophenolate mofetil has also been suggested as a potential alternative to azathioprine for the maintenance of disease remission. Although smaller studies suggested potential benefit to this strategy, the International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE) trial compared mycophenolate mofetil head-to-head against azathioprine for maintenance of remission (66). Relapses were found to be more common in the MMF group compared with azathioprine ($P = 0.03$). Adverse event rates were similar between groups. As such, azathioprine must be considered the superior agent and mycophenolate should be reserved for patients who cannot tolerate azathioprine or methotrexate.

Although almost all of the major randomized, controlled trials use a corticosteroid regimen during both the induction and maintenance of remission phases of management, the specific regimens used vary from study to study. In general terms, high-dose steroids are used during the induction of remission (e.g., an initial dose of oral prednisone or equivalent of 1 mg/kg/d) and slowly tapered toward a "low" maintenance dose (e.g., oral prednisone at 5–10 mg/d) until the steroids are ultimately tapered to off as long as disease remission is maintained. However, there is no widely accepted, well-validated corticosteroid protocol. A meta-analysis published by Walsh and colleagues analyzed 13 studies to determine whether low-dose glucocorticoids (GCs) contributed to the maintenance of disease remission. The authors found a lower disease relapse rate in patients receiving a low dose of GCs (67). Only 14% of patients on GCs suffered a relapse compared with 43% not receiving GCs. However, given the difference between GC regimens, maintenance therapies, and other confounders, it is difficult to extrapolate further from this analysis. Nevertheless, it would appear that GC dosage and duration itself are deserving of further investigation.

Another open question in the management of AAV is the duration of maintenance therapy. Although one may extrapolate from clinical trials that 18 months represents the lower end of an acceptable duration of therapy, the true optimal duration of therapy remains unknown. The Randomized Trial of Prolonged Remission-Maintenance Therapy in Systemic Vasculitis (REMAIN) study should further inform this question, directly comparing 24 months of maintenance therapy with 48 months of therapy. This trial completed recruitment in 2010, and results should become available in 2014–2015.

Another point of debate is the optimal management of patients after rituximab induction. Although the RAVE and RITUXVAS trials do not employ additional immunosuppressive therapies beyond low-dose corticosteroids, whether this represents optimal management is unknown. In published cases, disease relapse after rituximab is often managed with repeated rituximab dosing. However, other rheumatologic diseases use rituximab in conjunction with other disease-modifying therapies such that the long-term management of patients with AAV treated with rituximab is also deserving of further study.

Longitudinal Monitoring

One cannot overemphasize the role of a comprehensive approach to the care of the patient with vasculitis, ideally by a multidisciplinary team of health care professionals experienced in its management. Drug-specific monitoring of cytotoxic therapies is critical to avoid significant drug toxicity. The reader is directed to the American College of Chest Physicians guidelines on the monitoring of immunosuppressive agents, expected to be published soon, for further information on the specifics of monitoring each of these individual agents.

Disease-specific monitoring with regular assessments to look for early evidence of disease activity, infections, and complications of therapy should be incorporated into the plan of care. Indeed, these frequent clinical evaluations will more clearly establish the patient's baseline function and identify vasculitic "damage" that is not amenable to escalation of immunosuppressive therapy. Patients should receive vaccinations for influenza and pneumococcus. A regular exercise regimen to optimize musculoskeletal conditioning is recommended, and when appropriate, formal physical therapy, occupational therapy, and rehabilitation consultation. Bone health should be assessed by periodic bone densitometry as well as prophylaxis with calcium, vitamin D, and when indicated, other bone mineral–preserving therapies. Proper nutrition and sleep hygiene should be addressed.

Trimethoprim–sulfamethoxazole (T/S) therapy should be deployed for *Pneumocystis jirovecii* prophylaxis. Additional benefit might also accrue to patients receiving T/S therapy by the suppression of *Staphylococcus aureus* nasal carriage, which in turn is associated with a higher risk of disease relapse in GPA (68). At least one randomized trial has demonstrated reduced relapse rates in patients with GPA maintained on T/S as adjunctive therapy after the induction of remission with cyclophosphamide and corticosteroids (69).

DISEASE RELAPSE AND COMPLICATIONS

Vasculitis is a chronic, systemic disease characterized by periods of waxing and waning disease activity and many patients will suffer one or more disease relapses. In any patient with vasculitis with new signs or symptoms the differential diagnosis must always consider (*1*) vasculitis flare/disease activity, (*2*) infection, (*3*) thromboembolic disease, (*4*) drug toxicity, as well as (*5*) disease states unrelated to the vasculitis or its therapy. Indeed, the leading causes of death in patients with vasculitis are infection, pneumonia, and sepsis in particular, active vasculitis, cardiovascular disease (myocardial infarction, cerebrovascular accident, pulmonary embolus), and malignancy (13).

Infection represents a major cause of both morbidity and mortality in patients with vasculitis and the importance of identifying infection in these patients cannot be overemphasized. Infections account for 13–48% of deaths among patients with vasculitis (13, 29, 70). Patients may present with atypical clinical presentations and/or atypical infectious organisms. Infection represents not only a complication of vasculitis and the immunosuppressive therapies required for its treatment, but also serve as a triggering factor for disease flares, setting up a vicious negative reinforcing cycle of disease activity, immune dysfunction, and infection.

Similarly, venous thromboembolic disease (VTED) represents another underrecognized complication of vasculitis. The incidence of VTED in patients with GPA is 7.0 per 100 person-years, the same rate as for patients with a known prior history of VTED (71). As such, VTED should be considered in the differential diagnosis of any patient with vasculitis who presents with new chest or lower extremity symptoms.

CONCLUSIONS

Although the diagnosis of pulmonary vasculitis remains challenging, the identification and diagnosis of pulmonary vasculitis are critical to the care of these patients. Even though the vasculitides are both rare and heterogeneous, clinical investigators have been able to perform numerous well-designed controlled trials that have clearly advanced the field. Appropriate risk stratification and implementation of evidence-based, effective pharmacologic therapies combined with a comprehensive, multidisciplinary approach to care allows the clinicians who care for these patients to truly optimize individual outcomes.

Author disclosures are available with the text of this article at www.atsjournals.org.

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