Diagnosis and management of pulmonary vasculitis
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*Ther Adv Respir Dis* 2012 6: 375 originally published online 9 August 2012
DOI: 10.1177/1753465812454693

The online version of this article can be found at:
http://tar.sagepub.com/content/6/6/375
Therapeutic Advances in Respiratory Disease

Review

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Zulma X. Yunt, Stephen K. Frankel and Kevin K. Brown

Abstract: The pulmonary vasculitides are a heterogeneous group of disorders characterized pathologically by vascular destruction with cellular inflammation and necrosis. These disorders can affect small, medium, and large vessels and may be primary or occur secondary to a variety of conditions. Vasculitis involving the lungs is most commonly due to primary, idiopathic, small-vessel antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, which includes granulomatosis with polyangiitis (formerly Wegener’s granulomatosis), Churg–Strauss syndrome, and microscopic polyangiitis. From a clinical perspective these remain among the most challenging of diseases both in terms of diagnosis and treatment. This review will focus on diagnosis and management of ANCA-associated vasculitides.

Keywords: antineutrophil cytoplasmic antibody, antineutrophil cytoplasmic antibody-associated vasculitis, Churg–Strauss syndrome, granulomatosis with polyangiitis, lung, microscopic polyangiitis, pulmonary, vasculitis, Wegener’s granulomatosis

Introduction

The vasculitides are an uncommon group of disorders characterized pathologically by vascular inflammation, damage, and tissue necrosis. From a clinical perspective they are diagnostic challenges due to an overall low prevalence and the nonspecific nature of clinical symptoms which overlap with more common diseases such as infection, connective tissue disease, and malignancy. Management also presents a challenge as it can be difficult to distinguish progression of underlying disease, drug toxicity, and complications of immunosuppression, which may likewise be characterized by systemic symptoms, infection, or even malignancy.

Adding to the challenge is the lack of clarity amongst many physicians regarding classification for the vasculitides. Classification is often based on the size of affected vessels using the 1994 Chapel Hill Consensus Conference nomenclature [Jennette et al. 1994]. Vasculitides associated with the pulmonary system are predominately of the small-vessel type, however large- and medium-vessel vasculitis can also affect the lungs. Within the small-vessel vasculitides, further classification based on immunopathological characteristics as outlined in Figure 1 can be useful for recognizing disease mechanisms and possibly treatment approaches. The antineutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitides, including granulomatosis with polyangiitis (GPA, formerly Wegener’s granulomatosis), Churg–Strauss syndrome (CSS), and microscopic polyangiitis (MPA), most often involve the lung and will be the focus of this review.

Clinical findings suggestive of vasculitis

Diagnosis of systemic vasculitis relies first on a thorough history and a complete review of all organ systems. Even unrelated and seemingly insignificant signs and symptoms are important as they often point to a systemic process. While a broad range of symptoms and clinical findings have been reported in vasculitis, some are particularly characteristic and should prompt consideration of vasculitis when identified.

Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage (DAH) is an uncommon but severe and life-threatening manifestation
of systemic vasculitis. Hemoptysis, shortness of breath, alveolar infiltrates, and a drop in hematocrit are often but not always seen [Cordier and Cottin, 2011]. DAH is confirmed with bronchoscopic examination, demonstrating increasingly bloody fluid in sequential bronchoalveolar lavages. The differential diagnosis of DAH includes diseases characterized pathologically by capillaritis with a neutrophilic infiltration of capillaries and venules. ANCA, antineutrophil cytoplasmic antibody; CSS, Churg–Strauss syndrome; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus. [Modified with permission, original figure published in Murray and Nadel's Textbook of Respiratory Medicine, Volume 2, page 1246, Copyright Saunders 2010 [Mason et al. 2010].]

Rapid progressive glomerulonephritis
Renal dysfunction in AAV occurs in the form of rapidly progressive glomerulonephritis (RPGN) typically developing over a period of days to months. Clinically, patients may present with overt nephritic syndrome, including renal failure, gross hematuria, proteinuria, and hypertension or with more indolent disease characterized primarily by constitutional symptoms and an abnormal urinalysis or urine sediment [Falk et al. 1990]. Microscopic examination of a fresh urine specimen looking for active sediment is critical and should be done promptly in cases of suspected vasculitis. Diagnosis is formally made by renal biopsy, which demonstrates necrotizing crescentic glomerulonephritis, typically without immune deposits on immunofluorescence [Jennette, 2003].

Pulmonary renal syndrome
Pulmonary renal syndrome refers to the combination of pulmonary hemorrhage and acute glomerulonephritis, which may present simultaneously or sequentially. Almost all cases are due to systemic small vessel vasculitis, Goodpasture’s syndrome, or systemic lupus erythematosus (SLE). Recognition of this syndrome should immediately raise concern for the presence of AAV.
Upper airway lesions
Upper airway disease is common with both GPA and CSS [Hoffman et al. 1992]. In GPA, findings include intranasal inflammation, mucosal ulceration or necrosis, nasal obstruction, polyposis, sinusitis, and subglottic stenosis. Patients may report epistaxis, nasal congestion, nasal deformity, stridor, hoarseness, or hemoptysis. In CSS, upper airways disease consists mostly of allergic manifestations such as rhinitis, sinusitis, and nasal polyposis; the typical necrotizing lesions seen in GPA are exceedingly rare.

Refractory asthma
Asthma that is resistant to treatment or poorly controlled with standard asthma medications should prompt consideration of AAV and specifically CSS. Other differential diagnostic considerations include allergic bronchopulmonary aspergillosis (ABPA), bronchocentric granulomatosis, vocal cord dysfunction, chronic obstructive pulmonary disease, and cardiac dysfunction.

Pulmonary nodules
Lower respiratory tract involvement and associated radiographic abnormalities are common in AAV. Radiographic findings may include diffuse alveolar infiltrates, transient patchy infiltrates, and nodular lesions that are either cavitating or non-cavitating [Gomez-Puerta et al. 2009]. A finding of new nodular disease should raise concern for AAV vasculitis, particularly in the absence of malignancy and infection. Both nodular and cavitary disease are particularly frequent in GPA, occurring in 55–70% and 35–50% of patients respectively [Cordier et al. 1990; Reuter et al. 1998].

Palpable purpura
Palpable purpura are raised, non-blanching, erythematous skin lesions of varying sizes that reveal a leukocytoclastic vasculitis on biopsy. They may be idiopathic or secondary to a variety of conditions including systemic vasculitis, drug reaction, connective tissue disease, infection, cryoglobulinemia, HIV, and malignancy.

Mononeuritis multiplex
The reported neurologic manifestations of AAV are numerous and include mononeuritis multiplex, polyneuropathy, pseudotumor with optic nerve involvement, cranial neuropathy, cerebrovascular accident (CVA), intracranial or subarachnoid hemorrhage, and meningeal disease [Nadeau, 2002]. Of these, the syndrome of mononeuritis multiplex or peripheral nerve disease involving at least two separate nerve regions is particularly common and suggestive of vasculitis [Zhang et al. 2009].

Evaluation
The key elements in making a diagnosis of systemic vasculitis are the history, laboratory testing, imaging studies, and pathology. The importance of a complete history and review of systems cannot be overstated. This information is critical not only for recognizing the systemic nature of symptoms but for considering other possible diagnosis such as malignancy, infection, drug reaction, or connective tissue disease. Concurrent infection and malignancy in particular should be ruled out.

Laboratory testing
Antineutrophil cytoplasmic antibodies. Antibodies against cytoplasmic components of neutrophils were first linked to systemic small-vessel vasculitis in the mid 1980s and are now known to be important in the pathogenesis of AAV [van der Woude et al. 1985; Kallenberg, 2011; Falk and Jennette, 1988]. ANCA in AAV are typically directed against either proteinase 3 (PR-3) or myeloperoxidase (MPO) and testing for the presence of these antigen-specific antibodies is part of the routine laboratory evaluation for suspected vasculitis. PR-3 is most often the target antigen of diffuse cytoplasmic ANCA (C-ANCA) while...
MPO antibodies are more closely associated with perinuclear ANCAs (P-ANCAs).

ANCA and anti-PR-3/MPO antibodies are appropriate screening tools for AAV when there is clinical concern for vasculitis. The reported sensitivity of C-ANCA and anti-PR3 ELISAs for generalized Wegener’s is between 85% and 90% while specificity has been reported as high as 95% [Gaskin et al. 1991; Gross, 1995; Hagen et al. 1998; Nolle et al. 1989; Tervaert et al. 1989]. These values are decreased for patients with limited or relapsed disease. The reported sensitivity of P-ANCA and anti-MPO testing is lower at 35–75% for MPA and 35–50% for CSS [Ara et al. 1999; Hagen et al. 1998; Schonermarck et al. 2001; Tervaert et al. 1990, 1991]. P-ANCA/MPO antibodies may be present in patients with various non-vasculitic inflammatory conditions, including infection, rheumatoid arthritis, hepatitis, and inflammatory bowel disease and thus are less specific than C-ANCA/PR-3 tests for systemic vasculitis. These antibodies have not demonstrated efficacy as markers of disease activity in AAV [Savige et al. 1999, 2003; Tomasson et al. 2012].

Other laboratory tests. In addition to ANCA testing, other laboratory studies are important in the evaluation of suspected AAV both for determining disease severity and to rule out other diagnosis. Studies should include complete blood count (CBC), blood urea nitrogen (BUN), creatinine, liver function tests, urinalysis with microscopic examination, hepatitis panel, and cryoglobulins. Other pulmonary renal syndromes and secondary causes of small-vessel vasculitis should be evaluated with anti-GBM antibodies, rheumatoid factor, antinuclear antibodies, and antiphospholipid antibodies. Additional serologies may be sometimes be useful, including anti-SSA, anti-SSB, anticentromere, anti-Scl70, anti-Jo1, aldolase, and creatine phosphokinase.

Imaging studies
Imaging studies are helpful for characterizing the extent of disease in AAV and for assessing response to therapy. Since the lungs may be involved even in the absence of respiratory symptoms, chest imaging should be performed in all patients. Imaging of the sinuses with computed tomography (CT) scanning, as opposed to plain films, should be performed in patients with upper airway disease. Other studies including echocardiogram, CT of the abdomen, angiography, and brain magnetic resonance imaging may be important in certain clinical presentations.

Tissue biopsy
Tissue confirmation of small-vessel vasculitis is recommended when appropriate and depends upon the clinical scenario. Organ involvement dictates the location of biopsy with preference for sites requiring less invasive procedures such as the skin, nasal passages, and upper airways first though diagnostic yield from these sites may be limited. Nasal biopsies in particular often reveal only nonspecific inflammation.

Lung tissue for the purpose of confirming AAV should be obtained by surgical biopsy. Immunofluorescence studies, standard histopathology with special antibody staining, and culture should be performed. These studies require special intraoperative handling so the performing surgeon and pathologist should be informed of the suspicion for vasculitis in advance. Transbronchial biopsy, while considerably less invasive, has limited utility in diagnosing small-vessel vasculitis.

Percutaneous renal biopsy is indicated for new presentations of acute glomerulonephritis. In the setting of AAV, biopsy reveals necrotizing crescentic glomerulonephritis consistent with RPGN; however this finding is not specific for AAV. Accordingly, when there is concern for systemic vasculitis or evidence of a pulmonary renal syndrome, immunofluorescence and electron microscopy should also be performed to evaluate the presence and pattern of immune and complement deposition. Crescentic glomerulonephritis due to AAV may be differentiated from Goodpasture’s, SLE, and Henoch-Schonlein purpura by the absence of immune deposits (pauci-immune). Vascular inflammation and necrosis are typically not seen on renal biopsy in AAV.

Specific clinical disorders
Clinical manifestations for individual disorders depend on various disease- and patient-related factors. In a given patient, organ involvement may vary over time and clinical features may overlap between different syndromes. Common clinical manifestations and laboratory findings in GPA, CSS, and MPA are outlined in Table 1.
Table 1. Antineutrophil cytoplasmic antibody-associated vasculitides: clinical characteristics.

<table>
<thead>
<tr>
<th></th>
<th>GPA</th>
<th>CSS</th>
<th>MPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Common</td>
<td>Common</td>
<td>Very common (&gt;70%); weight loss, loss of appetite, asthenia, myalgias, fever</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Very common (65–95%); nodules, infiltrates, cough, hemoptysis, pleuritis. Tracheobronchial and endobronchial disease in 10–50%</td>
<td>Near universal asthma (&gt;96%); infiltrates, eosinophilic pneumonia common. Nodules and cavitation uncommon</td>
<td>Moderately common (25–55%); DAH occurs in 30%. Dyspnea, cough are common. Isolated lung involvement very rare. Lung fibrosis may be seen</td>
</tr>
<tr>
<td>Upper airway</td>
<td>Very common (70–95%); ulcerative, deforming lesions common. Often reason for initial presentation. Subglottic stenosis in 15–20%</td>
<td>Very common (45–85%); sinusitis without destructive lesions, polyposis, and allergic rhinitis</td>
<td>Moderately common (20–30%); milder disease than GPA and CSS</td>
</tr>
<tr>
<td>Renal</td>
<td>Very common, RPGN (80–90%)</td>
<td>Moderately common, RPGN [16–49%]</td>
<td>Near universal, RPGN (79–100%)</td>
</tr>
<tr>
<td>Neurological</td>
<td>Peripheral nervous disease 15–25%; mononeuritis multiplex most common. Central nervous system 5–10%</td>
<td>Peripheral nervous system 65–95%; most common mononeuritis multiplex. Central nervous system less common</td>
<td>Variable. Peripheral nervous disease more common (14–58%) than central. Mononeuritis multiplex most common manifestation</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Uncommon</td>
<td>Common (35–62%); abdominal pain, esophagitis, diarrhea, ischemia, perforated viscus</td>
<td>Common (30–56%); abdominal pain, nausea, vomiting, diarrhea. Ischemia, peritonitis associated with poor prognosis</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Uncommon (5–15%)</td>
<td>Common (30–60%); Major cause of death. Coronary involvement, conduction disease, heart failure, myocarditis, pericarditis</td>
<td>Uncommon (10–20%); heart failure more common than ischemia or pericarditis</td>
</tr>
<tr>
<td>Skin</td>
<td>Common (40–50%); palpable purpura, ulcers, vesicles, subcutaneous nodules, papules</td>
<td>Very common (40–75%); palpable purpura often necrotic, papules, nodules</td>
<td>Common (40–45%); palpable purpura, ulcers, mucocutaneous hemorrhage, nodules</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Common (50–70%); myalgias, arthralgias, monoarticular disease, migratory polyarteritis</td>
<td>Common (up to 50%)</td>
<td>Common. Myalgias, arthralgias frequently presenting symptoms (55–75%)</td>
</tr>
<tr>
<td>Ocular</td>
<td>Common (25–55%); conjunctivitis, scleritis, proptosis often painful, dacryocystitis</td>
<td>Uncommon</td>
<td>Approximately 30%. Scleritis, episcleritis, iridocyclitis</td>
</tr>
<tr>
<td>ANCA</td>
<td>Positive in &gt;90%. C-ANCA and PR-3 antibody positivity in &gt;85% with generalized disease</td>
<td>ANCAAs positive in approximately 40%; of these 69–74% are specific for P-ANCA/MPO antibodies</td>
<td>Positive in 45–79%. P-ANCA/MPO antibodies more common</td>
</tr>
</tbody>
</table>

ANCA, antineutrophil cytoplasmic antibody; C-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CSS, Churg–Strauss syndrome; DAH, diffuse alveolar hemorrhage; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear antineutrophil cytoplasmic antibody; PR-3, proteinase 3; RPGN, rapidly progressive glomerulonephritis.

Data from references [Guillevin et al. 1999b; Villiger and Guillevin, 2010; Adu et al. 1987; D’Agati et al. 1986; Savage et al. 1985; Serra et al. 1984; Frankel et al. 2006; Frankel and Jayne, 2010; Brown, 2006; Lane et al. 2005; Hoffman et al. 1992; Pagnoux et al. 2007; Sinico et al. 2005].
**Granulomatosis with polyangiitis**
(formerly Wegener’s granulomatosis)

GPA is classically characterized by the triad of upper airway disease, lower airway disease, and glomerulonephritis, though these features are not present in all patients. GPA is the most common AAV and the most likely to be associated with chest imaging abnormalities [Gomez-Puerta et al. 2009]. Various patterns of radiographic disease have been described, including unilateral and bilateral airspace disease, infiltrates, effusions, atelectasis, and single or multiple nodules with or without cavitation [Cordier et al. 1990]. Nodular and cavitary lesions are more common in GPA than other AAVs occurring in 55–70% and 35–50% of patients respectively [Reuter et al. 1998; Cordier et al. 1990; Figure 3]. Pathologically GPA is characterized by small- or medium-vessel necrotizing vasculitis with granulomatous inflammation; however microabscesses, giant cells, and poorly formed granulomas have also been described (Figure 4) [Travis et al. 1991].

**Microscopic polyangiitis**

Renal disease is nearly always present in MPA, and is often responsible for presenting symptoms [Lane et al. 2005]. Constitutional symptoms are very common and may be associated with a prolonged prodromal phase. Pulmonary disease occurs in only 20–30% of patients but frequently manifests as DAH [Guillevin et al. 1999b; Lhote et al. 1998; Lane et al. 2005]. Infiltrative lung disease, while not common, occurs in approximately 7% of patients with MPA [Arulkumaran et al. 2011]. Pathologic features include necrotizing small-vessel inflammation without granulomas, prominent eosinophilia, or giant cells.

**Churg–Strauss syndrome**

Unique features of CSS include asthma in nearly all patients, eosinophilia on pathology, and a lower frequency of ANCA positivity at approximately 40% compared with 75–95% in GPA and MPO [Savage et al. 1997; Sable-Fourtassou et al. 2005; Sinico et al. 2005; Jennette and Falk, 1997]. Asthma in CSS is often refractory to therapy or poorly controlled with standard asthma medications. In fact, when difficult to control asthma is confronted in the clinic, CSS should always be considered as a potential explanation, along with the usual contributors to poor asthma control. Patients with CSS may present with sinus disease and mononeuritis multiplex in addition to asthma [Hattori et al. 1999]. Cardiac involvement is common and accounts for 48% of deaths in CSS [Pela et al. 2006; Hellemans et al. 1997]. Three clinical phases have been described: a prodromal phase of asthma and atopic disease; an eosinophilic phase during which pulmonary and gastointestinal disease frequently manifests; and a vasculitic phase [Lanham et al. 1984; Guillevin et al. 1999a]. Chest imaging studies are often abnormal and commonly demonstrate transient patchy bilateral infiltrates [Pagnoux et al. 2007]. Biopsy may reveal necrotizing vasculitis in small- to medium-size vessels, often with an eosinophil-rich granulomatous inflammation (Figure 5).
The appropriate treatment approach for AAV is determined by severity of disease at the time of treatment initiation (Table 2). Accordingly, accurate assessment of disease activity taking into account all involved organ systems is important. Current guidelines outlined by the European Vasculitis Study Group (EUVAS) emphasize renal dysfunction as a major determinant of clinical severity while classification with respect to other organ systems is less clear. Given the implications for therapy it is worthwhile to consider some nonrenal disease manifestation that might also define severity; however it should be noted that nearly all therapeutic trials in AAV have used renal dysfunction as the major factor in determining severity.

Clinical findings that define severity
The appropriate treatment approach for AAV is determined by severity of disease at the time of treatment initiation (Table 2). Accordingly, accurate assessment of disease activity taking into account all involved organ systems is important. Current guidelines outlined by the European Vasculitis Study Group (EUVAS) emphasize renal dysfunction as a major determinant of clinical severity while classification with respect to other organ systems is less clear. Given the implications for therapy it is worthwhile to consider some nonrenal disease manifestation that might also define severity; however it should be noted that nearly all therapeutic trials in AAV have used renal dysfunction as the major factor in determining severity.

Early generalized
Patients with early generalized disease typically report constitutional systems and multisystemic disease that does not threaten organ function. Manifestations may include myalgias, arthralgias, fever, weight loss, headaches, mucocutaneous ulcers or granulomata, lymphadenopathy, episcle-ritis, and conjunctivitis. There is no significant renal impairment in this group with serum creatinine less than 120 μmol/liter (1.4 mg/dl).

Active generalized
Active generalized disease is defined by disease that poses a threat to organ function. Clinical manifestations associated with this grade of severity may include palpable purpura, gangrene, uveitis, retinal hemorrhage or thrombosis, hearing loss, subglottic stenosis, clinically significant parenchymal lung disease including nodules or cavity disease, pericarditis, peritonitis, sensory peripheral neuropathy, cranial neuropathy, mononeuritis multiplex. Renal impairment with serum creatinine less than 500 μmol/liter (5.7 mg/dl) is included in this group.

Severe disease
Severe disease is characterized most simply as disease that is organ or life threatening. Clinically this includes respiratory failure, DAH, coronary arteritis with ischemia, cardiomyopathy with heart failure, bowel ischemia, seizures, meningitis, and stroke. Renal disease with creatinine greater than 500 μmol/liter (5.7 mg/dl) is included in this group.

Determining the most appropriate severity grade and therapeutic regimen for patients with atypical presentations is one of the most challenging aspects of treating AAV and often merits a multidisciplinary approach with input from specialists experienced in managing these diseases. Referral to a specialized center is often appropriate.

Treatment
Immunosuppressive agents are the mainstay of treatment for vasculitis. In light of the complications and toxicities associated with these agents care must be taken to find an optimal balance between risk from therapy and risk from disease activity. The goal of therapy is to maintain disease remission while minimizing treatment-related complications. Frequent monitoring and assessment of disease is necessary to achieve this. The Birmingham Vasculitis Activity Score (BVAS) is widely used as a tool for monitoring disease activity in clinical trials, and though its use in routine clinical practice has not been validated, some clinicians find it is useful as a guideline to ensure all systems are routinely assessed [Luqmani et al. 1994].

Therapy for vasculitis is divided into two phases: remission induction and maintenance. Therapy for remission induction is determined by severity of disease at the time of treatment initiation (Table 2). In general, induction therapies are more aggressive and aimed at achieving rapid
control of disease while medications used for remission are of lower intensity but may be continued for longer duration with the goal of preventing relapse. At all points during the course of therapy measures must be taken to properly recognize and assess disease activity and to separate this from drug toxicity or other complication such as infection or malignancy. Clinicians should have a thorough understanding of the toxicities associated with each therapy and patients should be monitored on a regular basis for signs of adverse effects or treatment failure. Other important aspects of therapy include supplemental oxygen, immunizations, physical and occupational therapy, proper nutrition, treatment of comorbid conditions, and *Pneumocystis jirovecii* prophylaxis when appropriate.

**Remission induction**

**Limited disease.** Limited disease by definition is localized to the upper airways and is not associated with systemic symptoms, renal impairment, or other end-organ dysfunction. Therapy for these
patients can be limited to a single agent such as corticosteroids, methotrexate, or azathioprine. Aggressive forms of limited disease may require treatment regimens more similar to those of early or active generalized disease.

*Early generalized disease.* Early generalized disease differs from active generalized disease by its lack of renal impairment or threat to end-organ vitality. For many years cyclophosphamide plus corticosteroids was the mainstay of treatment in early generalized disease, however the Methotrexate versus Cyclophosphamide for Early Systemic Disease trial (NORAM) shown that methotrexate was also effective for inducing remission in this group [De Groot et al. 2005]. Both agents are now considered appropriate first-line therapy. Currently the EUVAS is conducting the Mycophenolate Mofetil versus Cyclophosphamide for Remission Induction in AAV (MYCYC) trial to determine whether mycophenolate mofetil may be another effective therapy for generalized vasculitis.

*Active generalized disease.* Cyclophosphamide plus corticosteroids became first-line therapy for active generalized vasculitis after the hallmark study of Fauci and colleagues [Fauci et al. 1983]. Prior to this the prognosis for systemic AAV was grim, with a 1-year mortality of 82% [Fauci et al. 1983]. Given the limitations of toxicity associated with cyclophosphamide, regimens with lower cumulative drug exposure through pulsed intravenous dosing received considerable attention over the ensuing decades [Adu et al. 1997; Haubitz et al. 1998; Hoffman et al. 1990; Guillevin et al. 1997]. The Cyclophosphamide versus Pulsed Intravenous Cyclophosphamide for Remission Induction in AAV (CYCLOPS) trial was a landmark multicenter randomized controlled trial comparing a daily oral regimen (2 mg/kg) of cyclophosphamide versus a pulsed intravenous regimen (15 mg/kg every 2–3 weeks) for efficacy in inducing remission in generalized vasculitis [de Groot et al. 2009]. The results showed no significant difference in rates of remission induction between the two regimens but significantly lower cumulative exposure and fewer episodes of leukopenia in the pulsed group. A retrospective long-term outcome study of the CYCLOPS patient cohort was recently published, demonstrating greater risk of relapse in the pulse group but no difference in mortality or adverse events [Harper et al. 2012]. In current practice, therapy with intermittent pulse cyclophosphamide has gained favor over daily oral dosing and is considered the preferred therapeutic regimen for remission induction when feasible.

While cyclophosphamide has revolutionized outcomes for systemic vasculitis, not all patients respond to treatment, many relapse, and over time, toxicities limit its use. Rituximab, an anti-CD20 monoclonal biological targeted against B cells, was found to have efficacy at the case series level in cases of refractory disease and in patients with contraindications to cyclophosphamide [Specks et al. 2001; Keogh et al. 2005, 2006; Brihaye et al. 2007; Tamura et al. 2007; Lovric et al. 2009; Roccatello et al. 2008; Sanchez-Can et al. 2008]. This led to two large multicenter randomized controlled trials published simultaneously in 2010 examining rituximab versus cyclophosphamide for induction of remission in AAV: Rituximab in ANCA-Associated Vasculitis (RAVE) and Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis (RITUXVAS) [Stone et al. 2010; Jones et al. 2010]. Both studies showed noninferiority of rituximab and results from RAVE suggested that rituximab was superior for the treatment of relapsed disease. Today both rituximab and cyclophosphamide are considered appropriate first-line agents for active generalized disease.

*Severe disease.* Therapeutic studies conducted in patients with severe renal vasculitis have demonstrated that plasma exchange in addition to cyclophosphamide and corticosteroids confer benefit in this group. The largest reported trial investigating plasma exchange therapy for renal vasculitis was the Methylprednisolone or Plasma Exchange for Severe Renal Vasculitis (MEPEX) study published in 2007 [Jayne et al. 2007]. This study demonstrated better renal recovery at 3 months with the addition of plasma exchange versus high-dose pulsed intravenous steroids to standard therapy in patients with a new diagnosis of AAV and creatinine greater than 500 μmol/liter (5.8 mg/dl). There was also a reduced risk for progression to end-stage renal disease at 12 months in the plasma exchange group but no difference in mortality or severe adverse events. Currently EUVAS is enrolling patients in the Plasma Exchange and Glucocorticoid dosing in the treatment of AAV (PLEXIVAS) trial which will examine the efficacy of plasma exchange in addition to immunosuppressive therapy and corticosteroids in reducing death and end-stage renal disease. It will also examine the noninferiority of a smaller dose of corticosteroids for reducing death and end-stage renal disease.
Plasma exchange may also confer benefit for patients with DAH and is typically performed in this setting, though it has not been studied in a prospective, controlled fashion [Klemmer et al. 2003; Mukhtyar et al. 2009]. For the scenario of DAH, consideration should be given to the risk of further bleeding with plasma exchange due to loss of coagulation factors and the risk of transfusion-related acute lung injury associated with administering blood products during the exchange. Other potential therapies for DAH include extracorporeal membrane oxygenation and activated human factor VII, though studies of these treatment methods are limited to case reports [Ahmed et al. 2004; Matsumoto et al. 2000; Betensley and Yankaskas, 2002; Dabar et al. 2011; Henke et al. 2004].

Refractory disease
Refractory disease is defined as disease that does not respond with at least a 50% reduction in disease activity after 4–8 weeks of treatment and also generally includes patients who are not able to tolerate first-line therapy or have contraindications to it [Hellmich et al. 2007; Rutgers and Kallenberg, 2011]. The rate of occurrence of refractory vasculitis has been reported between 4% and 5% in the major EUVAS-sponsored randomized trials [Rutgers and Kallenberg, 2011]. Remission is ultimately achieved in 35-83% of patients that are initially deemed refractory, but overall mortality is higher in this group [Hellmich et al. 2007; Hogan et al. 2005]. Currently there are no established guidelines for the management of refractory vasculitis and referral to a specialized center for management is appropriate. In practice, patients who fail pulsed cyclophosphamide therapy are often switched to a daily oral dosing regimen in the absence of drug toxicity. Efficacy of this approach was demonstrated retrospectively in patients from the Wegener’s Granulomatosis-Entretien (WEGENT) cohort [Seror et al. 2010]. Other therapeutic strategies that have demonstrated efficacy in small studies include anti-tumor necrosis factor α (anti-TNFα) agents, intravenous immunoglobulin, high-dose azathioprine, mycophenolate mofetil, alemtuzumab, deoxyspergualin, and autologous nonmyeloablative hematopoietic stem cell transplantation [Walsh et al. 2008; Benenson et al. 2005; Stassen et al. 2007; Jayne et al. 2000; Birck et al. 2003; Flossmann et al. 2009; Booth et al. 2004; Bartolucci et al. 2002; de Menthon et al. 2011; Kotter et al. 2005; Statkute et al. 2008; Schmitt et al. 2004].

Maintenance therapy
Today induction therapy achieves remission in approximately 85% of cases of systemic AAV [de Groot et al. 2001]. Thereafter immunosuppressive therapy is continued for the primary purpose of preventing relapse; however the optimal type, amount, and duration of this ‘maintenance’ therapy remain under debate. Timing of this transition was addressed by the EUVAS-sponsored Cyclophosphamide versus Azathioprine for Remission in Generalized Vasculitis (CYCAZAREM) trial [Jayne et al. 2003]. In this study patients were treated with standard doses of cyclophosphamide for 3–6 months to induce remission and thereafter randomized to either continue cyclophosphamide to complete 12 months or transition to azathioprine. The results showed no difference in the rate of relapse between the two groups and the early transition approach became the standard of care.

Azathioprine remains the most commonly used medication for maintenance therapy, however methotrexate also demonstrated efficacy in the WEGENT trial [Pagnoux et al. 2008b]. Mycophenolate mofetil was investigated in the International Mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE) trial and was found to be less effective than azathioprine for preventing relapse [Hiemstra et al. 2010]. Similarly the TNFα antagonist etanercept did not confer benefit when added to standard therapy in the Wegener’s Granulomatosis Etanercept Trial (WGET) [WGET Research Group, 2005].

Corticosteroids are used as adjuvant therapy for remission induction, however the precise duration of therapy and tapering regimen is variable [de Groot et al. 2001]. The impact of corticosteroid dosing in preventing relapse is not known and has received little attention. A meta-analysis of 13 studies examining duration of glucocorticosteroid treatment with respect to rates of relapse demonstrated fewer relapses with a longer course of low-dose steroids [Walsh et al. 2010]. Randomized studies focused on this component of standard therapy are needed.

The optimal duration of maintenance therapy is not known. Relapse occurs in 11–57% of patients who achieve remission, often after discontinuation of maintenance drugs [de Groot et al. 2001; Hogan et al. 2005; Pagnoux et al. 2008a; Nachman et al. 1996]. The EUVAS-sponsored Randomized Trial of Prolonged Remission-Maintenance Therapy in
Systemic Vasculitis (REMAIN) will compare 24 months of therapy with 48 months of therapy for prevention of relapse to better inform this question.

Longitudinal monitoring and managing complications

Despite significant advances in therapy and the use of less toxic regimens, patients with AAV continue to have an increased risk of complications and mortality even in remission. This is due to a variety of disease- and drug-related complications associated with AAV. Recognition and management of these complications is critical and now constitutes a major portion of the long-term care of patients with this disease.

Infection

Infection is the most common cause of death during the first year of treatment and must be at the forefront of the treating clinician’s mind when a patient reports new symptoms [Flossmann et al. 2011]. Long-term outcome data from patients enrolled in EUVAS-sponsored clinical trials indicate that infection accounts for 48% of deaths within the first year after diagnosis [Flossmann et al. 2011]. Both the disease itself and the medications used to treat it contribute to the higher risk of infection in these patients. When infection is diagnosed, these medications must be titrated downward as their risk may outweigh the benefits of disease-activity suppression during active infection.

Patients with AAV are subject to a variety of opportunistic and nonopportunistic infections. A thorough evaluation often including imaging studies and bronchoscopy with testing for viral, bacterial, fungal, and mycobacterial pathogens is warranted when patients report new pulmonary symptoms. Prophylaxis against Pneumocystis jirovecii as well as immunization against influenza and pneumococcal pneumonia is recommended.

Disease-related complications

Direct. Patients that achieve remission require close monitoring for evidence of disease flares which may clinically resemble the initial presentation or may manifest with new symptoms and findings. Routine monitoring should include a complete history, review of systems, and a evaluation with ANCA testing, CBC, BUN, creatinine, liver function tests, electrocardiogram, and chest imaging studies at regular intervals. In particular, clinicians should be watchful for silent changes in renal function that may signal recrudescence of active disease.

Disease flares are sometimes difficult to distinguish from baseline nonreversible organ damage, particularly when the extent of disease-related damage was not clearly established or discernable during the initial presentation. Close observation and frequent monitoring after remission induction are helpful in this regard. Once a flare of new or worsened vasculitic activity is identified, management includes reinduction therapy usually with escalation of immunosuppressive therapy. Referral to a center experienced in the administration and titration of these medications is appropriate.

Indirect. In addition to disease flares, patients with AAV are at risk for other disease-related complications, including infection, thromboembolism, and malignancy. Infection is of particular importance and has been discussed previously. Risk for venous thromboembolism is increased in this population as demonstrated in the Wegener’s Clinical Occurrence of Thrombosis (WeCLOT) study. This prospective observational cohort study identified an increased incidence of new deep vein thrombosis (DVT) at 7.0 per 100 person years in patients with GPA compared with less than 1 per 100 person years in patients with rheumatoid arthritis and the general population. Despite findings from this study, routine use of DVT prophylaxis in these patients has not been investigated. Malignancy is a recognized complication of AAV, however it remains unclear whether this is solely related to the use of immunomodulatory agents or if the disease process itself predisposes patients to solid and hematopoietic cancers [Knight et al. 2002; Hoffman et al. 1992; Faurschou et al. 2008; Flossmann et al. 2011].

Therapy-related complications

Direct. All of the immunosuppressive agents used in AAV have important toxicities that require close monitoring. In the setting of AAV, dose adjustments may be necessary with respect to renal impairment to limit adverse effects. Routine laboratory tests including CBC, BUN, creatinine, liver function studies, and urinalysis are necessary to monitor for toxicity.
Indirect. The major indirect complications of immunosuppressive therapy include infection and malignancy. Cyclophosphamide therapy in particular has been linked with higher rates of non-melanomatous skin cancer, leukemia, and bladder cancer [Faurschou et al. 2008; Knight et al. 2002]. Osteoporosis and secondary diabetes are common with prolonged steroid use. All patients beginning corticosteroid treatment should have a baseline dual-energy X-ray absorptiometry bone scan and initiate therapy with calcium and vitamin D. Follow-up scans should be performed periodically to discern the need for additional therapy.

Conclusions
Diagnosis and treatment of AAV requires careful evaluation and close monitoring of both disease- and therapy-related activity. In recent years several well conducted randomized controlled trials have provided important information about alternative immunosuppressive agents and regimens that are effective in this disease. Ongoing studies investigating the pathogenesis of this disease may ultimately provide insight into better disease-targeted therapies with good efficacy and lower toxicity.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement
There are no conflicts of interest to report.

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