Inflammation and necrosis of blood vessel walls occurs in a dozen or so primary vasculitic disorders. An attempt to classify these diverse forms of vasculitis resulted in the Chapel Hill international consensus definitions, which used vessel size as the determinant of classification [1]. Wegener's granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome are described as small vessel vasculitides and are commonly associated with anti-neutrophil cytoplasmic antibodies (ANCA).

The incidence of ANCA-associated vasculitis is 20 per million population occurring more often in an elderly population (peak age 55 to 70 yr) [2]. Prevalence rates are far higher since the introduction of successful immunosuppressant treatment regimes. Of the three entities, Churg-Strauss syndrome is the least common (1–3 per million population). Some studies of ANCA-associated vasculitis have suggested that pulmonary involvement is associated with a poor outcome [3, 4].

**Diagnosis**

The diagnosis of ANCA-associated vasculitis is made on the basis of the clinical findings, by biopsy of a relevant involved organ and the presence of ANCA. Testing for ANCA using both indirect immunofluorescence and antigen-specific enzyme-linked immunosorbent assay is recommended, and provides high sensitivity (approximately 99%) and good specificity (approximately 70%) in those with generalized Wegener's or microscopic polyangiitis [5]. ANCA testing may, however, be less sensitive in patients with more limited disease or Churg-Strauss syndrome [6].

**Pathology**

Wegener's granulomatosis classically represents a triad of inflammation and vasculitis of the upper and lower airway with glomerulonephritis. Microscopically there is vascular change including fibrinoid necrosis, inflammatory cell infiltrate with neutrophils, lymphocytes and plasma cells with granuloma formation [7]. In contrast, the pathology of Churg-Strauss syndrome is characterized by necrotizing vasculitis, eosinophilic tissue infiltrates and both intra- and extravascular granulomata [8]. Microscopic polyangiitis differs in that it is a small vessel vasculitis without evidence of respiratory tract granulomatous inflammation.

**Pathogenesis**

Wegener's granulomatosis and microscopic polyangiitis

The aetiology of these diseases remains unknown; however, significant advances have been made in understanding disease pathogenesis (several very good reviews have recently been published [9, 10]). The strong association of vasculitis with ANCA suggests an autoimmune disease and that these antibodies are directly pathogenic. ANCA activate cytokine-primed neutrophils and monocytes, which express the ANCA antigens, myeloperoxidase (MPO) and proteinase 3 (PR3), on the surface. Neutrophils respond by increasing adhesion to cytokine-activated endothelial cells, generating a respiratory burst, releasing proteolytic granule contents and secreting pro-inflammatory cytokines, resulting in destruction of the alveolar walls. Animal models support the view that these autoantibodies are pathogenic. Xiao et al. [11] immunized MPO knockout mice with murine MPO. Anti-MPO antibodies, purified from the serum of the immunized MPO knockout mice, were injected intravenously into both Rag2 knockout (which lack T and B cells) and wild-type recipients. The recipient mice developed pauci-immune focal necrotizing crescentic nephritis, demonstrating that anti-MPO antibodies alone were sufficient to cause disease. Another murine model using passive transfer of anti-murine PR3 showed exacerbation of local cutaneous inflammation following administration of tumour necrosis factor (TNF) compared with mice without anti-PR3 antibodies. Passive transfer of anti-PR3 antibodies alone did not induce vasculitis or granuloma formation [12]. ANCA, however, are not in themselves sufficient to induce disease in humans as patients may have ANCA but no evidence of disease activity.

Endothelial cells are also important in localizing inflammation. Endothelial cells develop an activated phenotype with enhanced expression of adhesion molecules that promotes interaction with circulating leucocytes. ANCA activation can convert rolling neutrophils to stationary adherent cells and increase transmigration [13]. Release of pro-inflammatory mediators, including nitric oxide, reactive oxygen species and proteolytic enzymes, might all contribute to damage to the vessel wall seen in vasculitis.

Activation of endothelial cells and neutrophils is important for the early development of vasculitic lesions, and progression is accompanied by recruitment of T cells and monocytes. Several studies have suggested that T cells can proliferate to myeloperoxidase or proteinase 3 [14, 15], and that they remain

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Review

Pulmonary manifestations of anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis


Inflammation and necrosis of blood vessel walls occurs in a dozen or so primary vasculitic disorders. An attempt to classify these diverse forms of vasculitis resulted in the Chapel Hill international consensus definitions, which used vessel size as the determinant of classification [1]. Wegener's granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome are described as small vessel vasculitides and are commonly associated with anti-neutrophil cytoplasmic antibodies (ANCA).

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Activation of endothelial cells and neutrophils is important for the early development of vasculitic lesions, and progression is accompanied by recruitment of T cells and monocytes. Several studies have suggested that T cells can proliferate to myeloperoxidase or proteinase 3 [14, 15], and that they remain
activated, with increased activation markers CD25 and HLA-DR on circulating T cells [16, 17], despite disease remission. These studies suggest that T cells contribute to the relapsing–remitting nature of ANCA-associated vasculitis.

Within the respiratory tract of patients with Wegener’s granulomatosis, accumulation of monocytes and T and B cells often manifest as granuloma. Although granulomatous inflammation is a characteristic response to intracellular pathogens (for review see [18]), attempts to isolate an infectious pathogen in Wegener’s granulomatosis have failed. Studies in patients with Wegener’s granulomatosis have shown an excessive Th1 response with significant production of interferon-γ and TNF [19, 20] similar to granuloma formation associated with infection. CD28-negative CD4-positive T cells are a major source of these cytokines in granuloma of patients with Wegener’s granulomatosis, and are uncommon in normal individuals [21, 22]. The excessive production of TNF and interferon-γ could serve to initiate and perpetuate the granulomatous inflammation characteristic of Wegener’s granulomatosis. Interestingly, exposure to silica, which may also result in granuloma formation, is associated with an increased risk of ANCA-associated vasculitis [23].

Environmental and genetic factors also influence disease pathogenesis (for review see [24]). There are no strong HLA associations with ANCA-associated vasculitis but patients with α1-anti-trypsin deficiency have an increased risk of disease and increased disease severity [25, 26]. Drug exposure may also precipitate ANCA-associated vasculitis, including exposure to propylthiouracil, minocycline and penicillamine [27, 28]. Infectious agents have long been suspected of playing a role in development of vasculitis. Chronic nasal carriage of *Staphylococcus aureus* appears to confer significant risk for disease relapse, and pulmonary infection frequently triggers a relapse [29–30].

**Churg–Strauss syndrome**

Observations of Churg–Strauss syndrome in cases of parasitic disease (e.g. ascaris, trichinosis) suggest that in many cases hyper-responsiveness to an antigenic stimulus underlies the syndrome. A number of cases of Churg–Strauss syndrome have been reported following the introduction of leokotriene receptor antagonists. However, of 126 cases, 88% developed disease during a period of steroid tapering, suggesting that these drugs may not in themselves cause disease [31].

Like Wegener’s granulomatosis and microscopic polyangiitis, Churg–Strauss syndrome is not associated with deposition of immune complexes. Activated eosinophils are able to induce activation of vascular endothelial cells and may be directly responsible for some of the classical disease features of Churg–Strauss syndrome by virtue of the release of stored cationic proteins. Thirty to fifty per cent of cases are associated with ANCA, particularly in those with evidence of vasculitis. The pathogenic role of these antibodies is unclear, but they may act to amplify inflammation. Cytokine profiles on the cells involved in Churg–Strauss syndrome are contradictory, but a Th2 cytokine profile may predominate. Interleukin-5 and TNF are elevated in the bronchoalveolar lavage.

**Pulmonary manifestations**

Pulmonary involvement is a characteristic feature of both Wegener’s granulomatosis and Churg–Strauss syndrome, less so in microscopic polyangiitis. The lung is the most commonly affected organ in Wegener’s granulomatosis with evidence of involvement in over 90% of patients during the course of their disease; in 9% it is the only organ affected. Pulmonary involvement ranges from subclinical changes evidenced by high-resolution computer tomography (HRCT) chest scans [32] and the finding of haemosiderin-laden macrophages in bronchoalveolar lavage fluid (BALF) to devastating haemoptysis [32]. Wegener’s granulomatosis can affect all parts of the respiratory tract, resulting in the variety of symptoms illustrated in Table 1. However, asymptomatic pulmonary involvement is common, occurring in over 30% of cases [33]. Approximately 5% of patients will have a fulminant presentation requiring assisted ventilation.

Churg–Strauss syndrome classically, although not always, presents with three distinct clinical phases of asthma, tissue eosinophilia and vasculitis. The phasic development of disease with its distinct pathological findings suggests the evolution of disease over time. Chronic asthma requiring long term steroids often precedes the vasculitic phase by 8–10 yr. With the onset of vasculitic phase, the severity of the asthma and exacerbations increase, although in rare cases these episodes may actually decrease. Allergic rhinitis is a common finding in Churg–Strauss syndrome [34] along with involvement of the nasal and paranasal sinuses (e.g. nasal obstruction, recurrent sinusitis and nasal polyposis) which may precede asthma.

Lung involvement is also common in microscopic polyangiitis. Lung haemorrhage occurs in up to a third of patients. Some patients with microscopic polyangiitis may present clinical, radiological and functional findings consistent with an interstitial process mimicking idiopathic pulmonary fibrosis [35].

**Pulmonary haemorrhage**

Diffuse alveolar haemorrhage (DAH) occurs as a consequence of pulmonary capillaritis in the ANCA-associated vasculitides, and is an important cause of morbidity and mortality in this condition [36]. It can also arise as a result of a major bleed from endobronchial disease. Published series, report the incidence of DAH as 7–45% in Wegener’s granulomatosis [7, 33, 37] and 10–30% in microscopic polyangiitis [38]. It is rare in Churg–Strauss syndrome [6], but almost invariable in isolated pauci-immune pulmonary capillaritis [39]. The acute mortality associated with DAH and underlying vasculitis is approximately 60%, six times greater than vasculitis without pulmonary haemorrhage [37, 40].

Haemoptysis and dyspnoea are the commonest clinical presentations of DAH [39]. However, approximately one-third of patients may have significant alveolar haemorrhage without reporting episodes of haemoptysis. Other features suggestive of DAH include new alveolar shadowing on the chest radiograph in the absence of heart failure or infection with or without
a falling haematocrit. Increases in carbon monoxide gas transfer ($K_{CO}$) of 30% or more from baseline, due to increased haemoglobin–carbon monoxide binding, is seen acutely almost universally [37].

Fibreoptic bronchoscopy may show diffuse blood staining throughout the endobronchial tree. Additional bronchoscopic features include increasing blood staining of sequential aliquots of bronchoalveolar lavage fluid and haemosiderin-laden macrophages [32]. Transbronchial biopsy or thoracoscopic lung biopsy is rarely required, but may be indicated in patients who present with diffuse alveolar haemorrhage in whom the underlying aetiology has not been identified by other means. With experienced operators, the risk of open lung biopsy in ventilated patients is relatively low [41].

**Subglottic stenosis**

Subglottic stenosis occurs in approximately 10–20% of patients with Wegener’s granulomatosis, and can present as its only manifestation [33]. Moreover, the stenotic segments may persist or progress despite control of the disease elsewhere in the body [42]. Subglottic stenosis in Wegener’s granulomatosis affects woman more frequently than men. Symptoms range from cough and shortness of breath to life-threatening stridor. Initial diagnosis can be confused with other pulmonary diseases, especially asthma. Voice changes can occur with glottic involvement. Some patients with Wegener’s granulomatosis also develop distal endobronchial disease which can lead to wheezing, stridor and dyspnoea.

The diagnosis of subglottic stenosis is made on bronchoscopy, flexible pernasal laryngoscopy or radiological imaging of the larynx. Macroscopically, Wegener’s granulomatosis appears as a red, friable circumferential narrowing below the vocal cords. Biopsy yield from the involved area is low and typically reveals non-specific inflammation [42]. Histological confirmation is more likely to come from the nasal mucosa. Severity is determined from clinical history, and measurement of the length and diameter of the stenosed segment using three-dimensional CT reconstruction or magnetic resonance imaging (MRI) of the trachea. Flow-loop studies allow sequential assessment of severity.

**Assessment of pulmonary involvement in ANCA vasculitis**

**Radiology**

Accurate assessment of disease activity within the lungs can be difficult since disease activity correlates poorly with pulmonary symptoms. A plain chest radiograph is routinely obtained to monitor disease activity in the lungs. Typical findings on plain radiograph include bilateral, multiple rounded opacities ranging from a few millimetres to 10 cm in diameter. There is commonly cavitation of these nodules (Fig. 1).

High-resolution CT scanning of the chest offers a more sensitive imaging technique in ANCA-positive vasculitis. High-resolution CT has a higher sensitivity in detecting nodules and masses; these are an important radiographic finding as the probability of having active lung disease is significantly increased when they are present [32] (Fig. 2). Table 2 outlines the broad range of HRCT abnormalities seen in Wegener’s granulomatosis [43]. Once a patient has started upon treatment, radiological abnormalities and pulmonary symptoms become even more challenging, as pulmonary infections affect up to 50% of cases at some point [44]. Clearly, there is a very broad differential diagnosis for these infiltrates [45–47]. Furthermore, since vasculitis patients are at increased risk of cancer, new pulmonary lesions need appropriate investigation [48].

Radiographic abnormalities in patients with Churg–Strauss syndrome are also varied [49–51] with the chest X-ray revealing

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**Table 2. CT findings in areas in 57 patients with Wegener’s granulomatosis**

<table>
<thead>
<tr>
<th>CT finding</th>
<th>Per cent of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodules or masses</td>
<td>89</td>
</tr>
<tr>
<td>Cavitated nodules</td>
<td>49</td>
</tr>
<tr>
<td>Segmental bronchial wall thickening</td>
<td>56</td>
</tr>
<tr>
<td>Septal lines</td>
<td>38</td>
</tr>
<tr>
<td>Consolidation</td>
<td>30</td>
</tr>
<tr>
<td>Lobar bronchial wall thickening</td>
<td>28</td>
</tr>
<tr>
<td>Ground glass attenuation</td>
<td>26</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>19</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>15</td>
</tr>
<tr>
<td>Tracheal wall abnormalities</td>
<td>14</td>
</tr>
<tr>
<td>Pleural irregularities</td>
<td>14</td>
</tr>
<tr>
<td>Hilar or mediastinal lymphadenopathy</td>
<td>14</td>
</tr>
</tbody>
</table>

Adapted from Lohrmann et al. [43].
changes from transient focal areas of consolidation to more extensive peripheral opacities similar to those found in eosinophilic pneumonia. Other manifestations include pulmonary haemorrhage and pleural effusion, which may be present in up to 30% of cases. As with Wegener’s granulomatosis, pulmonary abnormalities are better assessed by HRCT but the pattern is non-specific.

**Pulmonary function abnormalities**

Abnormalities of pulmonary function can be varied in vasculitis according to which part of the respiratory tract is involved. Airflow obstruction is common in Churg–Strauss syndrome but is also seen in patients with Wegener’s granulomatosis, with small airway involvement in both diseases. The chest X-ray is often normal in these patients (7/12 in one study) [52]. Parenchymal involvement can lead to either reduced gas transfer from interstitial involvement or increased gas transfer when there is pulmonary haemorrhage. Central airway obstruction due to subglottic stenosis gives a classical flow volume loop appearance (see Fig. 3). Respiratory muscle weakness may also be present even in those without obvious lung involvement [52].

![Flow volume loop showing typical flow limitation due to](image)

**The role of bronchoscopy**

Bronchoscopy and bronchoalveolar lavage can be useful in patients with vasculitis. Bronchoscopy allows visualization and biopsy of endobronchial disease and is helpful in excluding other pathologies. Bronchoalveolar lavage typically shows a neutrophilic alveolitis in Wegener’s granulomatosis with active disease and vasculitis. In some cases with purely granulomatous disease, lavage may be predominantly lymphocytic [56]. Haemosiderin-laden macrophages are suggestive of pulmonary haemorrhage, which is often subclinical. Transbronchial biopsies are seldom positive in Wegener’s granulomatosis patients unless they are taken from grossly abnormal lung areas [57].

**The role of respiratory tract biopsy**

Obtaining tissue confirmation of granulomatous inflammation is central to the diagnostic process. Biopsies can be obtained from the upper respiratory tract, by endobronchial or transbronchial biopsy, CT-guided biopsy or video-assisted thoracoscopic biopsy. The upper respiratory tract yields diagnostic biopsies in approximately 70% of patients [57]. Open lung biopsy provides histopathological data with a high diagnostic yield [7]. The concomitant pathological finds of necrotizing granulomatous inflammation and necrotizing vasculitis throughout the lung parenchyma is strongly suggestive of Wegener’s granulomatosis. However, these features are not invariably seen in biopsy samples and serial biopsy specimens may demonstrate variable features. It is important to emphasize that the absence of the typical features of Wegener’s granulomatosis does not exclude the diagnosis.

**Treatment**

### Specific therapy

**Disease remission.** Untreated ANCA-associated vasculitis has a 90% mortality rate within 2yr, usually due to respiratory failure [58]. Therapy of disease should be tailored to disease severity. In those with threatened vital organ loss, initial therapy requires high-dose cyclophosphamide and prednisolone (see Table 3). Cyclophosphamide is toxic, and risk of morbidity is dependent

<table>
<thead>
<tr>
<th>Table 3. Treatment regimens for vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Induction therapy</td>
</tr>
<tr>
<td>Prednisolone</td>
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<tr>
<td>Adjuvant therapy</td>
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<tr>
<td>Maintenance therapy</td>
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<td>Prednisolone</td>
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Little is known regarding the long-term effects on lung function in patients with early lung involvement. Previous vasculitic lung disease may cause persistent scarring and loss of the alveolar capillary bed. CT changes of ground glass opacification often resolve without scarring; however, one-third of nodules, masses and consolidation may heal with scarring and development of fibrosis. Small case studies have suggested that patients may be left with residual airflow obstruction, pulmonary fibrosis and reduced diffusion capacity [53–55]. We have also shown that patients with previous pulmonary involvement are more likely to have reduced transfer factor and exercise capacity [52].
on cumulative dose. A recent multicentre study suggested that 3 months’ cyclophosphamide changing to azathioprine to maintain remission is as effective as a more prolonged course of cyclophosphamide [59]. The efficacy of pulsed cyclophosphamide has been examined in ANCA-associated vasculitis. A meta-analysis suggested that pulsed cyclophosphamide may be less toxic with fewer adverse effects than daily oral cyclophosphamide and that it is at least as potent at inducing remission, but possibly at the risk of a higher relapse rate [60, 61]. In those without threatened vital organ involvement methotrexate may be used as an alternative; however, this may be at the expense of increased relapse [60, 62]. Methotrexate should be avoided in those with significant renal impairment.

Steroids are the mainstay of treatment in Churg–Strauss syndrome; however, cyclophosphamide should be added in those with more severe disease. The French Vasculitis Study Group reported that those with more severe disease (five factor score >2) had prolonged survival when treated with steroids and cyclophosphamide but associated with increased adverse effects [63].

The most important indicators of prognosis are pulmonary haemorrhage and severity of renal failure at diagnosis. Patients who present with fulminant disease require intensification of induction therapy with either methylprednisolone or plasma exchange. A recent trial of patients with severe renal involvement has shown improved outcome in patients receiving plasma exchange [64]. There are no randomized trials of patients with pulmonary haemorrhage, though retrospective case series suggest benefit of plasmapheresis and methylprednisolone [65].

Intravenous immunoglobulin (IVIg) has also been used as adjunctive therapy, but a randomized placebo-controlled trial of 34 patients suggested only a transient improvement. IVIg is associated with significant side-effects including renal failure [66].

TNF is thought to be important in the pathogenesis of ANCA-associated vasculitis, and several case series have suggested a benefit. However, a randomized controlled trial of patients with Wegener’s granulomatosis showed no benefit of etanercept (a TNF receptor fusion protein) in inducing disease remission or maintenance of remission when added to standard therapy (steroids and cyclophosphamide or methotrexate), compared with placebo (WGET) [67]. Methodological flaws may have contributed to the negative outcome of this study as more patients with relapsing disease or those who previously failed treatment were included in the etanercept limb. The relapse rate was higher than in previously reported studies, and 55% of patients suffered severe adverse events. Further, etanercept may be less effective in granulomatous inflammation than infliximab (an anti-TNF monoclonal antibody) as infliximab but not etanercept is effective in Crohn’s disease [68]. Further studies with infliximab are required.

Infection remains an important cause of morbidity and mortality in these patients. Pneumocystis carinii prophylaxis should be administered to those receiving cytotoxics, for example alternate-day septrin. An important risk for infection is neutropenia, a common complication of cyclophosphamide therapy. The use of granulocyte colony stimulating factor, a neutrophil-activating agent, appears safe and does not carry a high risk of inducing a flare of vasculitis [69].

Maintenance of remission. Relapse is common despite continued immunosuppressive therapy, with 50% of patients relapsing within 5 yr. In the EUVAS study assessing maintenance of remission, azathioprine was as effective as cyclophosphamide; however, at 18 months there was a 16% relapse rate in both limbs [59]. Azathioprine is recommended for maintenance therapy. However, a retrospective study has suggested that change to azathioprine when patients remain PR3-ANCA positive may increase the risk of relapse [70]. The optimal duration of therapy following disease remission is not clear; immunosuppressive therapy should be continued for at least 2 yr following successful remission. In those who remain ANCA positive or have had previous relapses, consideration should be given to long-term immunosuppression.

Other therapies have been piloted to maintain remission in an attempt to reduce relapse. In two pilot studies mycophenolate has shown promise in maintaining remission [71, 72], and a large randomized controlled trial comparing mycophenolate with azathioprine for maintenance of remission is under way. Leflunomide has also been used but is less promising. Maintenance of remission was achieved in a pilot study of 20 patients using leflunomide following disease induction with cyclophosphamide and prednisolone [73]. One patient had a major relapse and eight patients suffered minor relapse in a median follow-up of 1.75 yr. Side-effects were common: 40% of patients had mild respiratory infections, 35% of patients experienced arthralgia and 35% developed hypertension.

Colonization of the upper respiratory tract by Staphylococcus aureus may increase the risk of disease relapse. Eradication with septrin reduced the risk of respiratory relapse compared with placebo when added to conventional therapy, but there was a high rate of drug intolerance [29]. Septrin is not recommended for use at the expense of conventional immunosuppression.

**Rescue therapies for refractory or relapsing disease**

Standard induction therapy fails to induce remission in approximately 10% of patients. A further group of difficult patients are those who frequently relapse, necessitating recurrent use of cyclophosphamide.

Rituximab, a CD20 B-cell-depleting antibody, has been reported to induce disease remission in several reports in those with refractory disease. In a series of nine patients, this also resulted in a fall in ANCA titres but without depleting total immunoglobulin levels [74]. However, disease may relapse on recovery of B cells [75]. The efficacy and safety of rituximab in disease induction and maintenance of remission is being assessed in a randomized placebo-controlled trial.

Deoxyspergualin (DSG) is an immunosuppressant agent that has been successfully used in acute renal allograft rejection and various animal models of autoimmune disease. Its mode of action is not fully understood but it may interfere with activation of nuclear factor (NF)-κB. Interestingly, it has a bactericidal effect on S. aureus. In an open label multicentre pilot study, DSG was used to induce remission in 19 patients with active refractory Wegener’s granulomatosis, all of whom were unresponsive or refractory to standard therapy. Patients received 0.5 mg/kg DSG daily until white blood cells fell to 3 × 10⁴/l; they were then given a 14-day rest cycle before repeating six cycles over 6 to 8 months. Treatment was well tolerated with no deaths or episodes of septicaemia [76]. A follow-up study has suggested that continued use of DSG is effective and safe in patients refractory to standard therapy [77].

T cells play a role in disease pathogenesis. Anti-thymocyte globulin (ATG) is directed against surface antigens of activated lymphocytes and results in lymphocyte depletion. Fifteen patients with refractory Wegener’s granulomatosis, 11 with severe pulmonary involvement, received ATG. Thirteen patients responded, with four patients achieving complete remission and partial remission in 13. During a median follow-up of 21 months, eight patients relapsed (median time to relapse 8 months) and two patients died, one from infection and the other pulmonary haemorrhage following treatment [78]. ATG may be beneficial in patients with severe refractory disease.

Case reports have suggested that interferon-α may be beneficial in patients with refractory Churg–Strauss syndrome [79]. In one study with three patients with Churg–Strauss syndrome, all patients showed early clinical improvement in
pulmonary function studies and tapering of steroid dose [80]. However, benefit must be balanced with risk as most patients suffer adverse events such as flu-like symptoms; less frequently, neuropsychiatric symptoms and cardiotoxicity may occur.

Supportive treatment
Progressive respiratory failure during DAH often necessitates invasive mechanical ventilation which continues to be associated with a high mortality. Modern ventilation practise supports the use of protective ventilation strategies with lower tidal volumes to limit the extent of ventilator associated lung injury [81]. Anecdotal reports of improvements in oxygenation in the context of DAH have been seen after placing the patient prone during mechanical ventilation [82]. Prone positioning may improve ventilation perfusion matching through changes in inflation, ventilation, recruitment and perfusion of alveoli.

To date at least six reports describe success with the use of extracorporeal membrane oxygenation (ECMO) in DAH associated with ANCA-associated vasculitis [83]. However, ECMO requires specialist equipment and expertise that is not widely available and hence may limit its application in the clinical setting. Infusions of activated Factor VIIa have also been used successfully to treat DAH secondary to microscopic polyangiitis [84, 85]. Although coagulation studies are typically normal in patients with DAH, there are high levels of inhibitors to endogenous Factor VIIa/tissue factor complex. Treatment with high-dose exogenous activated Factor VIIa arrested life-threatening bleeding rapidly, whilst standard immunotherapy and plasmapheresis brought the pulmonary capillary inflammation under control.

For patients with subglottic stenosis, supportive management is dependent on the severity of the stenosis, the severity of symptoms, the activity of the Wegener’s granulomatosis [86] and the patient’s overall health. Subglottic stenosis often progresses despite immunosuppressive treatment [42]. Several approaches to limiting the stenosis are possible, including intralesional steroid injections and bougie dilatation [55, 87, 88]. These approaches have not received widespread acceptance in the UK and ultimately tracheostomy is required to achieve a permanent patent airway in approximately 60% of cases [89, 90]. Tracheostomy results in almost complete relief from symptoms and is usually well tolerated. Small case series have suggested that surgical resection of stable stenosis is feasible but should be considered only in centres with appropriate expertise [42, 91]. For patients with distal endobronchial stenosis, bougie dilatation and stenting are successful in experienced hands.

Conclusions
ANCA-positive vasculitis commonly affects the respiratory tract and has a wide range of manifestations. The differential diagnosis of all the manifestations is wide and diagnosis often requires several investigational tests spanning several medical and surgical specialties. Respiratory complications of vasculitis and its treatment can be life-threatening, necessitating detailed and intensive clinical follow-up. We believe this is best achieved in specialist clinics with an appropriately dedicated multidisciplinary team.

The authors have declared no conflicts of interest.

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