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section 18 Respiratory disorders 4200 Some patients with interstitial lung disease associated with con- nective tissue disorders are refractory to conventional immunosup- pression. Rituximab, a chimeric anti-CD20 monoclonal antibody, results in rapid depletion of B lymphocytes from the peripheral cir- culation and has shown significant clinical and functional benefit in severe, progressive CTD-ILD. Its efficacy is most impressive in patients with polymyositis/dermatomyositis, but it probably has no significant effect on progression of lung fibrosis in systemic scler- osis, and its effect in rheumatoid arthritis-associated interstitial lung disease is uncertain. FURTHER READING Alunno A, et al. (2017). Clinical, Epidemiological, and Histopathological Features of Respiratory Involvement in Rheumatoid Arthritis. Biomed Res Int, 2017, 7915340. doi: 10.1155/2017/7915340. Barnes H, et al. (2018). Cyclophosphamide for connective tissue disease-associated interstitial lung disease. Cochrane Database Syst Rev, 1:CD010908. doi: 10.1002/14651858.CD010908.pub2. Bouros D, et al. (2002). Histopathological subsets of fibrosing alveol- itis in patients with systemic sclerosis and their relationship to out- come. Am J Respir Crit Care Med, 165, 1581–6. Corte TJ, Du Bois RM, Wells AU. (2015). Infiltrative and interstitial lung diseases: connective tissue diseases. In: Broaddus VC, et al. (eds). Murray and Nadel's Textbook of Respiratory Medicine, 6th edn, pp. 1165–87. Elsevier Saunders, Philadelphia. DeMarco PJ, et al. (2002). Predictors and outcomes of scleroderma renal crisis: the high-dose versus low-dose D-penicillamine in early diffuse systemic

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18.11.5 The lung in vasculitis 4201 vasculitides, indicating those in which the lung is involved. According to Chapel Hill International's nomenclature (2012 re- vision), Churg–Strauss syndrome and Wegener's granulomatosis have been renamed as eosinophilic granulomatosis with polyangiitis (EGPA) and granulomatosis with polyangiitis (GPA), respectively. Clinical manifestations of pulmonary vasculitis Lung involvement in vasculitic disease can manifest as: • diffuse alveolar haemorrhage; • an isolated reduction in gas transfer (carbon monoxide diffusing capacity, DLco), with or without pulmonary hypertension. Investigations listed in Box 18.11.5.1 should be performed if pul- monary vasculitis is suspected. Diffuse alveolar haemorrhage The presenting features of diffuse alveolar haemorrhage include fever, weight loss, and other systemic symptoms in association with cough, breathlessness, and clinical signs suggestive of pneumonia. A history of previous haemoptysis is sometimes helpful, but in other cases diffuse alveolar haemorrhage presents acutely. Chest radiog- raphy shows consolidation, typically resolving within a matter of days, unlike the usual time-course in infective pneumonia. High- resolution CT may reveal an extensive ground-glass appearance, denoting partial alveolar filling. A fall in haemoglobin over a day or longer is diagnostically useful, and chronic iron-deficiency anaemia can arise from low-grade haemorrhage over a lengthy period. Bronchoalveolar lavage is usually diagnostic in the absence of haemoptysis, revealing overt blood staining in sequential lavage in the acute presentation, or the presence of numerous macrophages containing iron, identified by Perl's stain, in chronic disease. The gas transfer corrected for alveolar volume (Kco) is elevated in acute haemorrhage, but only if measured within 36 h, seriously limiting the diagnostic yield. Diffuse pulmonary haemorrhage occurring without identifiable cause or association is known as idiopathic pul- monary haemosiderosis (see Chapter 18.14.1). Isolated gas transfer deficit, with or without pulmonary hypertension Pulmonary vasculopathies other than alveolar haemorrhage present with breathlessness on exertion. Clinical examination of the respira- tory system and routine lung imaging are normal. Lung function tests show preservation of lung volumes with an isolated reduction of DLco. In severe pulmonary vascular disease pulmonary hyper- tension may be clinically overt, and in other cases it is detected by echocardiography, especially if tricuspid regurgitation allows Doppler Table 18.11.5.1 Pulmonary vascular disease Vasculitic Nonvasculitic Primary systemic Thromboembolic Secondary Primary pulmonary hypertension • Rheumatological Secondary pulmonary hypertension • Pulmonary–renal Systemic sclerosis • Behçet's syndrome Idiopathic pulmonary haemosiderosis • Chronic infection Arteriovenous malformations • Lymphoma • Drugs Penicillamine Hydralazine Propylthiouracil Nitrofurantoin Table 18.11.5.2 2012 revised International Chapel Hill consensus nomenclature of systemic vasculitis Systemic vasculitis Lung disease • Large vessel Giant cell arteritis Rare Takayasu's arteritis Frequent • Medium-size vessel Polyarteritis nodosa Rare Kawasaki disease No • Small vessel (medium-size vessel involvement may
be present) Granulomatosis with polyangiitis Frequent Eosinophilic granulomatosis with polyangiitis Frequent Microscopic polyangiitis Frequent Henoch–Schönlein purpura No Essential cryoglobulinaemia No Box 18.11.5.1 Investigations to be considered if lung vasculitis is suspected Imaging • Chest radiography and high-resolution CT Lung function tests • DLco/Kco Blood gases Renal function • Urine dipstick testing and microscopy for proteinuria, haematuria, and cellular casts; measurement of serum creatinine; consider renal biopsy (if evidence of nephritis) Immunology • Antineutrophil cytoplasmic antibodies (ANCA), antiglomerular base- ment membrane (anti-GBM) antibodies, immune complexes, rheuma- toid factor, antinuclear antibodies, antiphospholipid antibodies Bronchoscopy/Bronchoalveolar lavage • Iron-laden macrophages • Exclusion of low tract respiratory infections • Assessment of the large airways (stenosis-

endobronchial lesion) Biopsy • Renal • Skin • Lung (surgical)

section 18 Respiratory disorders 4202 estimation of pulmonary artery pressures. Vasculopathies other than vasculitis should be considered in this clinical context, including ab- lative vasculopathies (as in systemic sclerosis and primary pulmonary hypertension) and coagulopathies leading to thromboembolism or intrapulmonary microvascular thrombosis (see Chapter 16.15.2). The following sections discuss lung involvement in specific vascu- litic disorders, followed by discussion of key clinical problems, prog- nosis, and treatment. Eosinophilic granulomatosis with polyangiitis First described by Churg and Strauss in 1951, this rare condition has an estimated annual incidence of approximately 3 per million and mostly affects adults aged 30 to 50 (although the reported age range is 7–74 years). There is no strong gender predilection. Typically, asthma and eosinophilia are associated with the characteristic histo- logical findings (Fig. 18.11.5.1), consisting of profuse eosinophilic infiltration, extravascular granulomatous inflammation, and necro- tizing arteritis affecting small to medium-sized vessels. There is little information about geographical variation. Aetiology and pathogenesis The underlying pathogenetic mechanism is generally considered to be an eosinophilic granulomatous response to a foreign antigen, akin to the eosinophilic granulomatosis seen in schistosomiasis. In support of this hypothesis, immunological stimuli (vaccination or immunotherapy) have been reported to trigger the disease, al- though the pauci-immune nature of the histopathology has yet to be explained. The introduction of antileukotriene therapy for asthma has been associated with an increased incidence of EGPA, but it remains unclear whether the drug triggers the onset of dis- ease. It is also possible that reduction or withdrawal of corticoster- oids with better control of asthma unmasks the condition in some cases, although some individuals who have never received cortico- steroids have developed the syndrome with the introduction of an antileukotriene agent. The HLA-DRB1*04 and *05 alleles and the related HLADRB4 gene are associated with increased risk of developing EGPA. There is evidence suggesting that the disease is mediated by a Th-2 response through the release of cytokines such as IL-4,-13,-5. Th1 and Th17 cells are involved in advanced stages, whereas T regulatory cells are reduced in active disease. It has recently been proposed that B-cells can contribute to the development of the disease. Antineutrophil cytoplasmic antibodies (ANCA), first described in 1982, are frequently present in systemic vasculitides involving small and medium-sized vessels, including EGPA, GPA, and microscopic polyangiitis. ANCA are directed against cytoplasmic antigens in polymorphonuclear leucocytes and monocytes and are subcategorized according to their immunofluorescent staining pattern as C (cytoplasmic), P (perinuclear), or A (atypical). The pathogenetic significance of ANCA is unclear, but ANCA recep- tors on the surface of neutrophils are upregulated at disease sites, and ANCA can also interact with endothelial cells to cause injury and coagulation. All ANCA patterns have been reported in EGPA, but P-ANCA occur most frequently, usually directed against myeloperoxidase (MPO) and only very infrequently against pro- teinase 3 (PR3). Pulmonary presentation and diagnostic criteria Two sets of diagnostic criteria have been used: Lanham's criteria and the criteria of the American College of Rheumatology. In addition to systemic features such as fever and weight loss, Lanham defined the disease as requiring: • asthma • eosinophilia greater than 1.5 × 109/litre in the peripheral blood • evidence of systemic vasculitis in two or more organs other than the lung The American College of Rheumatology definition requires the satisfaction of at least four of the following six criteria: • the presence of asthma • eosinophilia greater than 10% in the peripheral blood • evidence of a neuropathy in a vasculitic pattern (e.g. mononeuritis multiplex) • transient pulmonary infiltrates • a history of sinus disease • evidence of extravascular eosinophilia on biopsy In most patients asthma

precedes vasculitic manifestations, often by years, although these features develop simultaneously in up to 20% of cases. Typically the prodromal phase consists of rhinitis with nasal polyps, which often lasts for years before the eventual devel- opment of late-onset asthma that is generally resistant to treatment. The second phase is characterized by eosinophilia in the peripheral blood and tissues and often follows a relapsing and remitting course. The final phase, systemic vasculitis, often follows the onset of the Fig. 18.11.5.1 A case of eosinophilic granulomatosis with polyangiitis showing a pulmonary artery surrounded by granulomatous inflammation and a florid mixed inflammatory cell infiltrate that includes abundant eosinophils.

18.11.5 The lung in vasculitis 4203 second phase by several years and is immediately preceded by im- provement in asthma. This pattern of evolution of disease is more than 95% specific and sensitive for EGPA. Respiratory failure and status asthmaticus account for 10% of deaths. Other organ involvement Skin lesions These are seen in about 60% of patients, generally manifesting as palpable purpura or subcutaneous nodules. Skin infarcts also occur. Cardiac involvement The heart may be involved diffusely, producing congestive cardiac failure or restrictive cardiomyopathy. Eosinophilic myocarditis is present in up to 50% of cases, with coronary artery vasculitis and pericardial effusions much less frequent. Cardiac disease is the most common cause of death. Renal disease This is much less common than in GPA or microscopic polyangiitis, but the histopathology is very similar, consisting of a focal segmental necrotizing glomerulonephritis. Renal disease is generally mild, but end stage renal failure is reported. See Chapter 21.10.2 for further discussion. Nervous system involvement Mononeuritis multiplex such as drop wrist or drop foot, confirmed by nerve conduction studies or sural nerve biopsy, is the most common manifestation, occurring in up to 75% of patients. Cranial nerve involvement is less common, but cerebrovascular disease may occur. Gastrointestinal involvement Vasculitis of the mesenteric vessels may produce bowel abnormal- ities, including perforation, and less commonly eosinophilic infiltra- tion may cause obstruction. Musculoskeletal system Arthritis is relatively common, as are myalgias. Investigation Chest radiography shows patchy lung infiltration in up to 80% of patients and pleural disease is present in up to 50%. High-resolution CT is much more sensitive than chest radiography, although the full spectrum of abnormalities has yet to be defined. The most frequent findings are patchy ground-glass infiltration and patchy consolida- tion. An extensive ground-glass appearance is usual in patients in whom alveolar haemorrhage is due to capillaritis, whereas consoli- dation is more suggestive of granuloma formation in association with involvement of medium-sized vessels. Pulmonary infiltrates are much more common than pulmonary nodules and, in contrast to GPA, cavitation of nodules is extremely rare. Bronchial wall thick- ening and bronchiectasis have also been described. Table 18.11.5.3 lists the major pulmonary manifestations. There is a peripheral blood eosinophilia, matched by a marked eo- sinophilia on bronchoalveolar lavage. The diagnostic role of ANCA continues to be debated. ANCA, usually P-ANCA-MPO, are present in up to two-thirds of patients, but in some series their prevalence is much lower and P-ANCA also occur in many other nonvasculitic autoimmune and infectious conditions. Thus, the presence of P-ANCA is no more than a useful ancillary finding, increasing the diagnostic likelihood, and the absence of P-ANCA should not ma- terially influence the diagnostic algorithm. ANCA-positive patients more frequently have peripheral neuropathy, glomerulonephritis, and purpura compared to ANCA negative patients, who have more frequent lung, myocardial, and gastrointestinal symptoms. Eotaxin-3, an eosinophil attracting chemokine, could be an at- tractive biomarker for the future, as at a cut-off level of 80 pg/ml it has a sensitivity and specificity of 87.5% and 98.6%, respectively, to diagnose active EGPA. The classical triad at lung biopsy consists of necrotizing angiitis, granulomas, and tissue

eosinophilia (Fig. 18.11.5.1). Giant cells and fibrinoid necrosis are present. However, it is not uncommon for histological appearances to be indeterminate, with the presence of some but not all of the characteristic features, and in some cases there is overlap with the histopathological appearances of GPA or microscopic polyangiitis. Surgical biopsies have a much higher diag- nostic yield than transbronchial biopsies, which seldom disclose vasculitis. Granulomatosis with polyangiitis The systemic features of GPA are described in Chapter 19.11.7. It is the third most prevalent systemic vasculitis (after giant cell arter- itis and vasculitis in rheumatoid arthritis), and occurs throughout the world with an annual incidence of 3–11 per million, depending upon the geographic region. It mainly affects adults aged 30–50 (al- though it may occur in any age group), and there is no gender pre- dilection. The histological abnormalities consist of granulomatous inflammation associated with necrotizing vasculitis, affecting small to medium-sized vessels (Fig. 18.11.5.2). Lung involvement occurs at some stage of disease in up to 85% of cases; upper respiratory tract and renal involvement (due to necrotizing glomeruloneph- ritis) are frequent. Aetiology and pathogenesis Studies of possible genetic associations have yielded conflicting re- sults, with linkage to HLA DR1 or HLA DR2 in some but not all Table 18.11.5.3 Distinguishing thoracic features in primary vasculitis Thoracic features Eosinophilic granulomatosis with polyangiitis Granulomatosis with polyangiitis Microscopic polyangiitis Subglottic stenosis + + Multiple nodules + + Solitary nodules + Cavities + Localized infiltrates + + Transient infiltrates + + Pleural involvement + + Cardiac involvement +

 populations. The importance of environmental factors is equally un- certain. Case–control studies have suggested that exposure to silica or silicone might be pathogenetic in some cases. ANCA-positive vasculitis mimicking GPA has been induced by propylthiouracil, hydralazine, and penicillamine, possibly by modifying MPO and thereby creating an antigenic stimulus. However, the most sug- gestive data relate to infection, especially with Staphylococcus au- reus. Chronic nasal carriage of S. aureus is substantially more prevalent in GPA than in control populations, and it has been sug- gested that staphylococcal acid phosphatase might be antigenic in susceptible individuals. An immunostimulatory role for S. aureus B-cell superantigens has also been proposed. The partial efficacy of prophylactic trimethoprim–sulfamethoxazole in reducing both infection and the likelihood of relapse of GPA provides further in- direct support for an infectious pathogenesis. Pathogenetic concepts are complicated by the histological spec- trum of disease, ranging from prominent granulomatous lesions, associated with a lymphocytosis on bronchoalveolar lavage, to ful- minant necrotizing vasculitis, in which a bronchoalveolar lavage neutrophilia is the rule. The genesis of granulomata is not well understood, but there is strong indirect evidence that neutrophils play a key role in initiating vasculitis. PR3 is the main target antigen for C-ANCA, which is found in about 90% of patients with gener- alized GPA (as compared to 50% of patients with localized disease). As in other ANCA-positive vasculitides, there is in vitro and animal model evidence to suggest that PR3-ANCA might interact with primed neutrophils, leading to neutrophil degranulation and thus to endothelial damage and further neutrophil recruitment. Pulmonary presentation Involvement of the upper and/or lower respiratory tract is the presenting feature in 90% of cases. Disease usually evolves in two phases. Initially there is chronic rhinitis, sinusitis, or mastoid- itis, after which most patients progress to generalized disease over months to years, with lower respiratory tract involvement in 65 to 85% often manifesting with cough, which may be purulent, and less frequently with haemoptysis due to diffuse alveolar haemorrhage. Systemic symptoms, including fever and weight loss, are frequent in generalized disease, along with variable involvement of other organs as

described in Chapter 19.11.7. Lung involvement is asymptomatic in about one-third of cases, with the main lung manifestations being (see Table 18.11.5.3): • one or more nodules, which can cavitate (Fig. 18.11.5.3a) • localized or diffuse infiltrates (Fig. 18.11.5.3b) • alveolar haemorrhage that may be part of a pulmonary–renal syndrome • large and small airway disease Investigations As in other vasculitides, classical features are not always present at biopsy, with many patients having only one or two of the three car- dinal histological features (granuloma, necrosis, vasculitis). If a lung Fig. 18.11.5.2 A case of granulomatosis with polyangiitis (GPA) showing an area of geographic necrosis around a partly destroyed pulmonary vessel. This focus is surrounded by chronic inflammation and fibrosis, within which there is granulomatous inflammation with the giant cells showing a somewhat pyramidal morphology. Fig. 18.11.5.3 GPA most often presents radiologically. CT scans may reveal one or more nodules, which can cavitate (a), or localized (b) or diffuse infiltrates.

18.11.5 The lung in vasculitis 4205 biopsy is required, surgical biopsy is preferred, transbronchial bi- opsies having a much lower diagnostic yield, especially when not targeted to areas with overt abnormalities on chest radiography or high-resolution CT. In advanced pulmonary disease the haz- ards of biopsy should prompt a search for an alternative biopsy site, including the kidney, skin, and skeletal muscles. Endoscopic nasal biopsy appearances are most often nonspecific, although positive features in a few cases provide a definitive diagnosis. Irrespective of the biopsy site, suggestive appearances may be diagnostic when combined with clinical and serological information even when diag- nostic histological features are absent. The two main patterns on chest radiography and high-resolution CT are nodules and consolidation, with pleural effusions an occa- sional finding. High-resolution CT offers the important advantage of better definition of nodule cavitation, a key diagnostic feature, and may also disclose abnormalities of the large intrathoracic and extrathoracic airways, including subglottic stenosis, stenosis of large airways, and bronchiectasis. Subglottic stenosis is present in up to 25% of cases and can develop without concomitant systemic disease activity. Fibre-optic bronchoscopy may show tracheobronchitis, including ulceration and ‘cobblestoning’ of the mucosa, or airway stenosis. Bronchoalveolar lavage fluid contains an excess of neutrophils and usually of eosinophils (with diffuse infiltrates) or lymphocytes (more interstitial disease), but is most useful in excluding alveolar haem- orrhage or infection, including opportunistic infection in treated patients. Haematological and biochemical investigations reflect the in- flammatory process. The diagnosis should never be based upon C-ANCA positivity in isolation because these are also found in other contexts, including other vasculitides, chronic bacterial infections, and cryoglobulinaemia. Microscopic polyangiitis The main description of microscopic polyangiitis occurs elsewhere (Chapter 19.11.7), but this necrotizing vasculitis affects small to medium-sized vessels, with few or no immune complex deposits, and lung disease occurs in 35–55% of cases. Pulmonary presentation Lung involvement is less frequent than in GPA. The major pres- entation (Table 18.11.5.3) is diffuse alveolar haemorrhage, which can have a poor prognosis. Pulmonary capillaritis may be associ- ated with evidence of disease outside the lung, particularly nec- rotizing glomerulonephritis, mononeuritis multiplex, and skin lesions. It is often difficult to distinguish microscopic polyangiitis from GPA clinically. The key histological distinction is the absence of granulomas, which are characteristically present in GPA. Renal biopsies can be identical in the two conditions. Microscopic polyangiitis also needs to be distinguished from polyarteritis nodosa that, by definition, only affects arteries, rarely arterioles, and never small vessels. Renal vasculitis with microaneurysm formation occurs in polyarteritis nodosa but not microscopic polyangiitis, and diffuse alveolar haemorrhage does not occur in

polyarteritis nodosa. Other diseases Other primary systemic vasculitides occasionally present with re- spiratory features. Takayasu's arteritis This arteritis affects predominantly the aorta and its main branches but involves the pulmonary arteries in up to 50% of patients, pre- senting with pulmonary vascular occlusion. Giant cell arteritis There is rarely objective evidence of lung involvement, but 25% of patients with giant cell arteritis have cough, hoarseness, and sore throat at presentation. The other systemic vasculitides that feature in the Chapel Hill International consensus nomenclature, but which rarely, if ever, pre- sent with lung disease, are Henoch–Schönlein purpura and essential cryoglobulinaemia. Behçet's disease This occurs predominantly in Mediterranean countries and can produce pulmonary vascular inflammation affecting all sizes of vessels and resulting in pulmonary arterial aneurysms, arterial and venous thrombosis, pulmonary infarcts, and pulmonary haemor- rhage. It is crucial to differentiate haemorrhage from thrombosis because of the treatment implications. Pulmonary veno-occlusive disease This is a disorder of unknown cause that manifests with progressive occlusion of the postcapillary venules, resulting in features similar to those of pulmonary oedema. There is no known effective treatment. Differentiation from cardiogenic causes of raised pulmonary venous pressure must be made. Key clinical problems in vasculitis Diagnosis Ideally, typical histological appearances should be present, and when they are not present the requisite number of clinical criteria should be met. However, formal diagnostic criteria are merely a basis for diagnostic negotiation in many cases. Classification systems fail to capture the entire spectrum of vasculitic disease, with many patients having features overlapping between diagnostic entities. With the advent of ANCA antibodies, formes frustes of full blown vasculitic syndromes are increasingly diagnosed, with transient or no fulfil- ment of full diagnostic criteria in many instances. Even in cases sat- isfying diagnostic criteria, the clinical heterogeneity of the vasculitic syndromes is notorious, it often being stated that no two patients are alike. An appreciation of these difficulties informs the clinician of the need for a versatile diagnostic approach. When vasculitis is suspected but full clinical criteria are not satisfied, a histological diagnosis should generally be sought, targeted to involved organs. Failure to capture typical appearances at biopsy does not necessarily exclude a diagnosis of vasculitis as vasculitic processes may be patchy and nonspecific inflammatory change may be evident: this

section 18 Respiratory disorders 4206 applies especially to upper airway biopsies in patients with GPA. An empirical diagnosis of a vasculitic syndrome must sometimes be made, and in these cases—which tend to foment a great deal of in- security in patients and clinicians alike—it is essential to do every- thing possible to exclude the most frequent differential diagnoses, namely infection and malignancy. When formal diagnostic criteria for a vasculitic syndrome are not fulfilled and empirical treatment is required, the general approach— including initial treatment and monitoring—should be as for the vasculitic syndrome most closely resembling the particular clin- ical presentation of the patient. When the diagnosis is uncertain the initial treatment should be definitive because a satisfactory re- sponse provides useful ancillary diagnostic support ('diagnosis by therapeutic challenge'): a tentative initial therapeutic approach often merely serves to prolong diagnostic uncertainty. Prognosis The outcome of the more frequent vasculitic syndromes was poor when they were first described, but has improved strikingly, as best illustrated by the mortality of GPA: the mean survival of 5 months in early reports has now been transformed, with complete initial re- mission in 75% of cases, increasing further with the recent use of rituximab. However, despite these improvements, long-term follow- up continues to be needed in GPA (relapse occurs in 50–70% of cases) and other vasculitides. The improvement in prognosis in GPA, also seen in EGPA,

in part reflects the increasing use of immunosuppressive agents in combination with corticosteroid therapy. However, the increasing detection of milder disease, including patients with limited involve- ment, has also undoubtedly improved average outcome. Localized GPA has a better outcome than disease with multiorgan involve- ment. The prognosis of EGPA is generally good for those with iso- lated intrathoracic disease (5-year survival 88%), but worsens with two or more extrapulmonary complications (5-year survival 54%), particularly with proteinuria more than 1 g/day, renal insufficiency (creatinine >140 µmol/litre), cardiomyopathy, gastrointestinal dis- ease, or central nervous system involvement. The causes of death in vasculitis can be broadly subdivided into sepsis (as a complication of treatment) and disease progression. In GPA death from progressive disease is most commonly due to renal failure or lung involvement. In EGPA the main cause of death is cardiac disease, followed by renal failure, cerebrovascular involve- ment, and gastrointestinal disease, with lung disease accounting for 10% of deaths. Treatment As a general rule, treatment of vasculitis includes two phases: induction of remission with aggressive therapy against vascu- litis; and maintenance of remission with the aim of establishing the minimum level of therapy required to prevent relapse. The choice of treatment is based on the activity and extent of disease (Table 18.11.5.4). Limited disease Treatment recommendations are based mainly on expert opinion, given the lack of clinical trials. Immunomodulation with oral cor- ticosteroid, given as monotherapy or in combination with a second- line immunosuppressive agent such as methotrexate, azathioprine, or mycophenolate mofetil is the most frequent regimen used in this group of patients. Early generalized disease The combination of corticosteroid and cyclophosphamide is most often used to induce remission. Methotrexate at a dose of 0.3/mg/kg/week has less side effects and is better tolerated than cyclophosphamide, but is associated with a higher rate of relapse. Generalized active disease The combination of oral corticosteroids and oral cyclophospha- mide achieves remission in 55–80% of cases. The initial dose of oral steroids is 1 mg/kg/day, but in more severe cases intravenous administration at the dose of 7.5–15 mg/kg/day for 1–3 consecu- tive days is preferred. A major benefit of initial pulsed therapy is that lower doses of oral corticosteroids can subsequently be used in rapid responders, thus minimizing long-term steroid-related side effects such as infections, diabetes, and osteoporosis. Treatment with steroids should be carried on for at least 6–12 months after the initial presentation of the disease as earlier discontinuation is asso- ciated with an increased risk of relapse. Cyclophosphamide can be administered orally (2 mg/kg/day) or intravenously (600 mg/m2 at three- to four-weekly intervals), depending on disease severity. The side effects include neutropenia and infections, haemorrhagic cystitis, late bladder cancer, and infer- tility (with bladder side effects less prevalent with the use of intra- venous regimens). Intravenous cyclophosphamide is also less toxic with regard to other side effects, but is associated with a higher rate of relapse compared to oral cyclophosphamide. Rituximab, an anti-CD20 monoclonal antibody, was initially used to treat relapsing disease (375 mg/m2 weekly for four weeks). More recently, it has proved to be more effective than oral cyclo- phosphamide for induction of remission, used in combination with steroid therapy, and equally effective in the treatment of al- veolar haemorrhage. When rituximab is used to induce remission, it is often possible to avoid or minimize maintenance therapy, of- fering an important advantage of over cyclophosphamide-based induction regimens. Taken together, trial data and accumulated clinical experience suggest that rituximab may be superior to cyclophosphamide as induction therapy, although not always ap- proved for use due to cost considerations. Rituximab is the agent of choice when there are contraindications to cyclophosphamide and for relapse following cyclophosphamide therapy (especially Table 18.11.5.4 EUVAS (European Vasculitis Study Group) classification EUVAS

classification Clinical features Limited Isolated upper airways disease Early generalized End-organ involvement that lacks a clear or immediate threat to organ function Generalized active End-organ involvement with clinically significant impairment of organ function Severe Immediate threat of organ failure or death Refractory Disease that was failed to respond to conventional therapies Remission (maintenance) No evidence of ongoing vasculitic activity

18.11.5 The lung in vasculitis 4207 when there is a high cumulative oral cyclophosphamide dose), and when there are concerns about infertility with the use of cyclophosphamide. Severe disease In severe disease with diffuse alveolar haemorrhage or renal failure, plasma exchange should be considered early, together with high doses of intravenous methyl-prednisolone and cyclophosphamide. In cases of life-threatening disease at presentation, the use of ini- tial combination intravenous therapy with methyl-prednisolone, cyclophosphamide, and rituximab should be considered, especially if plasma exchange is not available. Refractory disease Intravenous immunoglobulin has been used in refractory disease, particularly in the setting of recurrent infections and in pregnant woman who cannot receive immunosuppressive agents. This treatment is less toxic than the regimens described here, but is contraindicated in patients with severe renal disease (creatinine level >300 μmol/l). Maintenance of remission For the maintenance of remission, azathioprine (2 mg/kg/day) has been used after 3–6 months' treatment with cyclophosphamide, re- ducing total exposure to cyclophosphamide without an increase in the rate of relapse. Methotrexate at a dose of 25 mg/week is as ef- ficacious as azathioprine as maintenance therapy. Mycophenolate mofetil is associated with a higher rate of relapse than methotrexate or azathioprine and is not recommended as second-line therapy. It is usual practice to combine azathioprine or methotrexate with low dose oral prednisolone (e.g. 5–10 mg daily). In general, maintenance treatment should be continued for at least 18 months and must often be used for many years, but long-term treatment decisions can only be made on a case by case basis. Prophylactic co-trimoxazole (trimethoprim 160 mg/ sulfa methoxazole 800 mg three times weekly) is often recommended when long-term intense immunomodulation has been instituted to prevent opportunistic infection by Pneumocystis jirovecii. It has been efficacious in suppressing disease activity in GPA patients with localized upper respiratory tract or minor lower respiratory tract disease, but does not have an established ancillary role in aggressive systemic disease, although usually justifiable in this context as antipneumocystis prophylaxis. FURTHER READING Frankel SK, et al. (2012). The pulmonary vasculitides. Am J Respir Crit Care Med, 186, 216–24. Greco A, et al. (2015). Churg–Strauss syndrome. Autoimmun Rev, 14, 341–8. Guillevin L, et al. (1996). Prognostic factors in polyarteritis nodosa and Churg–Strauss syndrome. A prospective study in 342 patients. Medicine, 75, 17–28. Jayne D, et al. (2003). A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoanti- bodies. New Engl J Med, 349, 36–44. Jennette JC, et al. (2013). 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum, 65, 1–11. Keogh KA, et al. (2006). Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. Am J Respir Crit Care Med, 173, 180–7. Lanham JG, et al. (1984). Systemic vasculitis with asthma and eo- sinophilia: the clinical approach to the Churg–Strauss syndrome. Medicine (Baltimore), 63, 65–81. Lhote F, Guillevin L (1998). Polyarteritis nodosa, microscopic polyangiitis and Churg–Strauss syndrome. Semin Respir Crit Care Med, 19, 27–46. Nguyen Y, Guillevin L. (2018). Eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Semin Respir Crit Care Med, 39, 471–81. Pagnoux C, Guillevin L (2015). Treatment of granulomatosis with polyangiitis (Wegener's). Expert Rev Clin Immunol, 11, 339–48. Specks U (2011). Pulmonary vasculitis. In: Schwarz MI, King TE Jr (eds). Interstitial lung disease, 5th edn, pp. 765–804. People's Medical Publishing House, USA.

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