Treatment

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section 21 Disorders of the kidney and urinary tract 4994 The haemorrhagic risks of renal biopsy are increased by ur- aemia, anticoagulation, and clotting factor deficiency after plasma exchange. Renal biopsy should not be considered essential when ANCA is positive, and treatment should not be delayed while waiting for a biopsy or biopsy result. By contrast, biopsy is strongly recommended when PR3-ANCA and MPO-ANCA are negative. Imaging In small-vessel vasculitis, ultrasonography reveals normal-sized kidneys that may have increased cortical echogenicity if the disease is severe. The diagnosis of polyarteritis nodosa is usually made by angiographic demonstration of vascular irregularity, patchy areas of hypoperfusion, and aneurysms of medium-sized muscular arteries. Mesenteric, including hepatic, splenic, and renal, studies have the best diagnostic yield (Fig 21.10.2.5a). Biopsy of affected tissue reveals fibrinoid necrosis of involved vessels, accompanied by a marked in- flammatory response. Destruction of the internal elastic lamina and aneurisms may be seen (Fig. 21.10.2.5b). Acute-phase reactants are raised, but ANCA and other autoantibodies are negative. Differential diagnosis Secondary causes of vasculitis and diseases mimicking vascu- litis need to be excluded before a diagnosis of primary systemic vasculitis can be made (Box 21.10.2.2). Chronic inflammatory dis- orders such as bacterial endocarditis or rheumatoid arthritis can mimic vasculitis (e.g. with constitutional symptoms and renal im- pairment) or induce a systemic vasculitis syndrome such as an AAV. Chronic bacterial infection may be obvious, as in cystic fibrosis or bronchiectasis, but occult endocarditis or abdominal sepsis should be considered. Tuberculosis and other nonvasculitic causes of pul- monary cavities can mimic GPA. When suspected, bronchoscopy and bronchoalveolar lavage are indicated. Lung biopsy is now rarely performed to confirm a vasculitic diagnosis, but may be required if the serology is unhelpful and there is little extrapulmonary disease. Hepatitis C is the most common cause of cryoglobulinaemic vascu- litis and has also been linked to other forms of vasculitis. For those presenting with deteriorating renal function, other causes of rapidly progressive glomerulonephritis, myeloma kidney, atheroembolic renal disease, and other causes of acute kidney injury need to be considered. Treatment Without therapy, renal vasculitis will usually progress to endstage renal disease. Treatment aims to recover renal function, protect against further episodes of renal vasculitis, and address extrarenal features of disease activity. In patients with systemic disease, other organ involvement may dominate the therapeutic course, espe- cially if renal function is preserved. Disease state definitions have been established and treatment is adapted to the disease state (Table 21.10.2.4). Treatment protocols developed for AAV include an induction phase of 3 to 6 months to control active features of vasculitis and then a maintenance or remission phase of 1 to 4 years to consolidate disease control and prevent relapse. Treatment is then slowly withdrawn, but indefinite follow-up is required for the early detection of late relapse,

and the management of irrevers- ible damage caused by the disease and its treatment. A summary of current treatment recommendations for ANCA vasculitis is shown in Fig. 21.10.2.6.
Table 21.10.2.3 The Berden classification of renal histology in ANCA-associated vasculitis
Subgrouping Definition Endstage renal failure risk at 5 years Focal ≥50% normal glomeruli 0% Crescentic ≥50% cellular crescents 25% Mixed <50% normal with a mixture of cellular crescents and global sclerosis 50% Sclerotic ≥50% of glomeruli with global sclerosis 70% (a) (b)
Fig. 21.10.2.5 (a) A renal arteriogram from a patient with polyarteritis nodosa demonstrating multiple aneurysms. The elastic lamina has been destroyed and the artery has become aneurysmal. (b) A histological cross-section in polyarteritis nodosa from a renal artery. The elastic lamina has been destroyed and the artery has become aneurysmal.

Box 21.10.2.2 Secondary causes and mimics of renal vasculitis
Secondary causes • Infections: — Tuberculosis — Hepatitis B and C, HIV — Chronic bacterial infections • Malignancy • Drugs: — Penicillamine — Hydralazine — Cocaine/levamisole • Other inflammatory autoimmune disorders: — Rheumatoid arthritis — Systemic lupus erythematosus — Sjögren’s syndrome — IgG4-related disease — Behçet’s disease
Mimics of renal vasculitis • Atheroembolic disease • Antiphospholipid syndrome • Left ventricular failure • Infections: — Atypical pneumonia — Hantavirus • Myeloma
Table 21.10.2.4 Definitions of disease state in primary systemic vasculitis according to a European League against Rheumatism/ European Vasculitis Society consensus statement
Activity state Definition
Remission Absence of disease activity attributable to active disease, qualified by the need for ongoing stable maintenance immunosuppressive therapy. The term ‘active disease’ is not restricted to vasculitis only, but also includes other inflammatory features such as granulomatous inflammation in Wegener’s granulomatosis or tissue eosinophilia in the Churg–Strauss syndrome
Response A 50% reduction of disease activity score and absence of new manifestations
Relapse Reoccurrence or new onset of disease attributable to active vasculitis
Major relapse Reoccurrence or new onset of potentially organ- or life- threatening disease
Minor relapse Reoccurrence or new onset of disease which is neither potentially organ-threatening nor life-threatening
Refractory disease Unchanged or increased disease activity in acute AAV after 4 weeks of treatment with standard therapy with cyclophosphamide and corticosteroids Or Lack of response, defined as ≤50% reduction in the disease activity score after 6 weeks of treatment Or Chronic, persistent disease—defined as the presence of at least one major or three minor items on the disease activity score list after ≥12 weeks of treatment
Low activity disease state Persistence of minor symptoms (e.g. arthralgia, myalgia) that respond to a modest increase in the corticosteroid dose and do not warrant an escalation of therapy beyond a modest dose increase of the current medication
No organ threatening involvement CYC+ GC RTX + GC or or or or Disease control “on drug” remission “off drug” remission Maintenance Induction of Remission Diagnosis of AAV Disease assessment Switch to AZA or MTX Taper GC Taper AZA or MTX Stop RTX Continue RTX Taper GC add PLEX Vital organ/life threatening Creat>500µmol/L Consider MTX/MMF
Fig. 21.10.2.6 British Society of Rheumatology recommendations for the management of ANCA- associated vasculitis (AAV). AZA, azathioprine; CYC, cyclophosphamide; GC, glucocorticoid; MMF, mycophenolate mofetil; MTX, methotrexate; PLEX, plasma exchange; RTC, rituximab. Reproduced with permission from Ntatsaki E, et al. (2014). BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford), 53(12), 2306–9.

 Induction therapy The combination of cyclophosphamide or rituximab with gluco- corticoids is the routine induction regimen for renal AAV vasculitis. Cyclophosphamide is equally effective as a daily oral or pulsed intra- venous preparation. The pulsed protocols expose the patient to a lower cumulative cyclophosphamide dose and permit bladder protection through rehydration and the use of mesna, and leucopenia—an im- portant risk factor for severe infection and death—is more common with daily oral treatment. The elimination of cyclophosphamide and its active metabolites are influenced by age and renal function, hence doses must be modified accordingly. Close monitoring of the full blood count is required for the early detection of cytopenias and ap- propriate dose adjustment. Cyclophosphamide is continued for 3 to 6 months, by which time vasculitis will have been controlled in 80 to 90% of patients. The rituximab regimen is 375 mg/m2 per week for 4 weeks, although a simpler regimen of 1000 mg repeated after 2 weeks appears equally effective. Mycophenolate mofetil is an alternative in- duction agent for AAV for MPO-ANCA-positive patients. Improvement in renal vasculitis is recognized by improvement or stability of renal function, control of extrarenal vasculitis, and nor- malization of the C-reactive protein. Persisting nonvisible haema- turia does not have clinical significance, but ongoing proteinuria reflects more severe glomerular damage and a worse renal prog- nosis. ANCA levels are not used to guide the duration or intensity of induction therapy. Initial treatment with intravenous methylprednisolone (total dose 1000–3000 mg) is widely used for renal vasculitis without robust evi- dence, and may be commenced on suspicion of the diagnosis before ANCA testing or renal histology is available. Prednisolone is com- menced at high dose, 1 mg/kg per day, and reduced in steps to 5 to 10 mg/day by 6 months. Prophylaxis against Pneumocystis jirovecii pneumonia with low- dose sulfamethoxazole/trimethoprim is recommended, regardless of induction agent, as is prophylaxis against fungal infections, peptic ulceration, and steroid-induced bone disease. Plasma exchange improves the chances of renal recovery in those presenting in renal failure with serum creatinine levels over 500 µmol: it is also used for renal vasculitis with rapidly deteriorating renal function below 500 µmol, and in those with a poor response to induction drug therapy. The increasing evidence for the pathogen- icity of ANCA in renal vasculitis provides a rationale for its use, but removal of coagulation factors, cytokines, complement fragments, cell microparticles, and NETs may also be important. Plasma fil- tration or centrifugation appear equally effective, with a dose of 60 ml/kg and a total of seven daily or alternate-day exchanges recom- mended. The procedure requires central vascular access, and may be complicated by haemorrhage and thrombocytopenia. Progressive or refractory renal vasculitis following induction treatment should be treated with intravenous methylprednisolone and/or plasma exchange, with rituximab added following cyclo- phosphamide induction and cyclophosphamide added if rituximab induction was used. Treatment intolerance and severe infection are additional causes of treatment failure in the induction phase. Maintenance therapy Disease relapse occurs in 75% of those with GPA and 35% of those with MPA by 5 years. The goal of maintenance therapy is to pre- vent disease relapse, but this is at risk of increasing cumulative drug toxicity. Cyclophosphamide is withdrawn and substituted by azathioprine, methotrexate, or mycophenolate mofetil, with metho- trexate avoided in the presence of renal insufficiency. Azathioprine allergy or intolerance occurs in 5 to 10%, and testing for thiopurine S-methyltransferase activity identifies rare patients at risk of severe myelosuppression. Leflunomide is an alternative oral immunosup- pressive for this disease phase. Intermittent rituximab infusions, 500 to 1000 mg every 6 months, are more effective than azathioprine after cyclophosphamide induction. There is a controversy over the optimal relapse prevention agent after rituximab induction, where the relapse risk is high, with cur- rent data

favouring further rituximab without concomitant oral im- munosuppressive. The use of prednisolone to prevent relapse varies between expert centres. Glucocorticoid withdrawal increases re- lapse risk when an oral immunosuppressive is used for maintenance, but if rituximab is used to prevent relapse then glucocorticoid with- drawal is usually successful and rituximab permits reduced gluco- corticoid exposure. Several factors are known to influence relapse risk (Table 21.10.2.5). Nasal colonization with Staphylococcus aureus has con- sistently been shown to increase relapse risk and long-term treat- ment with sulfamethoxazole/trimethoprim has reduced relapse rates. An alternative approach is topical mupirocin, but this has not been fully evaluated. ANCA levels are not closely related to dis- ease activity, but the persistence of ANCA at 6 months after induc- tion therapy, or a rising ANCA level, indicate relapse is more likely. This is particularly useful when treatment is withdrawn and after rituximab, relapse being almost inevitable if ANCA remains posi- tive or returns after becoming negative. There is no consensus on the optimal duration of maintenance therapy. In those at low risk, this may be limited to 6 to 12 months after diagnosis, while higher-risk patients are typically treated for at least 2 to 4 years, and those with a history of relapse for longer. Relapse of vasculitis is classified as minor (nonsevere) or major (severe) depending on the threat to vital organ function, with the severity and consequences of relapse being dependent on how quickly relapse is detected. Relapse is usually associated with ANCA positivity and rises in erythrocyte sedimentation rate and C-reactive protein. Infection may trigger relapse and can be diffi- cult to distinguish from relapse. In GPA, the two processes often occur together in the respiratory tract, hence if relapse is being considered, thorough microbiological assessment, including studies for tuberculosis, fungi, and viral infections, are required, and aggressive treatment of infection is necessary for vasculitis therapy to be effective. Minor relapses are treated by an increase in prednisolone and return of immunosuppression to full dosage if it has been reduced. However, minor relapses almost always Table 21.10.2.5 Factors predictive of relapse in ANCA-associated vasculitis Clinical presentation Serology Treatment related GPA (Wegener’s) PR3-ANCA Steroid withdrawal Ear, nose, or throat involvement ANCA + after induction Immunosuppression withdrawal Better renal function (creatinine < 200 µmol/litre) Rise in ANCA Lower cyclophosphamide Exposure

 recur and multiple minor relapses require a trial of an alternative immunosuppressive or rituximab. Major relapse is treated by an increase in prednisolone, and rituximab is preferred to reintroduc- tion of cyclophosphamide. Adverse events of therapy The main early risk of treatment is sepsis, which is more likely with cyclophosphamide-associated leucopenia, in the elderly, and those with impaired renal function. Cyclophosphamide dosing should avoid neutropenia and be adapted for age and renal function. All types of infection are seen and these are the major cause of early mortality in ANCA vasculitis, hence infection should be diagnosed and treated promptly. If vasculitic therapy is reduced or interrupted disease control may be lost. There is limited data that rituximab is preferable to cyclophosphamide when treating vasculitis in the pres- ence of infection. Glucocorticoid-related side effects are very frequent and in- clude fluid retention, weight gain, hypertension, diabetes, and steroid-induced bone disease. Glucocorticoids are now the major reversible cause of serious adverse events, long-term damage and chronic morbidity of vasculitis. The treatment of elderly patients with severe renal disease is a particular challenge due to their high risk of infection and treatment intolerance. Glucocorticoid tox- icity can be quantitated using the Glucocorticoid Toxicity Index, which is a composite score of 31 toxicities that has been shown to correlate well with expert opinion. Rituximab may permit more rapid tapering and withdrawal of glucocorticoids. Rituximab induces

hypogammaglobulinaemia in some vasculitis patients. This appears to be an idiosyncratic effect not closely related to rituximab dose. A low IgG level before rituximab has been iden- tified as a risk factor. Falling IgG levels are associated with increased infective risk and such patients need to be monitored regularly, and given prophylactic antibiotics and replacement immunoglobulin when severe. Comorbidities Thromboembolic events, including pulmonary emboli, myo- cardial infarction, and stroke occur in 7 to 15% during the first year. Thromboprophylaxis may well have an important role in management, but this has not yet been determined. The occur- rence of thrombosis has been associated with antiplasminogen antibodies, but this awaits confirmation. The cardiovascular events, myocardial infarction and stroke, are common during the active phase of the disease and remain at increased risk during follow-up. In addition to the contribution of classical risk fac- tors including age and renal function, MPO-ANCA positivity and more extensive disease at diagnosis increase the risk of such events. A major concern of cyclophosphamide use has been the de- velopment of urothelial malignancy over the long term. This is a dose-dependent phenomenon and is more common with oral cyclo- phosphamide, when total exposure is higher, and is particularly frequent in those who develop haemorrhagic cystitis. It is now re- commended that patients never exceed a lifetime exposure of 25 g cyclophosphamide, although this figure is not adjusted for age and the relative risk for malignancy is higher in the young. Rates of all malignancies are increased in vasculitis patients, with a notably increased risk of nonmelanoma skin cancer. It appears that malignancy rates are reducing as alternatives to cyclophosphamide have become available, but this long-term risk needs to be borne in mind whenever immunosuppressive agents are being introduced or continued. Refractory vasculitis Refractory vasculitis is defined in Table 21.10.2.4. It occurs in around 20% of patients during the induction phase, but is more common later in the disease course, especially in PR3-ANCA- associated disease, when it is manifested by multiple relapses or a chronic state of persistent disease activity. The availability and ef- ficacy of rituximab has been of major benefit to patients with re- fractory disease, both achieving disease control and avoiding the increased toxicity risks associated with further exposure to gluco- corticoids and cyclophosphamide. High-dose intravenous immunoglobulin reduces levels of vas- culitic activity in persisting or relapsing vasculitis, reduces ANCA production, and is a useful short-term additional agent permitting reduction in immunosuppressive or steroid dosing. This is desirable in the face of active infection, in patients at high risk of infection, such as on the intensive care unit, and in pregnancy. Blockade of TNFα with infliximab or etanercept has led to remission when used as an additional agent, but prolonged use is ineffective and may in- crease the risk of infection. Progressive disease may continue to deteriorate after rituximab and additional prednisolone, hence cyclophosphamide or plasma exchange may be required for 6 to 8 weeks until rituximab takes effect. A failure to deplete peripheral B cells is associated with a failure to respond to rituximab. This is rare in naive patients but is seen occasionally after previous rituximab due to the induction of antichimeric antibodies. Monitoring The goals of monitoring are to assess control of disease activity and detect early relapse, to minimize drug-related toxicity, and manage disease-related damage and comorbidities. Disease activity assess- ment has been standardized by using the Birmingham Vasculitis Activity Score. Changes in C-reactive protein and the erythrocyte sedimentation rate are helpful but lack specificity. Treatment should not be adjusted according to ANCA levels, but these can be used to assess relapse risk. Concerning renal vasculitis, the return of haema- turia with proteinuria when they have disappeared might indicate renal relapse and a renal biopsy should be considered if the diagnosis of relapse is not supported by extrarenal disease activity. Persisting haematuria and proteinuria after diagnosis is not helpful in assessing renal activity, but persisting proteinuria is an

adverse renal prog- nostic factor. Cyclophosphamide dosing requires regular white blood cell count assessment to avoid leucopenia, and monitoring for liver dysfunction, hypersensitivity, infection, and malignancy is re- quired. Patients receiving rituximab should be screened for tuber- culosis and hepatitis B and C infection, and immunoglobulin levels

section 21 Disorders of the kidney and urinary tract 4998 should be measured before treatment and after every 6 months. Hypogammaglobulinaemia and recurrent infection appears more frequent when rituximab is used in vasculitis than for other auto- immune indications. Routine B-cell counts have been used to guide repeat rituximab dosing but are not necessary if a fixed-interval rituximab dosing regimen in used. Endstage renal disease and transplantation In renal-limited vasculitis, treatment with immunosuppression and prednisolone can be withdrawn once endstage renal disease is estab- lished. However, in GPA and MPA, continued therapy may be re-quired to control extrarenal vasculitic disease. Relapse rates of AAV are lower in patients with endstage renal disease, but relapse—espe- cially of the respiratory tract—may still occur. Patients with vascu- litis and endstage renal disease have a higher incidence of infection, which complicates therapy. The success of renal transplantation in AAV is similar to that for other nondiabetic causes of endstage renal disease. Transplantation reduces the risk of vasculitic relapse and can proceed in the face of a persistently positive ANCA. Previous cyclophosphamide and corticosteroid exposure places patients with a history of vasculitis at increased risk of opportunistic infection after transplantation. Over the long term, graft and patient survival is better for PR3- ANCA- than for MPO-ANCA-positive patients. Relapse of vascu- litis in the renal graft occurs in 2% and usually leads to irreversible loss of function. Management of other vasculitic syndromes involving the kidney IgA vasculitis (Henoch–Schönlein purpura) Although nephritis is not prevented by prednisolone, this is com- monly used to treat active renal disease causing progressive deterioration in renal function, often in combination with an im- munosuppressive, typically cyclophosphamide or mycophenolate mofetil. Plasma exchange has the rationale of removing IgA and IgA-containing immune complexes and may be considered when deterioration in renal function is refractory, and renal outcomes are better in severe acute kidney injury due to IgA vasculitis or IgA nephropathy after plasma exchange. Polyarteritis nodosa Treatment recommendations for polyarteritis nodosa reflect those for AAV with the exception of plasma exchange, which was inef- fective in one small trial, and rituximab, with which there has been little experience. Cryoglobulinaemic vasculitis When associated with hepatitis C, therapy is directed at controlling viral replication. Prednisolone may be required for initial therapy of inflammatory manifestations such as nephritis. Hepatitis C-negative ‘essential’ cryoglobulinaemia with nephritis is treated with gluco- corticoids, with an immunosuppressive agent, and plasma exchange. Rituximab has led to remissions in refractory hepatitis C-associated and essential cryoglobulinaemia. Takayasu’s arteritis Prednisolone and an immunosuppressive are used to arrest pro- gression of vascular disease, but renal artery involvement requires specific therapy if there is evidence of functional decline in the af- fected kidney. The stenoses are less amenable to angioplasty and stenting than in atheromatous renovascular disease, but this op- tion may still be effective. Renal autotransplantation appears to be a useful alternative. Prognosis Creatinine at presentation remains the strongest predictor of both patient and renal survival in renal vasculitis. Those presenting with a glomerular filtration rate below 50 ml/min per 1.73 m2 have a poorer outcome, with 50% reaching the composite endpoint of death or endstage renal failure by 5 years (Fig 21.10.2.7a). Mortality of AAV 0 0.00 0.25 0.50 Proportion with Renal Survival 0.75 1.00 (a) 2 4 Time (years) 6 8 100 (b) 90 80 70 60 0 10 20 30 Time to death (months) Cumulative Survival (%) Survival and age 40 50 60 70 Fig. 21.10.2.7 (a)

Renal and patient survival (composite endpoint) of patients presenting with ANCA-associated vasculitis with glomerular filtration rate above (red line) or below (blue line) 50 ml/min per 1.73 m2. (b) Long-term survival of patients with ANCA-associated vasculitis according to age above (orange line) or below (green line) 60 years at diagnosis. (a) Data from the European Vasculitis Society.

21.10.2 The kidney in systemic vasculitis 4999 at 1 and 5 years is 10 and 25%, respectively; for those under 60 years of age, it is 5% at 1 year, rising to 23% for those over 60, and 44% for those over 70 (Fig. 21.10.2.7b). In part, this is due to more ad- vanced renal disease with more chronicity on renal biopsy in elderly patients, but intolerance of therapy and infections are significant contributors. If treatment of renal vasculitis is unsuccessful and the patient progresses to endstage renal failure, mortality is particularly high. Dual positive presentations of anti-GBM disease and vasculitis are associated with particularly aggressive pulmonary and renal dis- ease and poor outcomes. Specific predictors of endstage renal disease include a lack of re- sponse to therapy, a high level of proteinuria during the recovery phase, and histological features with predominant glomerular scler- osis. A high level of disease activity at diagnosis, as measured by the Birmingham Vasculitis Activity Score, MPO-ANCA positivity, and the early accrual of irreversible damage are independent mortality predictors. There is gradual improvement in renal function over the first year in those presenting with renal impairment who respond to therapy. Glomerular filtration rate may then remain stable for many years, even if recovery is to a glomerular filtration rate below 30 ml/min per 1.73 m2. In this setting, vasculitis relapse with renal involvement carries a high risk of endstage renal disease. However, a few patients develop progressive glomerulosclerosis and lose renal function without reactivation of vasculitis; in these patients, blockade of the renin–angiotensin system may improve renal outcome but requires further study. Over 50% of relapses are mild, with no consequences on vital organ function. However, a protracted relapsing–remitting course, often seen in patients with ear, nose, and throat, or pulmonary dis- ease, does lead to progressive damage and a high cumulative drug burden. The risk of relapse declines with time, but follow-up should remain lifelong because late relapse can still occur with potentially devastating consequences. Quality of life and health economic aspects The quality of life of patients with AAV is severely depressed when their disease is active, and physical activity remains reduced during follow-up when features of active vasculitis are no longer present, with a plateau in recovery attained after 6 to 12 months. Respiratory function is often chronically impaired, and there are negative consequences on social and economic activity. First year direct health costs in uncomplicated ANCA vasculitis were $16 000 in a 2013 study from the United States of America, but rose sharply in those with a serious adverse event and to $62 000 in those with a disease relapse. The referral of patients to centres with experience in managing vasculitis is recommended, and in- tegrated multispecialty pathways for care are developing in larger vasculitis centres. Areas of uncertainty or controversy The diagnosis of vasculitis is often delayed due to a poor under- standing of many physicians as to when the possibility of a vasculitic illness should be considered, and a lack of diagnostic criteria both for vasculitis in general and for the specific vasculitic subgroups. The current phenotypic classification is likely to be replaced by one based on PR3 and MPO-ANCA due to their genetic associations. Phenotypic overlaps between syndromes are common and EGPA sits with difficulty in an ANCA vasculitis subgroup due to the low inci- dence of ANCA. There is controversy as to how to classify patients with overlapping features of vasculitis syndromes, for example, those with both middle-sized arterial involvement and microscopic vascu- litis. According to the Chapel Hill statement, they should be regarded as MPA, although features of polyarteritis nodosa are present. Renal biopsy is recommended for all patients with potential renal

vasculitis, but in the presence of ANCA positivity (both C-ANCA or P-ANCA and PR3-ANCA or MPO-ANCA) over 95% of biopsies will show renal vasculitis, hence it has been argued that biopsy is unnecessary for these patients. The prognostic value of renal biopsy for endstage renal disease is useful, but is not sufficiently well deter- mined to influence treatment in a particular individual. Nonvisible haematuria persists for many months after the commencement of therapy for renal vasculitis despite normalization of the inflamma- tory markers C-reactive protein and erythrocyte sedimentation rate. It is unclear how well haematuria correlates with histological activity and what the criteria for repeat biopsy should be. Although ANCA testing is widely used for the diagnosis of vas- culitis there is often confusion concerning the value of a negative result, this depending heavily on the clinical context, and in the in- terpretation of marginally positive results. In part, this is influenced by variable assay performance and differing referral practices. The role of ANCA in monitoring is more controversial, with the best evi- dence suggesting that ANCA positivity during the remission phase indicates a higher risk of subsequent relapse. The first consensus treatment guidelines published in 2007 were updated in 2016 and highlight areas where evidence is lacking and no clear direction can be given. The introduction of rituximab has been the major change, but uncertainty persists over rituximab dosing, dosing interval, and use of concomitant immunosuppres- sion. There is a paucity of quality evidence to guide glucocorticoid dosing, and clinical practice varies widely. The duration of main- tenance immunosuppression and glucocorticoid therapy also varies widely, between 6 months and over 4 years. The value and toxicity of prolonged therapy needs to be assessed. The short-term benefit of plasma exchange on renal recovery has been demonstrated, but it is not known whether this intervention influences long-term mor- tality or likelihood of endstage renal disease; there is also contro- versy over its role in other severe vasculitis presentations, such as in rapidly progressive glomerulonephritis without advanced renal failure and in lung haemorrhage with respiratory failure. Most clinical trials focus on AAV and there is less evidence sup- porting treatment in the less common vasculitis subgroups. IgA vasculitis in adults is a particular problem, with uncertainty as to the use of immunosuppressives, plasma exchange, and intravenous immunoglobulin. Likely developments in the near future Further genetic associations defining subgroups both for ANCA vasculitis and IgA vasculitis will be identified and their functional

 significance explored. This will influence the classification of vas- culitis. The development of computer-based diagnostic algorithms and widespread ANCA testing will help early detection of vasculitis. Urinary biomarkers, such as CD163 and monocyte chemoattractant protein 1, may be validated to assist in the assessment of renal ac- tivity of vasculitis. A transcriptomic biomarker has been identified from peripheral mononuclear cells that predicts relapse risk. The importance of the alternative complement pathway in ANCA vasculitis and the development of complement C5 ant- agonists as therapies for vasculitis might improve the speed of induction therapy and reduce or avoid glucocorticoid exposure. Preventing relapse will remain a challenge, but the dosing of rituximab will be optimized. Other biologics that may enter the clinical arena are more potent B-cell-depleting antibodies, B-cell cytokine antagonists, T-cell costimulation inhibitors, and prote- asome antagonists. Further study of long-term cohorts will more precisely define predictive biomarkers for the major comorbidities and advice on preventative strategies will develop. Improved organization of healthcare systems and delivery of current treatment recommenda- tions will be the largest benefit to patients in the near future. FURTHER READING Basu N, et al. (2010). EULAR points to consider in the development of classification and diagnostic criteria in systemic vasculitis. Ann Rheum Dis, 69, 1744–50. Berden AE, et al. (2010). Histopathologic classification of ANCA- associated glomerulonephritis. J Am Soc

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