Lupus nephropathy and vasculitis

Lisa Willcocks
Allyson Egan
Rachel Jones

Abstract

Multisystem autoimmune diseases, including systemic lupus erythematosus (SLE) and vasculitis, are inflammatory conditions of unknown cause. Renal involvement can occur in a variety of forms and usually represents a severe disease manifestation. SLE is complicated by renal involvement (lupus nephritis) in over one-third of patients. Small vessel vasculitides, including antineutrophil cytoplasmic antibody-associated and antiglomerular basement membrane disease, also frequently affect the kidneys, causing a rapidly progressive glomerulonephritis. Histologically, this manifests as a necrotizing, crescentic glomerulonephritis. This is potentially reversible, but if left untreated generally results in end-stage renal failure and death within days to weeks. A crescentic glomerulonephritis can also be seen in SLE, but this is not the typical pattern of lupus nephritis, which is usually characterized by immune complex deposition causing a diffuse, proliferative glomerulonephritis. Lupus nephritis and renal vasculitis are the most frequent causes of renal failure in multisystem autoimmunity.

Keywords Antineutrophil cytoplasmic antibody; granulomatosis with polyangiitis (Wegener's granulomatosis); immunosuppression; lupus nephritis; microscopic polyangiitis; MRCP; rapidly progressive glomerulonephritis; systemic lupus erythematosus; systemic vasculitis

Key points

Lupus nephritis:

- Lupus nephritis is common in patients with systemic lupus erythematosus and can be asymptomatic: urinalysis is important as haematuria and proteinuria suggest renal involvement
- Development of lupus nephritis strongly influences renal and patient survival
- Current treatments include corticosteroids and an immunosuppressive agents such as mycophenolate mofetil, cyclophosphamide or azathioprine, and tacrolimus or B cell depletion with rituximab where these agents have failed

Vasculitis:

- Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis is the most common cause of rapidly progressive glomerulonephritis (RPGN), occurring in 80% of patients
- If untreated, RPGN secondary to ANCA-associated vasculitis progresses rapidly to end-stage renal failure
- Haematuria and proteinuria, deteriorating renal function and ANCA positivity point to the diagnosis of RPGN
- About 90% of patients respond to treatment, and early detection and treatment is associated with improved renal outcomes
- Current treatment includes high-dose corticosteroids with cyclophosphamide or rituximab
- Renal impairment at presentation and older age are the strongest predictors of mortality; mortality at 1 year is 10% and treatment toxicity is a major early contributor
- Life-long follow-up is recommended in view of the high relapse rate and late complications of the disease and its treatment

Lupus nephritis

Epidemiology

Systemic lupus erythematosus (SLE) has a prevalence of 97 per 100,000 in the UK, with a peak age of incidence of 50–59 years. Female sex and Black Caribbean ancestry greatly increase the risk of developing it. Overt renal disease occurs in at least one-third of SLE patients and is the most common severe manifestation. In the 2012 Systemic Lupus International Collaborating Clinics (SLICC) diagnostic criteria, lupus nephritis in the presence of antinuclear antibodies or anti-double-stranded (ds) DNA antibodies is sufficient to make a diagnosis of SLE. Development of nephritis is closely linked to reduced survival and chronic morbidity: 10–20% of patients die and 10–25% reach end-stage renal disease (ESRD) within 10 years. However, there is considerable variation in presentation, pathology, course and outcome. Lupus nephritis responds to corticosteroid and immunosuppressive therapy, but drug toxicity contributes to the morbidity and mortality.

Pathology

Immune deposits in the glomeruli and mesangium are characteristic of SLE and stain positive on immunofluorescence for immunoglobulin (Ig) G, IgM, IgA and complement components C3, C1q and C4. Circulating autoantibodies to cellular antigens (particularly anti-dsDNA, anti-Ro and anti-C1q) and complement activation, with correspondingly reduced serum C3, C4 and C1q, are typical of lupus nephritis.

Lisa Willcocks *PhD FRCP is a Consultant in Nephrology and Vasculitis at Addenbrooke's Hospital, Cambridge, UK. She has a research interest in immune-mediated glomerulonephritis. Competing interests: none declared.*

Allyson Egan *BSc(Hons) MRCP is an Honorary University Lecturer at the University of Cambridge and Locum Consultant Nephrologist at Addenbrooke's Hospital, Cambridge, UK. Competing interests: none declared.*

Rachel Jones *MD FRCP is a Consultant in Nephrology and Vasculitis at Addenbrooke's Hospital, Cambridge, UK. She has a research interest in ANCA vasculitis. Competing interests: none declared.*

After the appearance of immune complexes, an inflammatory reaction develops, leading to mesangial cell proliferation, expansion of the mesangial matrix and infiltration of inflammatory leucocytes. Other pathogenic mechanisms include the infarction of glomerular segments, thrombotic microangiopathy, vasculitis and glomerular sclerosis. Extraglomerular features of lupus nephritis include tubulo-interstitial nephritis (70% of patients with nephritis), which involves lymphoid follicle formation and T cell tubulitis, renal vein thrombosis and renal artery stenosis. Thrombotic manifestations are associated with autoantibodies to phospholipids, which are detectable as circulating anticardiolipin autoantibodies or lupus anticoagulant.

Clinical features and prognosis

Nephritis is the first manifestation of disease in 25% of SLE patients. In 5% of cases, renal abnormalities occur several years before other diagnostic criteria or serological abnormalities. Lupus patients can present with asymptomatic urinary abnormalities on routine testing (microscopic haematuria or proteinuria, 40%). Less commonly, lupus nephritis presents as acute renal failure, which can be accompanied by other severe manifestations, such as myocarditis or cerebritis. Poor prognostic factors that should be considered in evaluating patients with lupus nephritis include:

- demography (black or Hispanic race and ethnicity; delay in diagnosis or start of therapy)
- impaired renal function (elevated serum creatinine, nephrotic range proteinuria, hypertension)
- anaemia with haematocrit <26%
- histopathology (severity of acute and chronic tubulointerstitial disease and interstitial inflammation, as well as presence of cellular crescents)
- higher relapse rate and failure to achieve partial or complete remission. After treatment, correction of proteinuria and absence of relapse of nephritis are the best predictors of a good outcome.

The histological appearance of glomerular disease has been classified according to the pattern and extent of immune deposition and inflammation (Table 1, Figure 1). Transformation to a more severe or less severe histological class is well documented; this can result from treatment or be part of the disease's natural history. The activity and chronicity of lesions identified at renal biopsy are used to assess whether treatment should be intensified, and chronicity indices predict long-term renal outcomes.[1]

The risk of cardiovascular disease is greatly increased in SLE and is a major cause of late mortality.

Management

Treatment of lupus nephritis is governed by histological stage. Most data suggest that International Society of Nephrology/Renal Pathology Society (ISN/RPS) class II lupus nephritis has a benign course, and treatment in the absence of other indications is usually not required. The outcome and treatment of class V disease are debated, reflecting differences in the interpretation of histological criteria. The decision to treat active ISN/RPS class III and IV lupus nephritis is less controversial.

The first phase of treatment (known as induction) aims to induce disease remission, achieved with a combination of corticosteroids and another immunosuppressive agent. Current guidelines regard intravenous (IV) cyclophosphamide or mycophenolate mofetil (MMF) as equivalent immunosuppressive agents, and there is increasing use of lower dose cyclophosphamide (six IV infusions of 0.5 g given every 2 weeks). Whether ethnic or geographical factors should influence the selection of the agent remains controversial. Induction therapy aims for a response by 3–6 months, although complete remission can take >24 months.[2]

A failure to reach complete remission, or early withdrawal of immunosuppression, increases relapse rates, so MMF or azathioprine with a low-dose corticosteroid are commonly used over the longer term to maintain remission; MMF is probably more effective at preventing relapse than azathioprine. The optimum duration of therapy is debated; continuing treatment for a significant disease-free period, such as 2–5 years, is recommended. Ciclosporin and tacrolimus are alternative agents, particularly for children and in class V, membranous, nephropathy with normal renal function. Recent data suggest that a combination of low-dose MMF (500 mg twice daily) with tacrolimus 2 mg twice daily may be at least as effective as IV cyclophosphamide in inducing remission. In a Phase II trial, combining the novel calcineurin inhibitor voclosporin with MMF was an effective steroid-minimizing approach.

International Society of Nephrology/Renal Pathology Society 2004 classification of lupus nephritis

Class I: Minimal mesangial lupus nephritis
- Normal glomeruli on light microscopy with mesangial immune deposits on immunofluorescence

Class II: Mesangial lupus nephritis
- Mesangial hypercellularity with mesangial immune deposits on immunofluorescence

Class III: Focal proliferative lupus nephritis
- Focal proliferative glomerulonephritis involving <50% of the glomeruli, typically with focal subendothelial immune deposits and leucocyte infiltration

Class IV: Diffuse proliferative lupus nephritis
- Diffuse proliferative glomerulonephritis involving ≥50% of the glomeruli, typically diffuse subendothelial immune deposits

Class V: Membranous lupus nephritis
- Thickening of the capillary walls and global or segmental subepithelial immune deposits

Class VI: Advanced sclerosis lupus nephritis
- ≥90% glomeruli globally sclerosed

Table 1

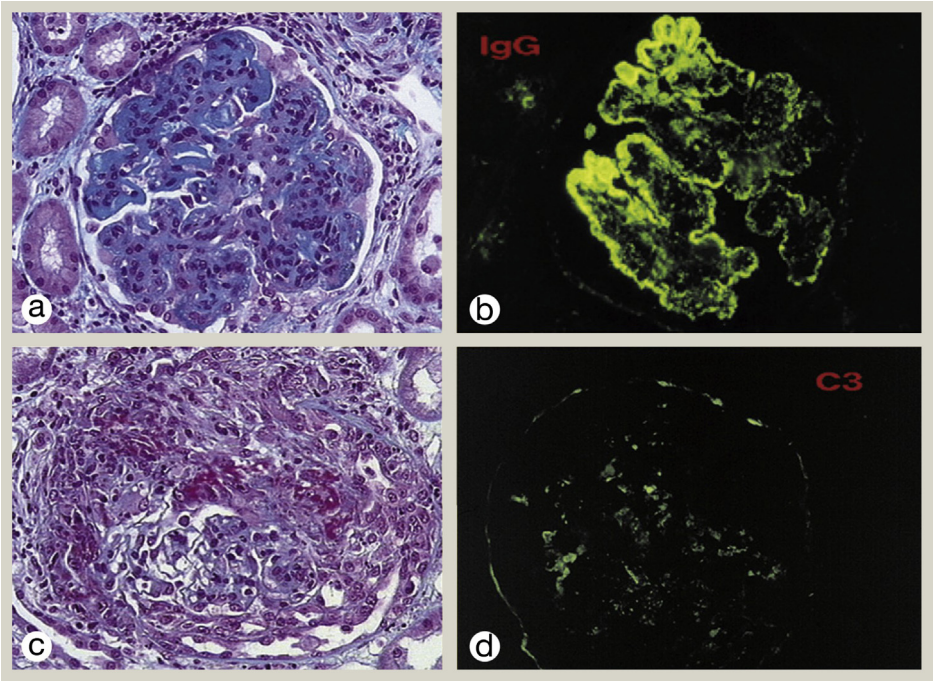

Figure 1 Renal histology in class IV lupus nephritis on (**a**) light microscopy and (**b**) immunofluorescence. Antineutrophil cytoplasmic antibody-associated 'pauci-immune' vasculitis on (**c**) light microscopy and (**d**) immunofluorescence. Source: Kindly provided by Dr Franco Ferrario, S. Carlo Borromeo Hospital, Milan, Italy.

Cyclophosphamide, MMF and azathioprine are associated with severe adverse effects. Cyclophosphamide is associated with infertility and premature menopause, myelosuppression, an increased risk of severe infections and (with total cumulative doses >20 g) bladder malignancy. The risk of infection during treatment with MMF and cyclophosphamide is similar. Both MMF and cyclophosphamide are teratogenic and should be avoided in pregnancy. Long-term azathioprine use is associated with an increased risk of non-melanoma skin cancer.

Treatment-related death and morbidity from infection are significant problems in SLE, and other less toxic agents should be sought. B lymphocytes play an important role in the pathogenesis of SLE, and recent studies have investigated the role of monoclonal antibodies in depleting or blocking stimulation of these cells. Although randomized trials have failed convincingly to demonstrate an additional benefit of rituximab (anti-CD20 chimaera monoclonal antibody) given in addition to MMF and glucocorticoids for remission induction in SLE and lupus nephritis, many non-randomized studies in SLE refractory to standard treatment have reported improvements after rituximab.

Phase III studies in patients with non-renal SLE have demonstrated the efficacy of another B cell-targeted monoclonal antibody, belimumab, which blocks the action of BAFF (also known as BLyS or TNF superfamily member 13b), a B cell-stimulating cytokine. Belimumab has been approved for the treatment of mild to moderate antibody-positive SLE but is currently not licensed for the treatment of lupus nephritis in USA and Europe. Phase III studies in SLE are ongoing for number of other novel therapeutic agents, including ustekinumab (which blocks interleukin (IL)-12 and 23) and baricitinib (a Janus kinase (JAK) inhibitor).

Pregnancy and lupus nephritis

SLE or its treatment can impair fertility, and pre-existing renal impairment, proteinuria or hypertension increases the risks of pregnancy for both mother and fetus. Secondary antiphospholipid syndrome frequently occurs in patients with lupus nephritis and is associated with recurrent miscarriage. Lupus nephritis can relapse during pregnancy, and treatment should therefore not be reduced before or during pregnancy— azathioprine, hydroxychloroquine and corticosteroids are all used during pregnancy. Antiplatelet therapy with aspirin and low-molecular-weight heparin are used to reduce the risk of placental failure in higher risk cases. The immediate postpartum period is associated with a high risk of relapse, and closer monitoring is required. Management by a specialist team before conception and during pregnancy is important in optimizing fetal and renal outcomes.

Systemic vasculitis and rapidly progressive glomerulonephritis (RPGN)

Primary systemic vasculitis

Primary vasculitides are rare, usually multisystem diseases characterized by inflammation and necrosis of blood vessels. They are classified according to the size of the blood vessel involved (Table 2).[3] The most common subgroup of primary vasculitis is the small vessel subtype of vasculitis, antineutrophil cytoplasmic antibody (ANCA)-associated (small vessel) vasculitis (AAV). This has an annual incidence of 19 per million population, peaking in the sixth and seventh decades of life. Renal involvement is common, occurring in 80% of patients with AAV. Renal vasculitis represents a severe disease manifestation, typically progressing over days or weeks

Classification of primary systemic vasculitis according to blood vessel size

Vessel involvement	ANCA-associated	Non-ANCA-associated
Small	Granulomatosis with polyangiitis (Wegener's granulomatosis)	Antiglomerular basement membrane disease
	Microscopic polyangiitis	IgA vasculitis (Henoch–Schönlein purpura)
	Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)	Mixed essential cryoglobulinaemia
Medium		Polyarteritis nodosa Kawasaki's disease
Large		Giant cell arteritis Takayasu's arteritis

Table 2

to ESRD, and is the most common cause of the syndrome of 'rapidly progressive glomerulonephritis'. The clinical course of RPGN results from a characteristic underlying histological process of glomerular capillary inflammation and fibrinoid necrosis, which leads to glomerular basement membrane (GBM) rupture and extracapillary proliferation (crescent formation) (Figure 1c). Early recognition and treatment is crucial to preserve renal function (Table 3).

ANCA-associated vasculitis

The AAV syndromes are distinguished by type of circulating ANCA, presence or absence of eosinophilia, and characteristic clinical features. ANCA testing should be performed using enzyme-linked immunosorbent assay (ELISA); the antigenic targets are either myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA) on ELISA. Indirect immunofluorescence assays are probably now redundant. PR3-ANCA with cytoplasmic (c-)ANCA occurs in 80% of patients with granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis). MPO-ANCA/perinuclear (p-)ANCA is the predominant subtype in microscopic polyangiitis; 40% of patients with eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) are ANCA-positive, usually with MPO-ANCA, although renal involvement occurs in only 15%.

The association of ANCA with pauci-immune RPGN led to the hypothesis that ANCAs are pathogenic. This is supported by the correlation of ANCA titres with clinical disease activity, by the ability of drugs, such as propylthiouracil and cocaine, to induce both circulating ANCA and pauci-immune RPGN, and by the induction of renal vasculitis by MPO-ANCA in animal models. It is important to note that neutrophils, monocytes, lymphocytes and complement have all been implicated in pathogenesis.

Causes of rapidly progressive glomerulonephritis

All types of small vessel vasculitis and SLE can cause RPGN. Clinical features, the presence and pattern of glomerular immune deposits, and assessment of circulating serology (ANA, ANCA, anti-GBM antibodies, rheumatoid factor, serum complement, cryoglobulins) are necessary for the classification and diagnosis of RPGN (Table 4). The most common cause is AAV, in which renal immune deposits are absent, creating a 'pauci-immune' appearance (Figure 1d). Rarer primary causes of RPGN include anti-GBM disease, IgA vasculitis (formerly known as Henoch–Schönlein purpura) and cryoglobulinaemic vasculitis.

Clinical features of ANCA-associated vasculitis

Active renal vasculitis is almost always associated with microscopic haematuria and proteinuria. RPGN occurs in 80% of patients at first presentation, often without symptoms. A total of 30% of patients with RPGN present with ESRD, requiring dialysis. Milder renal involvement with haematuria and proteinuria yet stable renal function can also occur, often identified when patients present with extra-renal disease.

Because of its multisystem involvement, AAV presents in a variety of ways. Constitutional symptoms such as fatigue, weight loss and fevers are common. The non-specific symptomatology and lack of clinical suspicion can unfortunately result in diagnostic delay for several months, with a major impact on long-term outcomes. Symptoms of other organ involvement (e.g. pulmonary haemorrhage, peripheral neuropathy, skin rash, joint or ear, nose and throat disease) tend to allow earlier diagnosis. The absence of extra-renal symptoms usually results in late diagnosis associated with worse renal function.

Diagnosing vasculitis

When vasculitis is suspected the following should be considered:

- Infections, malignancy and vasculitis can present with similar constitutional symptoms
- RPGN and a positive ANCA results can occur in infective endocarditis, malignancy and HIV
- Granulomatous conditions, such as tuberculosis and sarcoidosis, can mimic granulomatosis with polyangiitis (Wegener's granulomatosis)
- Cavitating lung lesions and lung haemorrhage can be asymptomatic, so a chest X-ray should be performed if vasculitis is suspected
- Blood tests for ANCA, eosinophil count, antiglomerular basement membrane antibody, antinuclear antibody, dsDNA, cryoglobulins, immunoglobulins, C3 and C4 are helpful in distinguishing causes of RPGN
- Haematuria and proteinuria and red cell casts on urine microscopy suggest glomerular bleeding and are highly suggestive of RPGN in patients with acute or acute-on-chronic kidney injury
- A renal biopsy with both light microscopy and immunofluorescence microscopy is the gold standard diagnostic test for RPGN
- Infections must be excluded before starting immunosuppressive therapy

Table 3

Differential diagnosis of RPGN

Disease	ANCA serology	Other diagnostic tests	Renal immunofluorescence	Granulomas	Other common or serious organ system involvement
Granulomatosis with polyangiitis (Wegener's granulomatosis)	PR3 > MPO		Negative (pauci-immune)	Yes	Constitutional, ear, nose and throat, joints, skin, lungs, peripheral nerves
Microscopic polyangiitis	MPO > PR3		Negative (pauci-immune)	No	Constitutional, joints, skin, lungs, peripheral nerves
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)	MPO > PR3	Eosinophilia	Negative (pauci-immune)	Yes	Asthma, peripheral nerves, ear, nose and throat (nasal polyps), myocarditis
Anti-GBM disease	30% positive (overlap with AAV)	Anti-GBM antibody	Linear IgG on GBM	No	Lung haemorrhage
Mixed essential cryoglobulinaemia	Negative 100%	Cryoglobulins C3, C4, rheumatoid factor	IgG, IgM, IgA C1q, C3, C4	No	Skin, joints, peripheral nerves
IgA vasculitis (Henoch–Schönlein purpura)	Negative 100%	None	IgA	No	Skin, gut, joints
SLE	Usually negative	ANA, dsDNA, ENAs, C3, C4, anticardiolipin antibody, lupus anticoagulant	IgG, IgM, IgA C1q, C3, C4	No	Skin, joint and many others

ANA, antinuclear antibody; ENA, extractable nuclear antigen.

Table 4

Management of ANCA-associated vasculitis

Suspicion and prompt diagnosis are vital for a good outcome of renal vasculitis. Early treatment of RPGN can reverse inflammation and renal failure, preventing irreversible kidney damage. Immunosuppressive therapies are used, and treatment is classified as remission induction, remission maintenance and relapse therapy.

Remission induction therapy: for 40 years, the standard treatment used to induce remission in patients with renal AAV has been cyclophosphamide and corticosteroids. Current treatment regimens allow remission rates of 80–90%. However, a 1-year mortality of 10% still exists, largely because of treatment toxicity. Cyclophosphamide and high-dose corticosteroids are associated with high infection rates and infertility.

Randomized controlled data support 3–6-month courses of pulsed intravenous cyclophosphamide (7.5–15 mg/kg, adjusted for age and renal function, given every 2–3 weeks), with similar remission rates to more prolonged oral cyclophosphamide therapy but reduced toxicity. Oral prednisolone is initiated at high dosage (1 mg/kg/day), often with pulsed intravenous methylprednisolone (1000–3000 mg total), and reduced over 6 months to <10 mg/day.[4] Plasma exchange can be beneficial in severe alveolar haemorrhage, the major vasculitic cause of early death. Rituximab is an approved alternative to cyclophosphamide, with similar efficacy for remission induction in severe AAV. MMF is another potential remission induction agent used with high-dose corticosteroids in non-dialysis-dependent renal AAV. A Phase III trial is assessing the addition of the C5a inhibitor avacopan to allow steroid minimization in induction therapy.

The goal of remission induction therapy is to achieve improvement and stabilization of renal function. Remission from RPGN is supported by the absence or reduction of blood and protein on urine dipstick testing and negative ANCA results.

Remission maintenance therapy: relapses are common in AAV so prolonged immunosuppression is used. After remission induction, cyclophosphamide is replaced by a less potent immunosuppressant. Azathioprine and methotrexate have equivalent efficacy in preventing relapse, but methotrexate is contraindicated if serum creatinine is >150 micromol/litre. MMF is an alternative, especially in the face of renal impairment. Recent randomized data show repeat rituximab dosing to be superior to azathioprine for remission maintenance in AAV.

Immunosuppressive treatment is typically continued for at least 2 years, usually with low-dose oral corticosteroids. Treatment withdrawal increases relapse risk, as do a positive ANCA after induction therapy, initial PR3-ANCA positivity, a history of previous relapse, ear, nose and throat involvement and the absence of severe renal vasculitis. Regular long-term monitoring is necessary to minimize drug-related toxicity, assess disease activity, detect early relapse and address the increased risk of cardiovascular disease and malignancy seen in these patients.

Immunosuppressive agents commonly used to treat lupus nephritis (LN) and AAV

	Mechanism	Dose	Adverse effects
Prednisolone	Anti-inflammatory, inhibits lymphocyte proliferation	Usually 1 mg/kg/day (maximum of 60 mg) initially in both LN and AAV, tapered over 6 months to 5–10 mg daily	Numerous, including infection, diabetes mellitus, osteoporosis, weight gain, fluid retention, hypertension, cataracts
Cyclophosphamide	Alkylating agent, inhibits DNA replication	LN: 500 mg IV every 2 weeks for 12 weeks AAV: 7.5–15 mg/kg IV, adjusted for age and renal function, six to ten doses	Infection, bone marrow suppression, infertility, nausea and vomiting, haemorrhagic cystitis, alopecia, increased malignancy risk (increased risk of bladder cancer if the cumulative dose is >20 g)
MMF	Pro-drug of mycophenolic acid, inhibits synthesis of guanosine nucleotides, thus targeting lymphocyte proliferation	Induction: 2–3 g/day in two or three divided doses Maintenance: 1–2 g/day in two divided doses	Infection, bone marrow suppression, nausea and diarrhoea, teratogenicity
Azathioprine	Pro-drug of mercaptopurine, inhibits cell proliferation, particularly lymphocytes	2 mg/kg daily	Infection, bone marrow suppression (especially in thiopurine *S*-methyltransferase deficiency), diarrhoea, pancreatitis, hepatotoxicity, malignancy (non-melanoma skin cancer with long-term use)
Methotrexate	Folate analogue, inhibits synthesis of purine and pyrimidine bases	Maximum dose 25 mg weekly, given with folic acid 5 mg weekly (on a different day)	Infection, bone marrow suppression, nausea, vomiting, hepatotoxicity, pneumonitis, teratogenic, renally excreted, contraindicated if creatinine >150 micromol/litre
Rituximab	Anti-CD20 monoclonal antibody, depletes B cells	Induction: 2 × 1 g IV 2 weeks apart, or 4 × 375 mg/m^2 weekly Maintenance: 0.5–1 g every 4–6 months for 2 years	Infection, infusion reaction, neutropenia, hypogammaglobulinaemia

Table 5

Relapse therapy: one-half of all patients with AAV relapse within 7 years. In cases of renal relapse, a repeat renal biopsy is useful to confirm the degree of disease activity. Reintroduction of high-dose corticosteroids with cyclophosphamide or rituximab is often used – rituximab is at least as effective as, and may be superior to, cyclophosphamide for relapses. For minor relapses where major organs are not affected, an increase in corticosteroid dosage can be sufficient. Around 10% of patients either have frequent relapses or are intolerant of standard therapies; use of rituximab as both induction and maintenance therapy may be successful for these patients.

Prognosis: renal prognosis and patient survival depend on the extent of kidney failure at diagnosis. Good outcomes are usually obtained in individuals presenting with a serum creatinine <500 micromol/litre, with 90% surviving with independent renal function. In patients with advanced renal failure, there is 25% mortality at 1 year, and 25–50% develop ESRD.[5] Renal histology can predict survival without ESRD; patients presenting with >50% normal glomeruli have the best 5-year renal survival, whereas those with >50% globally sclerosed glomeruli have the worst. Earlier diagnosis and optimization of the use of conventional agents is leading to improvements in survival and the risks associated with ESRD in these patients (Table 5). ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 19-year-old woman presented with pain and swelling of the left calf. She had also intermittently noted some pleuritic chest pain in the previous 3 months.

On clinical examination, she was alert and orientated with a facial rash. Her temperature was 37.0°C, heart rate 92 beats/minute, blood pressure 125/80 mmHg, respiratory rate 22/minute, and oxygen saturations 95% on air. The left calf was swollen and tender. Urinalysis showed blood 1+ and protein 2+.

Investigations

- Haemoglobin 98 g/litre (130–180)
- Erythrocyte sedimentation rate 65 mm in first hour (<20)
- Creatinine 95 micromol/litre (60–110)
- Urine protein:creatinine ratio 80 mg/mmol (<30)
- Antinuclear antibody test positive by ELISA, with anti-ds DNA antibodies
- Cardiolipin antibodies positive
- Ultrasonography of the leg confirmed a deep vein thrombosis
- Renal biopsy showed class III lupus nephritis

In addition to warfarin, what is the most appropriate initial treatment?

A mycophenolate mofetil, pulsed methylprednisolone IV
B azathioprine, rituximab
C plasma exchange
D Oral prednisolone alone in high doses
E Hydroxychloroquine

Question 2

A 48-year-old man presented for review. He felt well. Eighteen months previously, he had been found to have microscopic polyangiitis with pulmonary renal syndrome. He had been treated with three pulses of intravenous methylprednisolone followed by tapering oral prednisolone and six intravenous pulses of cyclophosphamide with complete clinical and biochemical remission (normal estimated glomerular filtration rate and urinalysis). He had then commenced azathioprine maintenance therapy at 2 mg/kg/day, and the dose of prednisolone had been gradually reduced and then stopped.

Clinical examination at review was non-contributory. Urinalysis showed protein 2+ and blood 1+.

Investigations

- Creatinine 110 micromol/litre (60–110)
- C-reactive protein 56 mg/litre (<10)
- Anti-myeloperoxidase antineutrophil cytoplasmic antibody titre 25 U/ml (<10)

What is now the next most appropriate action?

A Perform a renal biopsy
B Commence pulsed methylprednisolone IV
C Change azathioprine to weekly methotrexate
D Recommence cyclophosphamide
E Commence plasma exchange