Lupus nephropathy and vasculitis

Dominic McGovern

Lisa Willcocks

Rachel Jones

Abstract

Multisystem autoimmune diseases, including systemic lupus erythematosus (SLE) and vasculitis, are inflammatory conditions of unknown cause. Renal involvement occurs 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 individuals. Small vessel vasculitides, including antineutrophil cytoplasmic antibody-associated vasculitis, 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 autoimmune disease.

Keywords Antineutrophil cytoplasmic antibody-associated vasculitis; autoimmune disease; granulomatosis with polyangiitis; immunosuppression; lupus nephritis; microscopic polyangiitis; 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

- The development of lupus nephritis strongly influences renal and patient survival

- Current treatments are glucocorticoids with an immunosuppressive agent, mycophenolate mofetil, or cyclophosphamide plus hydroxychloroquine

- Other treatment options include calcineurin inhibitors (voclosporin, tacrolimus, ciclosporin) and B cell therapies (rituximab, belimumab) or azathioprine

ANCA-associated vasculitis:

- Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is the most common cause of rapidly progressive glomerulonephritis (RPGN)

- 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 renal AAV. If detected early, haematuria and proteinuria can be present with normal renal function, highlighting the importance of urinalysis and ANCA testing

- About 90% of patients respond well to treatment, and early detection and treatment is associated with improved renal outcomes

- Current standard initial treatment includes high-dose corticosteroids with rituximab or cyclophosphamide

- 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 the incidence peaking in the sixth decade. Female sex and Black Caribbean ancestry greatly increase the risk of developing SLE. Overt renal disease occurs in up to 40% of individuals with SLE and is the most common severe manifestation. In the 2012 Systemic Lupus International Collaborating Clinics diagnostic criteria, lupus nephritis in the

Dominic McGovern *BM BCh MRCP is an Academic Research Fellow at the University of Cambridge, UK. He has a research interest in ANCA vasculitis. Competing interests: none declared.*

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.*

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.*

presence of antinuclear antibodies (ANA) or anti-double-stranded DNA antibodies (anti-dsDNA) is sufficient to make a diagnosis of SLE.

The development of nephritis is closely linked to reduced survival and chronic morbidity: 10–20% of patients die and 10–25% reach end-stage kidney disease (ESKD) within 10 years. However, there is considerable variation in the 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 lupus nephritis 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.

After the appearance of immune complexes, an inflammatory reaction develops, leading to mesangial cell proliferation, expansion of the mesangial matrix and the 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 individuals 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 approximately 5% of cases, renal abnormalities occur several years before other diagnostic criteria or serological abnormalities. 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 to be considered when evaluating individuals with lupus nephritis include:

- demography (black or Hispanic race and ethnicity; delay in diagnosis or starting therapy)
- impaired renal function (elevated serum creatinine, nephrotic range proteinuria, hypertension)
- anaemia with haematocrit <26%
- histopathology (severity of acute and chronic tubulo-interstitial disease and interstitial inflammation; presence of cellular crescents)
- higher relapse rate and failure to achieve partial or complete remission
- suggestions from recent trial evidence that proteinuria at 12 months is the single best predictor of ESKD.

The histological appearance of glomerular disease has been classified according to the pattern and extent of immune deposition and inflammation by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) (Table 1, Figure 1). Transformation to a more 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; secondary prevention therapy for cardiovascular disease should be considered.

Management

The treatment of lupus nephritis is governed by the ISN/RPS histological stage. Most data suggest that class I and class II lupus nephritis have benign courses, and treatment in the absence of other indications (e.g. significant extra-renal manifestations) is usually not required. Immunosuppressive treatment is recommended in active ISN/RPS class III/IV disease. The best treatment for class V disease is under debate, but the emerging consensus is that if individuals have significant proteinuria (nephrotic range or >1 g/24 hour despite an optimal use of renin—angiotensin—aldosterone system blockers), they should be given immunosuppressive treatment.

The first phase of treatment (known as induction) aims to induce disease remission, and this is achieved with a combination of corticosteroids and another immunosuppressive agent. Induction therapy aims for a response by 3—6 months, although complete remission can take over 24 months. There is a growing awareness of the adverse effect burden of corticosteroids, and the cumulative corticosteroid dose should be limited as much as is clinically safe to do (initial total intravenous methylprednisolone doses of 500—3000 mg (in 1-3 doses, maximum of 1000 mg per dose) are used according to disease severity by practitioners experienced in treating lupus nephritis, with lower dose oral prednisolone thereafter).[2]

In addition to corticosteroids, low-dose intravenous cyclophosphamide (six intravenous infusions of 0.5 g given every 2 weeks) or mycophenolate mofetil (MMF; 2—3 g/day) are recommended first-line therapies;[1] MMF is preferred in patients of Hispanic, Latin American or African ancestry and in women where preservation of fertility is important. Higher dose cyclophosphamide dosing can be considered in individuals with reduced kidney function or histological predictors of severe disease (crescents or necrosis in >25% of the glomeruli). Hydroxychloroquine is recommended for all individuals with lupus nephritis to prevent relapse. However, it can cause retinal toxicity so regular ophthalmic screening is essential.

Many individuals with lupus nephritis fail to achieve complete proteinuric remission with MMF or cyclophosphamide. These patients may require either a switch between cyclophosphamide and MMF or the addition of another therapy. Calcineurin inhibitors (tacrolimus, voclosporin, ciclosporin) can be used with low-dose MMF for patients with preserved renal function.

B lymphocytes play an important role in the pathogenesis of SLE and lupus nephritis. Belimumab, which blocks the action of B-cell activating factor (BAFF) is safe and effective as add-on therapy to cyclophosphamide or MMF in lupus nephritis. The B cell-depleting therapy rituximab is also widely used in addition to either MMF or cyclophosphamide, while another B cell-depleting therapy — obinutuzumab — is being investigated alongside MMF in clinical trials of lupus nephritis.

A failure to reach complete remission with induction therapy, or early withdrawal of immunosuppression, increases relapse rates, so longer term maintenance therapy with MMF or azathioprine (alongside low-dose prednisolone) is commonly used. MMF is more effective at preventing relapse than azathioprine. Voclosporin, ciclosporin and tacrolimus can also be used to maintain remission. The optimum duration of therapy is debated — continuing treatment for at least 36 months is recommended,

---

ISN/RPS 2004 classification of lupus nephritis[4]

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

---

and repeat biopsy to assess for disease activity can be used to predict the risk of flare if immunosuppression is withdrawn.

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. The effects of rituximab on B cells can last for over a year, impairing subsequent vaccine responses — if possible coronavirus disease (COVID-19), pneumococcal and influenza vaccination should be performed before rituximab administration.

Pregnancy and lupus nephritis

SLE and 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 individuals 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. Pregnancy is not recommended when lupus nephritis is active and for at least 6 months after complete remission has been achieved. Antiplatelet therapy with aspirin and low-molecular-weight heparin is 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
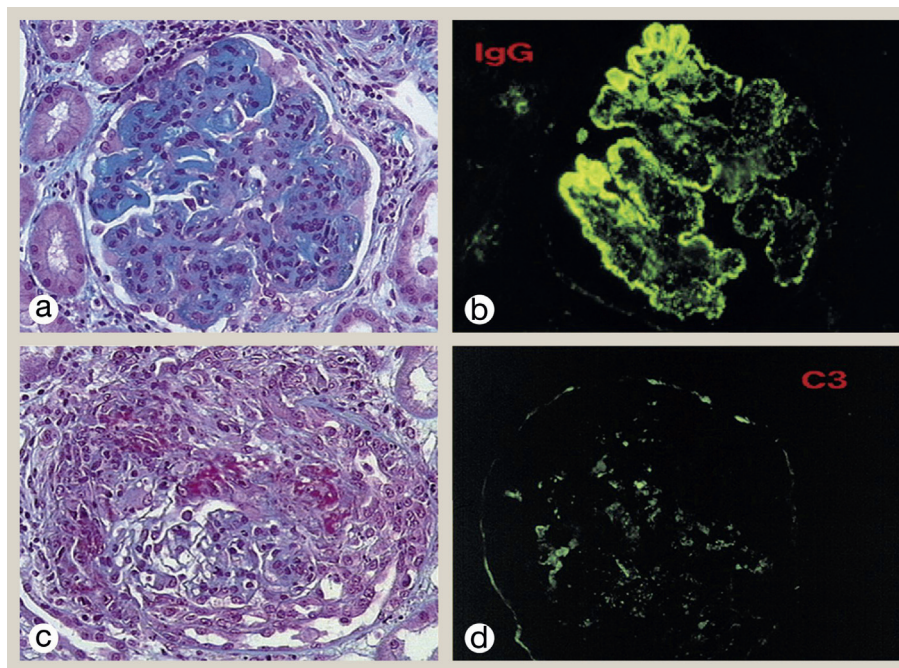

Figure 1 Renal histology in class IV lupus nephritis on (**a**) light microscopy and (**b**) immunofluorescence. Antineutrophil cytoplasmic antibody-associated 'pauci-immune' vasculitis on (**c**) light microscopy and (**d**) immunofluorescence. Source: Kindly provided by Dr Franco Ferrario, S. Carlo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

monitoring is required. Management by a specialist team before conception and during pregnancy is important in optimizing fetal and maternal renal outcomes.

Systemic vasculitis and rapidly progressive glomerulonephritis (RPGN)

Primary systemic vasculitis

Primary vasculitides are rare diseases that usually affect multiple organ systems and are characterized by inflammation and necrosis of the 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 to ESKD. Early recognition and treatment is crucial to preserve renal function (Table 3).

Causes of rapidly progressive glomerulonephritis

All types of small vessel vasculitis and SLE can cause the syndrome of RPGN, although AAV is the most common cause. 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 (also known as crescent formation; Figure 1c). Clinical features, the presence and pattern of glomerular immune deposits, and an 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). In AAV, 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.

ANCA-associated vasculitis

The AAV syndromes are distinguished by the 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 myeloperoxidase (MPO-ANCA) and proteinase 3 (PR3-ANCA) on ELISA. Indirect immunofluorescence assays are less useful because of their lower sensitivity and specificity.

PR3-ANCA with cytoplasmic (c-)ANCA is present in 80% of patients with granulomatosis with polyangiitis (GPA, formerly known as Wegener granulomatosis). MPO-ANCA with perinuclear (p-)ANCA is the predominant subtype in microscopic polyangiitis. Around 40% of patients with eosinophilic granulomatosis with polyangiitis (eGPA, formerly known as Churg—Strauss syndrome) are ANCA positive, usually with MPO-ANCA; renal involvement occurs in only 15% of eGPA patients.

In addition to their diagnostic role, ANCA titres show some correlation with disease activity and are routinely measured in the follow-up of patients with AAV. Drugs such as propylthiouracil and cocaine are able to induce circulating ANCA and should be considered in the differential diagnosis of AAV. It is important to note that neutrophils, monocytes, lymphocytes and complement have also been implicated in the pathogenesis.

Clinical features of ANCA-associated vasculitis

Active renal vasculitis is almost always associated with microscopic haematuria and proteinuria. RPGN occurs in 80% of individuals at first presentation, often without symptoms. Approximately 30% of patients with RPGN present with ESKD, requiring dialysis. Milder renal involvement with haematuria and proteinuria but 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.

Management of ANCA-associated vasculitis

A high clinical suspicion and prompt diagnosis are vital for a good outcome in renal vasculitis. Early treatment of RPGN can reverse inflammation and renal failure, preventing irreversible

Classification of primary systemic vasculitis according to blood vessel size

Vessel involvement	ANCA-associated	Non-ANCA-associated
Small	Granulomatosis with polyangiitis (Wegener 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 disease
Large		Giant cell arteritis
		Takayasu arteritis

Table 2

Diagnosing vasculitis

When vasculitis is suspected the following should be considered:
- Infections, malignancy and vasculitis can present with similar constitutional symptoms
- RPGN and positive ANCA results can occur in infective endocarditis, malignancy and HIV
- Granulomatous conditions, such as tuberculosis and sarcoidosis, can mimic granulomatosis with polyangiitis (Wegener 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, anti-GBM antibody, ANA, 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

kidney damage. Immunosuppressive therapies are used, and treatment is classified as remission induction, remission maintenance or relapse therapy. In cases of organ- or life-threatening disease, immunosuppressive treatment should not be delayed to wait for a kidney biopsy, providing a clinician with experience in vasculitis has been consulted.

Remission induction therapy: for 40 years, the standard treatment used to induce remission in patients with renal AAV has been cyclophosphamide and corticosteroids. However, rituximab is now also used routinely as a first-line therapy, as an alternative to cyclophosphamide.

Cyclophosphamide is given as a 3−6 month course, either intravenously or as daily oral dosing. Intravenous dosing is as effective as oral for remission induction (7.5−15 mg/kg, adjusted for age and renal function, given every 2−3 weeks) and allows lower cumulative exposure and toxicity (less infection and malignancy). Rituximab induction therapy (four intravenous doses of 375 mg/m^2 given weekly or two intravenous doses of 1 g, 2 weeks apart) is preferred over cyclophosphamide in adolescents, pre-menopausal women, men with fertility concerns, frail older individuals and patients with PR3-ANCA positive disease. However, cyclophosphamide may still be preferred in cases of severe renal impairment as there are fewer trial data supporting rituximab in this subgroup.

Differential diagnosis of RPGN

Disease	ANCA serology	Other diagnostic tests	Renal immunofluorescence	Granulomas	Other common or serious organ system involvement
Granulomatosis with polyangiitis (Wegener 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

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

	Mechanism	Dose	Adverse effects
Prednisolone	Anti-inflammatory, inhibits lymphocyte proliferation	AAV: 1 mg/kg/day (maximum of 60 mg) LN: 0.5 mg/kg/day orally, tapered over 3–6 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 i.v. every 2 weeks for 12 weeks AAV: 7.5–15 mg/kg i.v., adjusted for age and renal function, 6–10 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 orally in two divided doses	Infection, bone marrow suppression, nausea and diarrhoea, teratogenicity
Azathioprine	Pro-drug of mercaptopurine, inhibits cell proliferation, particularly lymphocytes	1–2 mg/kg daily oral	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 (oral or i.m.), 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 i.v. 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, impaired vaccine responses
Belimumab	Blocks BAFF, a B-cell stimulating cytokine (only in LN)	Induction: 10 mg/kg i.v. in weeks 1, 3 and 5 Maintenance: 10 mg/kg i.v. every 4 weeks or 200 mg s.c. weekly	Low risk of infection and infusion reaction, depression, diarrhoea
Voclosporin	Calcineurin inhibitor (only in LN)	23.7 mg twice daily orally	Can cause a reduction in glomerular filtration rate and should be avoided in patients with significant renal impairment
Tacrolimus	Calcineurin inhibitor (only in LN)	4 mg daily orally, adjustments guided by trough concentrations	Infection, tremor, bone marrow suppression, paraesthesia
Avacopan	C5a receptor inhibitor, inhibits neutrophil chemotaxis (only in AAV)	30 mg twice daily orally	Possible derangement of liver function

i.m., intramuscularly; i.v., intravenously; s.c., subcutaneously.

Table 5

Intravenous methylprednisolone is used with cyclophosphamide or rituximab for organ- or life-threatening disease, followed by a tapering course of oral prednisolone (starting at 1 mg/kg). High-dose prednisolone contributes to infection risk, and recent studies have shown that a more rapid reduction in prednisolone is effective and allows a reduction in infection rates. Avacopan (a C5a receptor antagonist) has recently been shown to be an effective alternative to prednisolone. This therapy not only allows a substantial reduction in prednisolone use, but also a greater improvement in glomerular filtration rate recovery in renal AAV.

For individuals with the most severe renal disease or pulmonary haemorrhage, the additional use of plasma exchange should be considered. Plasma exchange does not improve mortality or ESKD rates in all AAV patients but can benefit patients presenting with severe renal impairment (creatinine >500 mmol/litre) or significant pulmonary haemorrhage.

MMF is another potential remission induction agent when used with high-dose corticosteroids in non-dialysis-dependent renal AAV. MMF is associated with higher subsequent relapse rates, so is considered a second-line therapy that is reserved for patients where rituximab or cyclophosphamide is contra-indicated, as well as for patients with the lowest risk of relapse (e.g. with MPO-ANCA).

The goal of remission induction therapy is to achieve an 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, either intravenous rituximab or daily oral azathioprine is the first-line treatment to maintain remission. Rituximab maintenance therapy (0.5−1 g every 4−6 months for 2 years) is preferred over azathioprine in patients with relapsing or PR3-ANCA disease and in frail older adults.

Immunosuppressive treatment is typically continued for at least 2 years, usually with low-dose oral corticosteroids. Treatment withdrawal increases relapse risk, as does the re-emergence of a positive ANCA titre 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.

Relapse therapy: half of all patients with AAV relapse within 7 years. PR3-ANCA disease is associated a greater risk of relapse than MPO-ANCA disease. In cases of renal relapse, a repeat renal biopsy is useful to confirm active disease.

The first-line treatment is reintroduction of high-dose corticosteroids with rituximab, particularly in patients who have previously been given cyclophosphamide (for whom rituximab is superior to cyclophosphamide for relapses). Higher cumulative exposure to cyclophosphamide increases risks of malignancy (particularly bladder cancer), which should be considered when considering repeat courses of cyclophosphamide for relapsing disease. In individuals with refractory disease (either at diagnosis or in relapse) combination therapy with cyclophosphamide and rituximab can be used.

For minor relapses where major organs are not affected, an increase in corticosteroid dosage or addition/dose change of an oral immunosuppressive therapy (azathioprine, MMF, methotrexate) can be sufficient, although methotrexate is not safe in patients with significant renal impairment.

Prognosis: renal prognosis and patient survival depend on the extent of kidney failure at diagnosis. 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.

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 ESKD. Renal histology can predict survival without ESKD; individuals 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, as well as the use of newer therapies, is leading to improvements in survival and risk of ESKD (Table 5). ◆

KEY REFERENCES

1 Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int* 2021; **100:** S1−276.
2 Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis* 2020; **79:** 713−23.
3 Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum* 2013; **65:** 1−11.
4 Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int* 2018; **93:** 789−96.

FURTHER READING

Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med* 2020; **382:** 622−31.

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 71-year-old woman presented with a 6-week history of weight loss, fever and arthralgia. She had a past medical history of a thyroidectomy (at age 23 years) and hypertension.

On clinical examination, she was comfortable, with mild ankle oedema. Her temperature was 37.5°C, heart rate 96 beats/minute, blood pressure 140/80 mmHg, and oxygen saturations 97% on air.

Investigations
- Haemoglobin 98 g/litre (115−165)
- C-reactive protein 185 mg/litre (<10)
- Creatinine 711 micromol/litre (60−110)
- Urea 32 mmol/litre (2.5−7.0)
- Potassium 5.8 mmol/litre (3.5−5.5)
- Chest X-ray showed clear lung fields
- Urinalysis showed blood 4 + and protein 4 +

What is the most appropriate next action?
A. Perform immunology screen; ANCA, anti-GBM antibody, ANA, C3 & C4
B. Perform emergency dialysis line insertion and haemodialysis
C. Commence intravenous methylprednisolone
D. Perform plasma exchange therapy
E. Administer broad-spectrum intravenous antibiotics

Question 2
A 22-year-old woman presented with significant swelling of her legs and frothy urine. She had a history of systemic lupus erythematosus affecting her skin and joints. She was taking methotrexate and hydroxychloroquine in line with her prescription. She does not have any children but this is something she would like in the future.

Investigations
- Haemoglobin 110 g/litre (130−180)
- White cell count 3.5×10^9 (4−10)
- Platelets 105×10^9 (150−400)
- Creatinine 115 micromol/litre (40−120)
- Albumin 22 g/litre (37−49)
- Estimated glomerular filtration rate 42 ml/min/1.73 m^2 (>60)
- Anti-dsDNA positive, ANA positive 1:640
- C3 normal, C4 low
- Urinalysis showed blood 2 + and protein 4 +
- Erythrocyte sedimentation rate 105 mm in first hour (<30)

What is the next best step in this patient's management?
A. Stop the methotrexate and switch to mycophenolate mofetil
B. Commence a short course of high-dose oral corticosteroids and review in 2 weeks
C. Arrange an urgent renal ultrasound and kidney biopsy
D. Commence tacrolimus
E. Refer for routine renal outpatient follow up