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Dr Andy Salmon
BSc, MBChB (Hons), MRCP, PhD
Clinician scientist
Richard Bright Kidney Unit, Southmead Hospital,
Bristol and Microvascular Research Laboratories,
Bristol Heart Institute, University of Bristol

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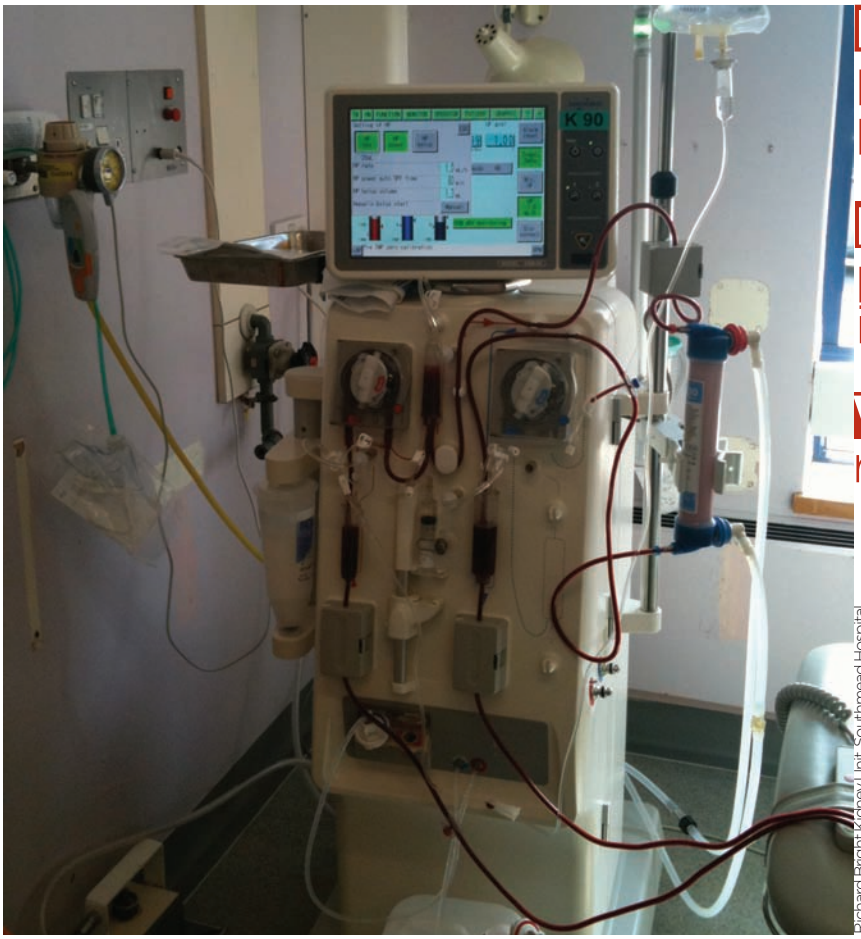
AUTHOR
Dr Andy Salmon
BSc, MBChB (Hons), MRCP, PhD
Clinician scientist Richard Bright Kidney Unit, Southmead Hospital, Bristol and Microvascular Research Laboratories, Bristol Heart Institute, University of Bristol



Richard Bright Kidney Unit, Southmead Hospital

FIGURE 1
Early treatment of acute glomerulonephritis can prevent irreversible loss of renal function, and hence the need for long-term renal replacement therapy

How do patients present in primary care?

How should patients be investigated?

When is urgent referral indicated?

GLOMERULONEPHRITIS IS A HISTOLOGICAL DIAGNOSIS MADE ON RENAL BIOPSY, and is defined as inflammation of the glomeruli. Many forms of acute glomerulonephritis respond well to treatment (albeit intensive immunosuppression) if treated early, but result in serious irreversible loss of renal function if this early treatment opportunity is not recognised or swiftly followed up.

Across all age groups, glomerulonephritis is the second most common renal disease leading to end-stage renal disease in the UK, but is relatively more common in those requiring renal replacement therapy under the age of 65.[1] The incidence of glomerulonephritis is reported as 73 cases per million population per year.[2] This equates to one new presentation per GP practice in the UK approximately every other year. With an average 10-year survival of 63%[2], however, most practices are likely to have a small number of patients with chronic glomerulonephritis at any one time.

PRESENTATION

Glomerulonephritis may present in a variety of ways, from incidental detection of asymptomatic abnormalities in chronic indolent disease to the acutely unwell patient with rapidly progressive glomerulonephritis (RPGN), because of the wide range of different diseases that cause inflammation of the glomeruli.

Asymptomatic renal function abnormalities (e.g. abnormal urinalysis or impaired eGFR) may come to light incidentally, at routine screening visits (e.g. early pregnancy assessments, insurance medicals, or vascular checks for those aged 40-75), or following identification of a heritable renal condition in a family member.

Symptoms or signs of the condition causing the glomerulonephritis may constitute the initial presentation e.g. facial rash and polyarthralgia of systemic lupus erythematosus (SLE); rhinorrhoea, haemoptysis and purpuric rash of small vessel vasculitis.

The initial renal function abnormalities may themselves cause abnormal clinical features e.g. oedema of nephrotic syndrome, cola-coloured »

Table 1

Criteria for nephrology referral for asymptomatic haematuria and eGFR >60 ml/min

Refer patients with persistent haematuria (after excluding transient causes e.g. UTI and after negative urological investigation) and eGFR >60 ml/min if one or more of the following are present:

- urine albumin:creatinine ratio >30 mg/mmol (urine protein:creatinine ratio >45 mg/mmol)
- hypertension
- visible haematuria coinciding with intercurrent infection (usually upper respiratory tract)
- positive family history of haematuria or renal disease
- confirmed declining eGFR (>4 ml/min in past 12 months, or >10 ml/min any time in past 5 years)[7]

Table 2

Criteria for nephrology referral for non-nephrotic proteinuria and eGFR >60 ml/min

Refer patients with asymptomatic persistent non-nephrotic proteinuria and eGFR >60 ml/min if one or more of the following are present:

- proteinuria >1 g/day (equates to urine ACR >70 mg/mmol or urine PCR >100 mg/mmol)
- suspected underlying systemic disease (e.g. SLE, vasculitis, myeloma etc)
- confirmed declining eGFR (>4 ml/min in past 12 months, or >10 ml/min any time in past 5 years)
- significant positive family history of renal disease
- proteinuria >0.5 g/day (equates to urine ACR > 30 mg/mmol or urine PCR >45 mg/mmol) if urinalysis also positive for blood

urine that coincides with an upper respiratory tract infection (so-called synpharyngitic haematuria typical of IgA nephropathy).

Acute and chronic glomerulonephritis may present with symptoms and/or signs of end-stage renal disease, such as lethargy, anorexia, vomiting, pruritus, oedema, and seizures.

One key aspect of the initial presentation is the duration of the condition. Failure to recognise RPGN may mean that the opportunity to treat these aggressive conditions, with immunosuppression, early in the disease is lost. The consequent irreversible loss of renal function may result in the, potentially avoidable, need for long-term renal replacement therapy.

A number of key steps will help identify RPGN:

- Recognising that the clinical pattern is compatible with this condition (see nephrotic syndrome and acute kidney injury below)
- Comparing current information (both urinalysis and serum creatinine/estimated glomerular filtration rate (eGFR) with historical results
- Additional testing to confirm, quantify and identify the pattern of abnormal results. By measuring serum creatinine when urinary abnormalities are first detected (and vice versa), and by repeating both urinalysis and serum creatinine/eGFR within five days of the initial abnormal result,[3] the rare but devastating consequences of RPGN can be treated appropriately. It is also important to acknowledge that rises in creatinine are often detectable only 24-48 hours after rapid worsening of renal function,[4] and that estimates of glomerular filtration rate by mathematical formulae (such as the MDRD equation used to calculate eGFR) are not accurate when renal function is changing rapidly (such as in RPGN).[5]

RENAL SYNDROMES

Asymptomatic haematuria

Asymptomatic non-visible haematuria is often detected on routine screening, and affects up to 1:25 of the general population. If persistent (2 of 3 dipsticks positive at ≥1+ for blood), urinary tract infection (UTI), particularly if the dipstick is also positive for leucocytes and/or nitrites, and structural causes need to be excluded. Urology referral is recommended for patients with visible haematuria, and those with persistent asymptomatic non-visible haematuria aged ≥50.[5,6]

In the absence of a urological cause, haematuria may indicate an underlying (typically chronic) glomerulonephritis. The most common disease is IgA nephropathy, but Alport's disease and thin membrane disease are important alternatives. Criteria for referral to a nephrologist are listed in table 1, above.

Typically, renal biopsy to confirm the underlying diagnosis is not required, unless additional features (e.g. proteinuria, impaired or falling eGFR) are also present. Community-based follow-up is appropriate for those with eGFR > 60 ml/min, with at least annual monitoring of urinalysis, quantification of urine protein excretion, serum creatinine/eGFR and blood pressure.[7] Abnormalities identified at presentation or annual follow-up visits that meet the criteria in table 1, left, should prompt referral to a nephrologist.

Asymptomatic non-nephrotic proteinuria

Asymptomatic proteinuria is usually detected as positive urinalysis for protein, often on routine screening. Positive urinalysis for protein (≥1+) should prompt the following:[5]

- MSU for culture to exclude UTI
- Repeat urinalysis for proteinuria on two further occasions, preferably on the first voided sample in the morning to maximise the sensitivity of the test and to exclude postural proteinuria
- Quantification of urinary protein excretion. Spot measurements of the ratio of protein (total protein, or albumin) and creatinine concentrations in urine has now largely replaced 24-hour urinary collections, since the results of spot ratios and 24-hour collections correlate extremely well, and because the practical difficulties encountered by patients when trying to collect all urine in a 24-hour period renders many 24-hour collections incomplete and inaccurate. The Department of Health recommends urine albumin:creatinine ratio (urine ACR) in preference to urine protein:creatinine ratio (urine PCR) despite the increased cost, partly because urine ACR is a more sensitive and precise measurement, particularly at low but clinically significant levels of proteinuria.[8]
- Clinical review e.g. recent urinary tract or systemic symptoms, recent medication changes including herbal remedies, symptoms of an underlying systemic disorder associated with glomerulonephritis e.g. connective tissue disease, vasculitis, myeloma, blood pressure check, urinalysis to assess for haematuria, and measurement of eGFR.

Nephrology referral should be made for those meeting the criteria listed in table 2, above. In general, patients with <1 g/day proteinuria (which approximately equates to a urine ACR of < 70 mg/mmol and urine PCR of <100 mg/mmol) are not offered renal biopsy, since under these circumstances most renal biopsies do not yield a diagnosis that will alter the patient's management.[5]

Table 3

Common differential diagnoses of nephrotic syndrome in adults in the UK

Primary disease	Secondary causes and associations
Diabetic nephropathy	Type 1 and type 2 diabetes mellitus
Membranous nephropathy	NSAIDs, gold, penicillamine Hepatitis B and C SLE Malignancy
Minimal change disease	
Focal segmental glomerulosclerosis	Lymphoma HIV Heroin use
IgA nephropathy	
Membranoproliferative glomerulonephritis	
Amyloidosis	Myeloma Chronic infection (e.g. osteomyelitis) Chronic inflammation (e.g. rheumatoid arthritis)

It is important to remember that the relationship between urinary albumin and total urinary protein is non-linear. Albumin makes up about 20% of total urinary protein in the normal range of urinary protein excretion (<150 mg urinary protein/day), but makes up about 70% if total urinary protein reaches 1 g/day.

Follow-up in the community for patients with urine PCR of <100 mg/mmol and eGFR >60 ml/min is reasonable. Monitoring (as for haematuria) should be performed at least annually, with referral if coincident haematuria, hypertension, impaired eGFR, symptoms of an underlying systemic disorder or progressively rising urine ACR/PCR are detected.

Nephrotic syndrome

Nephrotic syndrome is the triad of oedema, heavy proteinuria (>3 g/day, approximately equal to a urine ACR >250 mg/mmol or PCR >300 mg/mmol) and hypoalbuminaemia (<25 g/L).[9] The most common cause of nephrotic syndrome in the UK is diabetic nephropathy; other common causes are listed in table 3, above.

Urgent referral to a nephrologist is indicated, since a renal biopsy is usually required to identify the cause of nephrotic syndrome in adults, and therefore inform treatment.

In children, minimal change disease is the most common underlying disease, and renal biopsy is usually reserved for children whose nephrotic syndrome does not respond to steroids. Adult patients with nephrotic syndrome who have diabetes, and particularly those with evidence of microvascular diabetic complications elsewhere (particularly retinopathy), often do not undergo biopsy unless there are reasons to believe that a disease other than diabetic nephropathy may be causing their nephrotic syndrome.

Initial management[9] should include salt restriction (<100 mmol/day; <3 g/day), fluid restriction (<1.5 L/day) and loop diuretics, with careful attention to fluid balance. Weight loss at a rate of approximately 0.5 kg/day is ideal: losses exceeding 1 kg/day may result in excessive intravascular volume depletion and increased risk of both acute kidney injury and thromboses. Blockade of the renin-angiotensin system, with ACE inhibitors (ACEi) and/or angiotensin 2 receptor blockers (ARB), and statins are also advised. Complications of nephrotic syndrome, and the appropriate management steps, are listed in table 4, below.

Acute kidney injury

Patients may present with oedema, hypertension, and oliguria (<0.5 ml/kg body weight/hour equates to approximately 800 ml/day for a 70 kg man). In addition, symptoms of an underlying systemic disease may also highlight the urgency of the situation. For example, non-specific malaise, ENT and ocular symptoms, arthralgia and a purpuric rash are typical symptoms of a small vessel vasculitis. Acute kidney injury with significantly raised creatinine may remain largely »

Table 4

Complications of nephrotic syndrome (including cardiovascular disease)

Complications of nephrotic syndrome	Contributing factors	Management
Oedema	Excessive salt and water retention	Minimise salt intake Loop diuretics Fluid restriction (variable)
Increased risk of venous and arterial thrombosis	Altered production and urinary loss of clotting factors Excessive diuretic use	Avoid immobility Subcutaneous heparin if admitted Role of warfarin controversial
Increased risk of infections (especially encapsulated bacteria e.g. pneumococcus)	Urinary loss of immunoglobulins and complement	Immunisation Early treatment of infection
Hyperlipidaemia	Increased hepatic synthesis of LDL cholesterol	Statin
Muscle wasting	Hypercatabolism	Nutritional assessment ± supplements
Cardiovascular disease	Endothelial dysfunction	Rigorous assessment and treatment of cardiovascular risk factors Use of ACEi/ARB

Table 5

Blood pressure management in patients with chronic glomerulonephritis

	Threshold for initiating antihypertensives	Target blood pressure
CKD	140/90	130/80
If urine PCR >100 mg/mmol	130/80	125/75

Table 6

Immunosuppressive agents and common side effects

Class of agent	Common side effects
Corticosteroids	Hyperglycaemia Mood change Weight gain Infection Osteoporosis Peptic ulceration
Calcineurin inhibitors (cyclosporin, tacrolimus)	Renal impairment Hypertension Hyperglycaemia Hypertrichosis Gum hypertrophy
Azathioprine	Bone marrow suppression Hepatotoxicity Skin cancer
Mycophenolate mofetil	Diarrhoea Bone marrow suppression (especially anaemia)
Cyclophosphamide	Bone marrow suppression (especially neutropaenia) Malignancy Infertility Haemorrhagic cystitis
Plasma exchange	Bleeding Allergic reaction

asymptomatic, however.

Initial testing may reveal an elevated creatinine. In the absence of historical results for comparison, or if previous tests were normal, an acute kidney injury should be assumed and confirmed by an urgent (<5 days[3] or sooner depending on the degree of impairment) repeat test. In the case of an acute glomerulonephritis, the elevated creatinine will typically be accompanied by haematuria and proteinuria.

Small vessel vasculitis is an important cause of acute glomerulonephritis, since renal function may decline extremely rapidly (RPGN). Early kidney biopsy and urgent testing for autoantibodies i.e. anti-neutrophil cytoplasmic antibodies (ANCA) are therefore required to ensure that the appropriate immunosuppressive therapy is started as early as possible.

Chronic kidney disease (CKD)

It is relatively common for glomerulonephritis to grumble indolently without generating symptoms or signs sufficient to prompt medical review, and therefore chronic glomerulonephritis may first present as CKD of any stage, including end-stage renal disease. Patients with chronic glomerulonephritis typically have haematuria, proteinuria and hypertension, and if the disease is advanced small kidneys may be detected by renal ultrasound.

For patients with abnormal urinalysis and CKD, referral to a nephrologist should be made at an earlier stage (i.e. stage 1/2 CKD, as above) than for those with negative urinalysis. This is because testing for underlying autoimmune, malignant and infectious causes of glomerulonephritis, as well as kidney biopsy, are undertaken for most patients with suspected chronic glomerulonephritis. Patients at or near end-stage renal disease will often not undergo biopsy, since the early, active inflammatory component of the glomerulonephritis typically initiates irreversible renal fibrosis in later stages. Not only does this result in renal scarring and small kidneys, which increases the risk of kidney biopsy, but also means that immunosuppression is unlikely to yield a significant improvement in renal function.

Alongside the nephrologist's decision to investigate and/or actively manage the underlying glomerulonephritis, patients should be entered into the same treatment and follow-up programmes as other patients with CKD. The goals of treating both the underlying glomerulonephritis and the consequent CKD are to retard progression of the disease, prevent complications and prepare patients for renal replacement therapy in a timely and appropriate manner.

EVIDENCE-BASED MANAGEMENT

Proteinuric renal disease

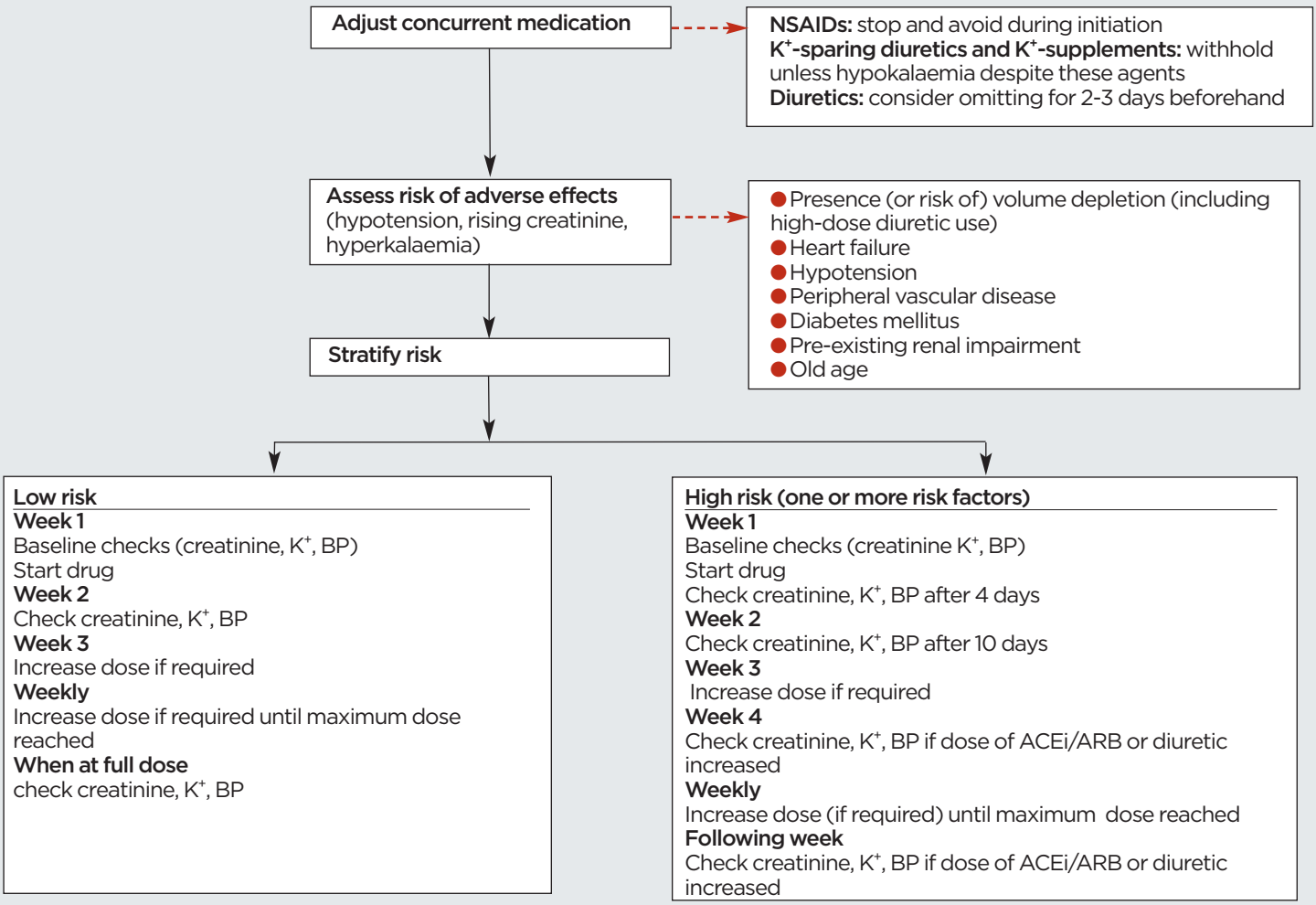
Inhibition of the renin-angiotensin system with an ACEi and/or ARB reduces proteinuria independent of blood pressure-lowering effects,[9] and delays progression of CKD in many forms of glomerulonephritis. These agents should therefore be considered standard management in patients with proteinuria[5] as a consequence of chronic glomerulonephritis.

ACEi/ARB should be included in the antihypertensive regimen if:

- proteinuria >1 g/day (urine ACR

Figure 2

Algorithm for initiation of renin-angiotensin system inhibition



Response to results of monitoring blood tests

Change in renal function	creatinine rise >20% over baseline eGFR fall >15% over baseline	Stop ACEi/ARB. Refer to nephrologist
Change in serum K^+	K^+5-5.5	Recheck in 7 days
	K^+5.6-6	Stop ACEi/ARB and recheck in 7 days
	K^+6.1-6.5	Stop ACEi/ARB and recheck immediately
	K^+>6.5	Stop ACEi/ARB and recheck urgently*

*Seek hospital attention if values likely/proven to be real i.e. not haemolysed

N.B. under certain circumstances , dietary modification, stopping other medications and stable but modestly elevated serum K^+ levels may be acceptable

N.B. consider additional testing of renal function and serum creatinine, or temporarily stopping ACEi/ARB, if the patient develops a severe intercurrent illness, particularly if there is a risk of hypovolaemia

Adapted from ACE inhibitors: how to start (www.edren.org)

>70 mg/mmol or urine PCR >100 mg/mmol)
- the patient has diabetes with microalbuminuria
- the patient has other indications for using ACEi/ARB (e.g. heart failure)

Patients with CKD are at high risk of hyperkalaemia and deteriorating renal function when ACEi/ARB are started. A suggested algorithm for initiation of ACEi/ARB in chronic glomerulonephritis is shown in figure 2, above.

Proteinuria and impaired renal function (i.e. reduced eGFR) are both strong and independent risk factors for cardiovascular disease. Patients with chronic glomerulonephritis typically display both risk factors and are therefore often at greater risk of cardiovascular disease than patients with CKD of different causes. As such, aggressive management of lifestyle factors is required:
- salt intake (<100 mmol/day)
- five portions of fruit and vegetables per day
- weight (target BMI 20-25 kg/m^2)
- regular aerobic exercise »

key points

SELECTED BY
Dr Peter Saul
GP, Wrexham and associate GP Dean for North Wales

Glomerulonephritis is a histological diagnosis made on renal biopsy, and is defined as inflammation of the glomeruli. It is the second most common renal disease leading to end-stage renal disease in the UK. Many forms of acute glomerulonephritis respond well to treatment if treated early, but result in serious irreversible loss of renal function if this early treatment opportunity is not recognised.

Glomerulonephritis may present in a variety of ways, e.g. incidental detection of asymptomatic renal function abnormalities, symptoms or signs of the condition causing the glomerulonephritis, abnormal clinical features arising from the initial renal function abnormalities and symptoms and/or signs of end-stage renal disease.

A number of key steps will help identify rapidly progressive glomerulonephritis: recognising that the clinical pattern is compatible with this condition; comparing current information (both urinalysis and serum creatinine/eGFR) with historical results; and additional testing to confirm, quantify and identify the pattern of abnormal results.

Urology referral is recommended for patients with visible haematuria, and those with persistent asymptomatic non-visible haematuria aged ≥50. In the absence of a urological cause, haematuria may indicate an underlying (typically chronic) glomerulonephritis. The most common disease is IgA nephropathy, but Alport's disease and thin membrane disease are important alternatives. Community-based follow-up is appropriate for those with eGFR >60 ml/min, with at least annual monitoring of urinalysis, quantification of urine protein excretion, serum creatinine/eGFR and blood pressure.

Positive urinalysis for protein (≥1+) should prompt: MSU for culture to exclude UTI; repeat urinalysis for proteinuria on two further occasions, preferably on the first voided sample in the morning to maximise the sensitivity of the test and to exclude postural proteinuria; quantification of urinary protein excretion and clinical review. Follow-up in the community for patients with urine PCR of <100 mg/mmol and eGFR >60 ml/min is reasonable.

Patients with chronic glomerulonephritis typically have haematuria, proteinuria and hypertension, and if the disease is advanced small kidneys may be detected by renal ultrasound. The goals of treating both the underlying glomerulonephritis and the consequent chronic kidney disease are to retard progression of the disease, prevent complications and prepare patients for renal replacement therapy in a timely and appropriate manner.

- advice on smoking cessation
- reducing alcohol intake to nationally recommended targets (3 units/day for men; 2 units/day for women)

Cardiovascular prophylaxis

Cardiovascular prophylaxis (lipid-lowering therapy, antihypertensive therapy and antiplatelet therapy) is important. In general, patients should be managed according to standard national cardiovascular disease guidelines, since there is little or no evidence specific to individuals with chronic glomerulonephritis. At least one trial (SHARP[10]) is, however, due to report shortly on the use of statins in primary prevention for patients with pre-dialysis CKD.

Appropriate blood pressure control (see table 5, p30)[3] achieves two important outcomes for patients with chronic glomerulonephritis: reduced cardiovascular risk, and slower progression of CKD. Patients with chronic glomerulonephritis will often require a number of agents (including ACEi and/or ARB, as described above) to achieve these blood pressure targets. Refractory hypertension (BP >150/90mmHg despite combination therapy with three drugs from complementary classes) warrants referral to a nephrologist.[5]

Follow-up of patients with glomerulonephritis typically involves close liaison between primary and secondary care physicians. For example, managing the fluid balance of patients with nephrotic syndrome requires a high degree of patient co-operation (daily weights are ideal), and frequent adjustment of diuretic dose. Frequent testing for the side effects of immunosuppressive therapies sometimes required for glomerulonephritis (e.g. weekly full blood count monitoring for patients starting cyclophosphamide) is often performed and interpreted by primary and secondary care teams working together. In the chronic setting, managing the complications of CKD also requires good communication between GPs and specialists.

Immunosuppression

A variety of immunosuppressive regimens are used for glomerulonephritis, with the most intensive usually reserved for those with RPGN causing acute kidney injury and/or nephrotic range proteinuria. The evidence base for these immunosuppressive regimens is usually specific to individual glomerulonephritides causing clearly defined clinical criteria (e.g. plasma exchange for patients with ANCA-positive small vessel vasculitis with coincident anti-glomerular basement membrane antibodies and pulmonary haemorrhage). The most commonly used immunosuppressants, along with side effects, are listed in table 6, p30.

CONCLUSION

Glomerulonephritis can present in varied forms, and clinical suspicion coupled with timely testing of renal function (by analysing both urine and plasma) will help ensure appropriate referral to secondary care. Kidney biopsy is required to confirm and categorise the diagnosis, and additional testing for underlying conditions is often required. Treatment and follow-up of patients with both acute and chronic forms of glomerulonephritis often occurs across the boundaries of primary and secondary care, requiring active patient participation and good communication between care teams.

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Useful information

For healthcare professionals:
Edinburgh Renal Unit www.edren.org
The Renal Association's eCKD Guide
www.renal.org/whatwedo/InformationResources/CKDeGUIDE.aspx

For patients:
www.renal.org/whatwedo/InformationResources/Patients.aspx
The UK National Kidney Federation
For local kidney patient associations and other information:www.kidney.org.uk