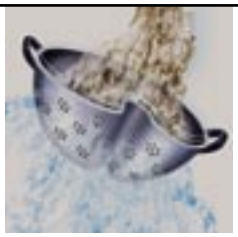

Glomerulonephritis

Management in general practice

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BACKGROUND Glomerulonephritis (GN) is an important cause of both acute and chronic kidney disease, however the diagnosis can be difficult due to the variability of presenting features.

OBJECTIVE This article aims to develop a structured approach to the investigation of patients with markers of kidney disease, and promote the recognition of patients who need further assessment. Consideration is given to the importance of general measures required in the care of patients with GN.

DISCUSSION Glomerulonephritis is not an everyday presentation, however recognition and appropriate management is important to prevent loss of kidney function. Disease specific treatment of GN may require specialist care, however much of the management involves treatment of the associated complications such as oedema, achievement of target blood pressure and proteinuria reduction, and prevention and treatment of associated complications.

Glomerular disease remains an important cause of renal impairment (and is the commonest cause of end stage kidney disease [ESKD] in Australia).[1] Early diagnosis is essential as intervention can make a significant impact on improving patient outcomes. However, presentation can be variable – from indolent and asymptomatic to explosive with rapid loss of kidney function. Pathology may be localised to the kidney or part of a systemic illness. Therefore diagnosis involves a systematic approach using a combination of clinical features, directed laboratory and radiological testing, and in many (but not all) cases, a kidney biopsy to establish the histological diagnosis. Management of glomerulonephritis (GN) involves specific therapies directed at the underlying, often immunological cause of the disease and more general strategies aimed at delaying progression of kidney impairment. In addition, the general practitioner has an important role in the identification and management of the complications of both the disease and immunosuppressive therapies.

Diagnosis of GN

The assessment of GN is best approached as a diagnostic challenge in which information needs to be drawn from the clinical combination of symptoms and signs, which often occur in recognisable clusters (*Figure 1*), urine analysis, specific serological tests and histology.

Asymptomatic microscopic haematuria and/or proteinuria often presents as an incidental finding during insurance medicals or the assessment of newly diagnosed hypertension. The Ausdiab[2] study demonstrated that haematuria was present in 4.6% and proteinuria in 2.4% of participants. In the majority,

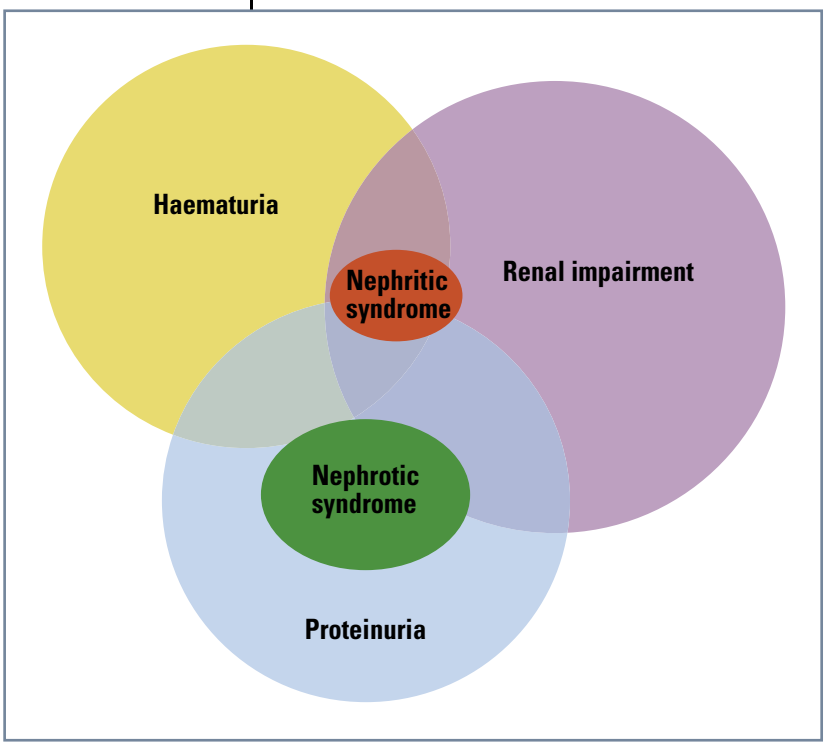

Figure 1. The diagnosis of GN is made easier by thinking about the clustering of symptoms and signs that form recognisable patterns

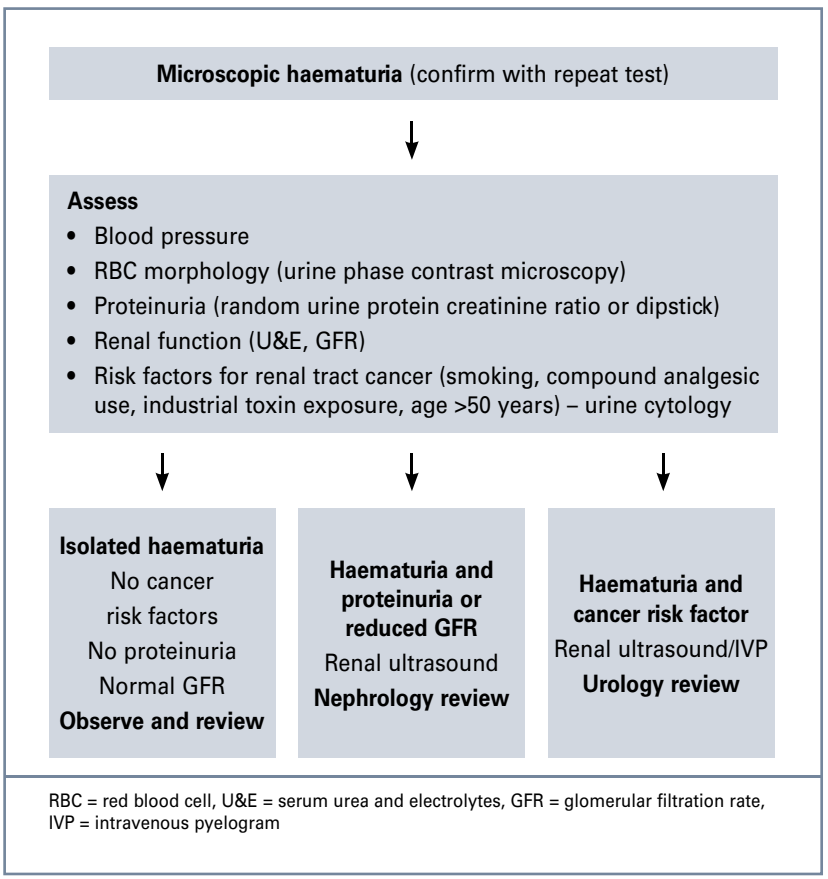

Figure 2. Assessment of microscopic haematuria

haematuria occurred in the absence of other indicators of kidney damage and predominantly related to menstruation or urinary tract infection. Haematuria related to significant glomerular disease is usually associated with proteinuria, hypertension or reduced glomerular filtration rate (GFR). Urinary red blood cells (RBC) have abnormal morphology (assessed by phase contrast microscopy of fresh urine). The finding of haematuria also warrants closer assessment to exclude a significant urological pathology such as malignancy, stones or prostatic disease in older patients (>50 years) or at risk groups (smokers) (*Figure 2*).

Proteinuria is a powerful predictor of progressive renal disease and even low level proteinuria (1+ dipstick) is associated with a twofold increased risk of ESKD.[3] The more severe the proteinuria the more likely patients are to have progressive decline in kidney function. Proteinuria is a hallmark of both diabetic and hypertensive nephropathy and it is likely that these conditions contribute the majority of patients in population studies. Significant proteinuria (>1 g/day) in the absence of an identifiable cause (eg. longstanding diabetes) should be further investigated (*Figure 3*).

Nephritic syndrome and rapidly progressive GN

Nephritic syndrome is an uncommon but critical diagnosis requiring urgent investigation and treatment so as to avoid irreversible loss of kidney function. Patients present with:

- macroscopic haematuria (tea or 'cola' coloured urine)
- severe hypertension, and
- progressive oliguria and renal impairment.

Onset is often abrupt and patients are often unwell. The disease process may be limited to the kidney or occur as part of a systemic illness (*Table 1*). Acute nephritic syndrome is associated with an active immunological response (cellular and antigen/antibody mediated) within the kidney and serological tests can aid in reaching a specific diagnosis.

Nephrotic syndrome

The nephrotic syndrome is defined as a triad of:

- heavy proteinuria (>3.5 g/day)
- hypoalbuminaemia, and
- oedema.

Proteinuria develops due to the disturbance of the glomerular filtration barrier, which is composed of glomerular capillary wall, glomerular basement membrane (GBM) and podocyte. There is little

inflammation within the kidney, and haematuria is uncommon or low grade. Hypoalbuminaemia arises due to both renal losses and a blunted response by the liver to increase albumin synthesis and is not improved by increasing protein intake. The pathogenesis of oedema is related to low serum albumin, loss of plasma oncotic pressure and a defect in the excretion of sodium by the distal nephron with sodium and water retention that, in conjunction with the lower oncotic pressure, results in interstitial oedema.

Loss of specific proteins in the urine and an indiscriminate increase in synthesis by the liver have metabolic consequences that may present in general practice. Patients are hypercoagulable and at risk of venous thromboembolism,[4] particularly when serum albumin is less than 20 g/L. Nephrotic patients are prone to bacterial infection and cellulitis is particularly common. Hyperlipidaemia is so common that it is considered an integral part of the syndrome; total cholesterol can be greater than 10 mmol/L. Patients with long standing nephrotic syndrome have about a fivefold increase in cardiovascular death.

The major causes of nephrotic syndrome are outlined in *Table 1*. It is important to recognise that the commonest cause of the nephrotic range proteinuria is advanced diabetic nephropathy. Patients will usually have had diabetes for more than 10 years and commonly have evidence of retinopathy. Serological tests are less informative in the diagnosis of nephrotic syndrome and patients will often require a kidney biopsy to determine the cause.

What next?

Ultrasound is an important part of the workup. It is noninvasive and has no requirement for radiological contrast that can be nephrotoxic. Urological abnormalities such as renal cell carcinoma may be detected (note a cystoscopy may be required to exclude carcinoma of the bladder). Useful information on renal size is also obtained with small kidneys suggesting that the disease is longstanding and may not be reversible. Often the cortex is described as echogenic, this is a nonspecific finding but suggests parenchymal disease such as GN.

In some cases, diagnosis can be made on clinical grounds and treatment commenced empirically. In other cases, a renal biopsy will be required to establish the diagnosis, guide treatment and provide prognostic information. Biopsies are performed using ultrasound guidance under local anaesthetic. Interestingly, although glomerular histology makes the diagnosis, it is the degree of tubulointerstitial injury that provides the best indication of prognosis.

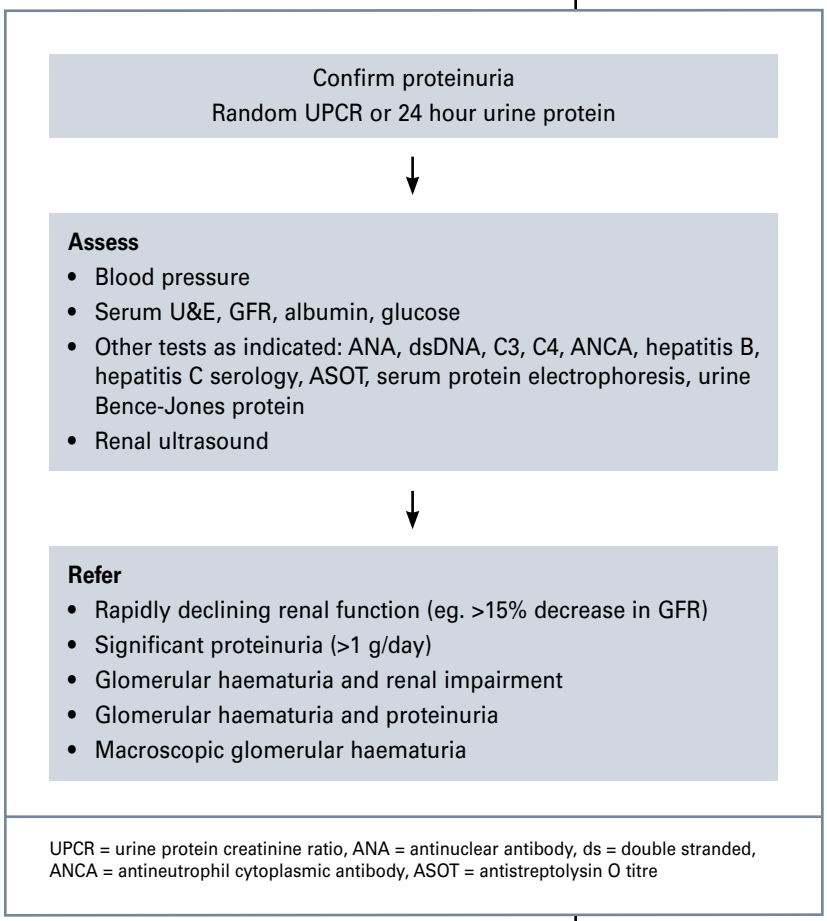

Figure 3. Assessment of proteinuria

Who to refer for nephrologist review?

- Rapidly declining renal function (eg. >15% decrease in GFR)
- Significant proteinuria (>1 g/day)
- Glomerular haematuria and renal impairment
- Glomerular haematuria and proteinuria
- Macroscopic glomerular haematuria.[5]

Thumbnail sketches of significant GN

IgA nephropathy

IgA nephropathy is the commonest primary GN and most frequently occurs in adolescents and adults aged less than 50 years. IgA may present as macroscopic haematuria at the same time as an upper respiratory infection or as a more indolent process, often diagnosed in the setting of hypertension or chronic kidney disease. The aetiology is unknown, but may relate to abnormal glycosylation of IgA.[6] There is no evidence that any

Table 1. Common presentations of glomerulonephritis

Presentation	Cause	Specific test
Nephritic syndrome	IgA nephropathy	
	Poststreptococcal GN	ASOT, anti-DNAase B, C3
	SLE	ANA, anti-ds DNA, C3, C4
	Anti-GBM disease	Anti-GBM antibody
	ANCA vasculitis	ANCA
	Mesangiocapillary GN	C3, HBsAg
Nephrotic syndrome	Minimal change disease	
	Membranous GN	HbsAg, chest X-ray, mammogram*
	FSGS	
	SLE	ANA, anti-ds DNA, C3, C4
	Diabetes	Fasting glucose
	Amyloid	Urine Bence-Jones protein, serum and urine protein electrophoresis
GN and infection		
• URTI	Flare of IgA nephropathy	
• Streptococcus	Poststreptococcal GN	
• Hepatitis B	Membranous GN	
• Hepatitis C	Mesangiocapillary GN	
• Endocarditis	Mesangiocapillary GN	
GN and drugs		
• NSAID	Minimal change disease	
• Gold, penicillamine	Membranous GN	
• OCP, quinine	HUS	FBE (schistocytes), LDH, haptoglobin
GN and purpuric skin rash	IgA/HSP	Skin biopsy with immunoflouresence
	SLE	
	ANCA vasculitis	
GN and cancer	Membranous GN	

* Simple assessment for common cancers may include rectal examination, breast examination, mammogram and chest X-ray

GN = glomerulonephritis, SLE = systemic lupus erythematosus, GBM = glomerular basement membrane, ANCA = antineutrophil cytoplasmic antibody, ASOT = antistreptolysin O titre, ANA = antinuclear antibody, ads = double stranded, FSGS = focal segmental glomerulosclerosis, NSAID = nonsteroidal anti-inflammatory drug, OCP = oral contraceptive pill, HUS = haemolytic uraemic syndrome, HSP = Henoch Schonlein Purpura, FBE = full blood examination, LDH = lactate dehydrogenase

one particular environmental stimulus is involved, and food antigens in particular, have been studied without convincing evidence to date. There is a spectrum of activity and the predictors of poor outcome are heavy proteinuria (>1 g/day), abnormal renal function at diagnosis, hypertension, and interstitial scarring on biopsy. The most important treatment strategies are angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blocker (ARB) therapy[7,8] to reduce proteinuria and to target blood pressure below 125/75. Patients with heavy proteinuria or renal impairment require ongoing specialist care. Corticosteroid therapy[9] and high dose fish oil therapy[10] have been successful in a subset of patients.

Poststreptococcal GN

Poststreptococcal GN is the commonest cause of nephritic syndrome in children, and although the overall incidence has decreased, it is still a significant problem in socially disadvantaged populations. Haematuria and renal impairment follows 10–21 days after a streptococcal infection – throat or skin. Treatment is supportive and the prognosis is usually good.

Rapidly progressive GN

This subset of autoimmune glomerular diseases are uncommon and the role of the GP is rapid recognition and referral, as timely treatment is crucial in preventing irreversible loss of kidney function.

Systemic lupus erythematosus

About a third of patients with systemic lupus erythematosus will have evidence of renal involvement. Systemic lupus erythematosus tends to occur in patients with evidence of more systemically and serologically active disease.

Antiglomerular basement membrane disease

Also known as Goodpasture's disease, this is caused by the development of auto-antibodies to the noncollagenous domain of type IV collagen, which is an essential component of the GBM. Type IV collagen is also found in the lung and haemoptysis may also be a feature, particularly in smokers. Young males are most commonly affected, but it can occur at any age or in any gender. Patients present with macroscopic haematuria, progressing rapidly to oliguria. Renal failure may occur within days of onset of symptoms. If treatment (plasma exchange, corticosteroids and cytotoxic therapy) is started early, the disease can be cured and relapses are rare.

ANCA vasculitis

The kidney is often the target in systemic small vessel vasculitis (including Wegener's granulomatosis and microscopic polyangiitis). Auto-antibodies against components of neutrophil cytoplasm (antineutrophil cytoplasmic antibodies [ANCA]) are probably involved in the pathogenesis of the injury and are measurable in the serum but not detectable within the kidney. Older patients are more commonly affected and the presentation is extremely diverse and often nonspecific. It is worth keeping ANCA related disease in mind when assessing patients with nonspecific inflammatory conditions such as fever, malaise, weight loss, myalgias and arthralgias. Cutaneous involvement is relatively common with a petechial/purpuric rash often involving the lower legs. Renal function can be progressively lost, usually over a period of weeks, although on occasion the disease can be florid and present with acute renal failure and lung haemorrhage. The trick is in making the diagnosis, as once identified, the disease usually responds well to immunosuppressive therapy.

Membranous nephropathy

Membranous nephropathy (MN) is the commonest cause of nephrotic syndrome in older patients (>60 years). Immune complexes deposit in the glomerular subepithelial space. The precipitating antigen is unknown in the majority of cases (idiopathic MN), however a wide range of systemic conditions can be associated with secondary MN. Most patients present with gradual peripheral oedema; many will have a benign or indolent course and disease specific therapy (corticosteroids and cytotoxic therapy) is reserved for patients with heavy proteinuria or progressive loss of kidney function.

Focal segmental glomerulosclerosis

The primary form of this disease most commonly occurs in children and young adults. Patients may present with the abrupt onset of the nephrotic syndrome, which may be severe. Thirty to 40% of patients will respond to high dose immunosuppressive therapy.[11] Nonresponders often progress rapidly to ESKD.

The role of the GP

While disease specific therapy will often be directed by the treating nephrologist, the GP plays an important and often under-recognised role in both the treatment to target blood pressure and proteinuria reduction, and supportive care including management of oedema, osteoporosis and cardiovascular risk reduction, vaccination and early recognition of infectious complications.

In common with many forms of kidney disease, control of blood pressure and reduction in proteinuria are particularly important in delaying the progression of renal injury in GN. The heavier the proteinuria, the greater the benefit seen in achieving these outcomes. The target arterial blood pressure for patients with proteinuria (>1 g/day) is <125/75 mmHg and often multiple (3–5) antihypertensive agents are required. Normotensive patients with significant proteinuria will benefit from ACE inhibitors and/or ARBs as antiproteinuric agents, which should be increased to the maximum tolerated dose.

Management of oedema is often problematic in this group. The mainstay of therapy is loop diuretics accompanied by moderate fluid and sodium restriction (60–80 mmol/day). Asking a patient to monitor their weight on bathroom scales at home is often useful and a weight loss of 0.5 kg per day is usually well tolerated.

Vaccination against influenza and pneumococcus (pneumovax 23 in adults) is recommended in all patients with nephrotic syndrome or chronic kidney disease.[12] Attenuated viral vaccines (hepatitis B, IPV, DTP) are safe, however live viral vaccines (MMR, OPV, varicella-zoster and BCG) are contraindicated in patients who

are heavily immunosuppressed (>60 mg prednisolone/day or steroid plus other immunosuppressant). The response to vaccination in immunosuppressed patients may be decreased.

Summary of important points

- Check urine and kidney function in patients with nonspecific systemic illnesses and consider renal vasculitis as a rare but treatable condition.
- Urine microscopy should be performed on fresh urine and provides a guide to the 'activity' of GN. In proliferative GN, the urine will contain significant numbers of dysmorphic RBC and cellular casts. Hyaline casts (proteinaceous) are associated with proteinuria.
- Macroscopic haematuria is always significant and should be investigated. It is not however, a cause of significant blood loss (only 1 mL of blood is required for macroscopic haematuria). The presence of blood clots indicates lower tract bleeding. Haematuria in at risk groups should have urological review.
- Urine protein can be assessed on a random urine sample. Twenty-four hour urine protein excretion has been considered the gold standard for quantitative protein assessment but the recognised difficulty in collecting reliable 24 hour urine samples makes routine use problematic. Urine protein/albumin can be assessed in 'spot' urine samples by assessing urine protein concentration (UPC), urine albumin concentration (UAC), or as a ratio with creatinine (protein creatinine ratio [PCR], albumin creatinine ratio [ACR]). The excretion of creatinine is fairly constant in an individual patient and represents a method of standardising protein excretion in a single void specimen to correct for variation in hydration.
- Control of blood pressure and reduction in proteinuria are important measures in reducing progression of renal impairment and GP's play a key role in ensuring treatment to target.
- Be mindful of the complications of the nephrotic syndrome, ie. increased risk of DVT, increased risk of infection, accelerated atherosclerosis.

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