

# CLINICAL PRACTICE GUIDELINES

## Glomerulonephritis



Chapter of Renal Physicians  
College of Physicians, Singapore



College of Family Physicians,  
Singapore



MINISTRY OF HEALTH  
SINGAPORE



Academy of Medicine,  
Singapore

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## Levels of evidence and grades of recommendation

### Levels of evidence

Level	Type of Evidence
<b>Ia</b>	Evidence obtained from meta-analysis of randomised controlled trails.
<b>Ib</b>	Evidence obtained from at least one randomised controlled trail.
<b>IIa</b>	Evidence obtained from at least one well-designed controlled study without randomisation.
<b>IIb</b>	Evidence obtained from at least one other type of well-designed quasi-experimental study.
<b>III</b>	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
<b>IV</b>	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

### Grades of recommendation

Grades	Recommendation
<b>A</b> (evidence levels <b>Ia</b> , <b>Ib</b> )	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
<b>B</b> (evidence levels <b>IIa</b> , <b>IIb</b> , <b>III</b> )	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
<b>C</b> (evidence level <b>IV</b> )	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.
<b>GPP</b> (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

**CLINICAL PRACTICE GUIDELINES**

# **Glomerulonephritis**

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## **Statement of Intent**

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

## Foreword

Glomerulonephritis is the second leading cause of renal failure after diabetes mellitus in Singapore. Based on the National Renal Registry data, glomerulonephritis was the underlying cause of kidney failure in 35.7% of the patients starting dialysis in 2000.

The Ministry of Health released its first guidelines on Glomerulonephritis in 2001 to equip practitioners with the appropriate skills and knowledge to reduce the burden of renal failure caused by this disease. These Guidelines were drawn up by the National Committee on Renal Care. Since then, further evidence have emerged in the area of diagnosis and management of haematuria and proteinuria, management of specific types of glomerulonephritis and management of hypertension in glomerulonephritis.

Apart from updating the guidelines in these areas, the second edition also focuses on complications of chronic renal disease including bone disease, hypertension and anaemia.

I hope that all practitioners involved in the care of patients with renal disease will benefit from these guidelines and use them actively in their practice.

PROFESSOR K SATKU  
DIRECTOR OF MEDICAL SERVICES

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## Executive Summary of Recommendations

Details of recommendations can be found in the main text at the pages indicated.

### Management of haematuria and proteinuria

**C** Screening to detect microscopic haematuria and proteinuria in asymptomatic population is not recommended. However, screening using dipstick analysis should be done for individuals at risk for kidney disease (pg 30).

**Grade C, Level IV**

**B** Patients with microscopic haematuria ( $\geq 3$  RBCs/hpf) should undergo evaluation to exclude renal/urinary tract disease (pg 30).

**Grade B, Level III**

**B** Urine phase contrast microscopy under standard conditions is useful in differentiating glomerular from non-glomerular sources of haematuria (pg 30).

**Grade B, Level III**

**B** Patients with microhaematuria should be evaluated for the presence of hypertension, proteinuria and renal impairment (pg 31).

**Grade B, Level III**

**B** Patients with isolated glomerular microhaematuria should remain on follow-up at 6-12 month intervals to monitor blood pressure, proteinuria and renal function (pg 31).

**Grade B, Level III**

**B** Patients with microhaematuria of non-glomerular origin should undergo evaluation to exclude urinary tract disease (pg 31).

**Grade B, Level III**

**Table 5**

**C History, physical examination and laboratory evaluation for patients with haematuria**

<p><b>History</b></p> <p>Urinary Symptoms:</p> <ul style="list-style-type: none"><li>• Dysuria, frequency</li><li>• Previous gross haematuria</li><li>• Ureteric or renal colic</li><li>• Symptoms suggestive of bladder outlet obstruction such as poor stream and dribbling</li></ul> <p>Past Medical History:</p> <ul style="list-style-type: none"><li>• Autoimmune diseases</li><li>• Pelvic oncological radiotherapy</li><li>• Sexually transmitted diseases pre-disposing to urethritis and urethral stricture</li><li>• Renal trauma</li><li>• Previous renal or extra-renal tuberculosis</li><li>• Lower or upper urinary tract infections</li></ul> <p>Drug History:</p> <ul style="list-style-type: none"><li>• Warfarin</li><li>• Non-steroidal anti inflammatory drugs</li><li>• Previous cytotoxic/immunosuppressive therapy</li><li>• Exposure to chemicals (benzene, aromatic amines, leather dyes, chemicals in rubber or tyre manufacture)</li><li>• Cigarette smoking</li><li>• History of consuming herbal slimming remedies (example: those containing aristocholic acid)</li><li>• Drugs that may cause a false positive dipstick reaction such as certain antiseptic solutions</li></ul>
<p>Family History of:</p> <ul style="list-style-type: none"><li>• Primary renal disease</li><li>• Hypertension</li><li>• Adult polycystic kidney disease (APCKD)</li><li>• Deafness suggestive of Alport's syndrome</li><li>• Urolithiasis</li><li>• Microscopic haematuria</li></ul>



**Table 5 (con't)**

<p><b>History (con't)</b></p> <p>Other:</p> <ul style="list-style-type: none"><li>• Recent upper respiratory tract infection (URTI) or tonsillitis suggesting post-infectious glomerulonephritis</li><li>• Ongoing URTI and/or gastroenteritis (GE), suggesting Ig A nephropathy</li><li>• Constitutional symptoms such as myalgia, arthralgia and cutaneous rash, suggesting Henoch-Schonlein purpura or crescentic glomerulonephritis</li><li>• Diabetes mellitus and diabetic nephropathy</li><li>• Evidence of a bleeding diathesis</li></ul>
<p><b>Physical Examination for Patients with Haematuria</b></p> <p>Blood pressure</p> <p>Skin examination for purpura, digital vasculitis</p> <p>Throat/tonsil inspection</p> <p>Cardiac auscultation for murmurs</p> <p>Signs of fluid overload</p> <p>Abdominal examination for enlarged, ballotable kidneys or other organomegaly</p> <p>Digital rectal examination of the prostate in males</p>
<p><b>Initial Laboratory Investigations for Patients with Haematuria</b></p> <p>Full blood count</p> <p>Renal function tests: serum urea, creatinine and electrolytes</p> <p>Urine culture</p> <ul style="list-style-type: none"><li>• microbiologically proven urinary tract infections should first be treated and urinalysis re-checked before further tests are done</li></ul> <p>Urine phase contrast microscopy</p> <p>Urine protein measurement (24-hour urinary protein or urine protein / creatinine ratio)</p>

(pg 32-33)

**Grade C, Level IV**

**C** In the absence of contraindications, intravenous urography (IVU) is the recommended initial imaging of choice for investigation of non-glomerular bleeding and may be complemented by ultrasonography (pg 34).

**Grade C, Level IV**

**B** Patients with orthostatic proteinuria have a good renal prognosis and do not require follow-up (pg 34).

**Grade B, Level III**

**B** Patients with proteinuria should be evaluated for the presence of microhaematuria, hypertension and renal impairment (pg 34).

**Grade B, Level III**

**B** Patients with intermittent isolated proteinuria have a favourable renal prognosis but should be followed up until resolution of proteinuria (pg 35).

**Grade B, Level III**

**B** Patients with persistent isolated proteinuria should be followed-up indefinitely with monitoring of blood pressure and renal function since the risk of subsequently developing renal insufficiency is higher (pg 35).

**Grade B, Level III**

**B** Patients with persistent proteinuria  $\geq 1$  g/day should undergo renal biopsy as they are at risk for adverse renal histopathology and therefore worse renal outcome (pg 35).

**Grade B, Level III**

## **Table 6** **GPP** **History, physical examination and laboratory evaluation for patients with proteinuria**

### **History:**

#### Urinary Symptoms:

- dysuria, frequency to exclude urinary tract infection

#### Past Medical History of:

- childhood glomerulonephritis
- pre-eclampsia in women
- autoimmune conditions
- diabetes
- cardiac failure

#### Drug History:

- gold, penicillamine and captopril in relation to secondary membranous nephropathy
- Non-steroidal anti-inflammatory drugs (NSAIDs) or penicillins in relation to (allergic) interstitial nephritis

**Table 6 (con't)**

<p><b>Physical Examination:</b></p> <ul style="list-style-type: none"><li>Blood pressure</li><li>Signs of end organ damage due to hypertension</li><li>Signs of renal failure</li><li>Signs of diabetes or auto-immune disease</li><li>Oedema</li></ul>
<p><b>Initial Laboratory Investigations:</b></p> <ul style="list-style-type: none"><li>Urinalysis for haematuria and glycosuria (if not already performed)</li><li>Fresh mid-stream urine specimen for culture</li><li>Serum urea, creatinine and fasting glucose (in the presence of glycosuria)</li><li>Serum albumin</li><li>24-hour urine collection for quantification (24-hour UTP)</li><li><u>or</u></li><li>Random or spot urinary protein and creatinine measurement to derive the urinary protein/creatinine ratio (PCR). PCR <math>\geq 200</math> mg/g indicates elevated urine protein content.</li><li>Exclusion of monoclonal gammopathy in subjects &gt;45 years of age</li><li>Ultrasound of the kidneys to evaluate structure and size</li><li>Urine phase contrast microscopy</li><li>24-hour urinary creatinine clearance (CCT)</li><li><u>or</u></li><li>Glomerular Filtration Rate (GFR) Calculation</li></ul>
<p><b>Nephrological Evaluation:</b></p> <ul style="list-style-type: none"><li>Renal biopsy if proteinuria <math>\geq 1</math> g/day and/or rapidly worsening renal dysfunction in the absence of other causes (both renal and systemic causes)</li></ul>

(pg 36-37)

**GPP**

**B** Patients with microhaematuria and either proteinuria or hypertension or renal impairment should be referred to a nephrologist for further evaluation (pg 37).

**Grade B, Level III**

**B** All patients with gross haematuria should be evaluated for urological pathology with a combination of ultrasound, intravenous urography and flexible cystourethroscopy (pg 38).

**Grade B, Level III**

## **General Measures in Management of Patients with Glomerulonephritis**

**A** Patients with glomerulonephritis should be evaluated to establish the type of glomerulonephritis and identify its severity (pg 42).

**Grade A, Level Ib**

**A** Testing for level of renal function, degree of proteinuria, renal biopsy and other investigations should be performed as indicated (pg 42).

**Grade A, Level Ib**

**C** Patients should be followed up to assess progression of glomerulonephritis. Renal function, proteinuria and other markers should be monitored on follow up, as indicated by type of glomerulonephritis and severity of condition. The severity of kidney disease should be identified based on these markers (pg 42).

**Grade C, Level IV**

**A** Specific therapy of glomerulonephritis should be instituted as indicated by type and severity of underlying condition (pg 44).

**Grade A, Level Ia**

**A** As the level of proteinuria predicts the rate of progression of renal disease, general measures should be instituted to reduce proteinuria in patients with glomerulonephritis (pg 44).

**Grade A, Level Ia**

**A** Angiotensin converting enzyme inhibitors should be used to reduce proteinuria and retard progression, in the absence of hypertension, in patients with glomerulonephritis (pg 45).

**Grade A, Level Ia**

**B** Angiotensin receptor blockers can be used as an alternative to Angiotensin converting enzyme inhibitors to reduce proteinuria and retard progression in patients with glomerulonephritis (pg 45).

**Grade B, Level IIb**

**A** Angiotensin converting enzyme inhibitors can be combined with Angiotensin receptor blockers to reduce proteinuria and retard progression in patients with glomerulonephritis (pg 45).

**Grade A, Level Ib**

**B** Proteinuria should be reduced to  $<0.5$  g/day with therapy in patients with glomerulonephritis (pg 46).

**Grade B, Level III**

**GPP** Patients with glomerulonephritis and renal failure (GFR  $<25$  mL/min), who are not on maintenance dialysis and have no evidence of malnutrition, should be considered for a low-protein diet providing 0.8 g protein/kg body weight/day. At least 50% of dietary protein should be of high biologic value (pg 46).

**GPP**

**C** A diet providing 35 kcal/kg body weight/day is recommended in patients with renal failure (GFR  $<25$  mL/min) to maintain neutral nitrogen balance, to promote higher serum albumin concentrations and more normal anthropometric parameters (pg 47).

**Grade C, Level IV**

## **Management of Hypertension in Patients with Glomerulonephritis**

**A** Hypertension, defined as blood pressure  $\geq 140/90$  mm Hg, should be treated in patients with glomerulonephritis in order to retard the rate of deterioration of renal function (pg 48).

**Grade A, Level Ia**

**C** Hypertension should be treated in patients with glomerulonephritis so as to reduce the risk for cardiovascular disease (pg 48).

**Grade C, Level IV**

**A** A target blood pressure less than 130/80 mm Hg (Mean arterial pressure <98 mm Hg) is recommended for patients with glomerulonephritis and proteinuria  $\leq 1$  g/day (pg 49).

**Grade A, Level Ia**

**A** A target blood pressure less than 125/75 mm Hg (Mean arterial pressure <92 mm Hg) is recommended for patients with glomerulonephritis and proteinuria >1 g/day (pg 49).

**Grade A, Level Ia**

**A** More than one anti-hypertensive drug may be required to achieve target blood pressure in patients with glomerulonephritis (pg 50).

**Grade A, Level Ib**

**A** Any anti-hypertensive agent may be used to control blood pressure in patients with glomerulonephritis (pg 50).

**Grade A, Level Ia**

**A** Angiotensin converting enzyme inhibitors are recommended as preferred treatment of hypertension in patients with glomerulonephritis as they confer greater renoprotection (pg 50).

**Grade A, Level Ia**

**B** Angiotensin receptor blockers can be used as an alternative to Angiotensin converting enzyme inhibitors to treat hypertension in patients with glomerulonephritis (pg 51).

**Grade B, Level IIa**

**B** Angiotensin receptor blockers may be used in combination with Angiotensin converting enzyme inhibitors to treat hypertension in patients with glomerulonephritis (pg 51).

**Grade B, Level IIa**

**A** Diuretics are preferred 2<sup>nd</sup> line antihypertensive agents in patients with glomerulonephritis as they reduce the risk for cardiovascular disease (pg 52).

**Grade A, Level Ib**

**B** Beta blockers and calcium channel blockers can be used alternatively to control blood pressure in patients with glomerulonephritis (pg 53).

**Grade B, Level IIa**

**C** Lifestyle modifications should be begun simultaneously as part of a comprehensive strategy to lower blood pressure and cardiovascular risk (pg 53).

**Grade C, Level IV**

**C** Patients with hypertension and glomerulonephritis should be monitored regularly for blood pressure, renal function and level of proteinuria (pg 54).

**Grade C, Level IV**

**C** Patients receiving an Angiotensin converting enzyme inhibitor or Angiotensin receptor blocker should be monitored for decrease in renal function and hyperkalaemia (pg 54).

**Grade C, Level IV**

**C** Angiotensin converting enzyme inhibitors or Angiotensin receptor blockers can be continued in patients with decrease in renal function of <30% over 4 months or serum potassium  $\leq 5.5$  mmol/L (pg 54).

**Grade C, Level IV**

**C** Angiotensin converting enzyme inhibitors or Angiotensin receptor blockers should not be used in pregnant patients or in those with drug-induced angioedema or allergy. They should also be used with caution in patients with renal artery stenosis or severe hyperkalaemia (pg 54).

**Grade C, Level IV**

## **Management of Renal Dysfunction in Patients with Glomerulonephritis**

**B** Patients with glomerulonephritis and estimated glomerular filtration rate  $<60$  mL/min/1.73 m<sup>2</sup> should be assessed for complications of renal failure, including anaemia and bone disease (pg 56).

**Grade B, Level III**

**C** Patients with glomerulonephritis should be monitored for complications of the underlying condition, risk factors for cardiovascular disease and side effects of therapy (pg 56).

**Grade C, Level IV**

**B** Patients with renal dysfunction should be initiated on renal replacement therapy when indicated by symptoms of renal failure and/or biochemical investigations (pg 57).

**Grade B, Level III**

**B** Patients with glomerulonephritis and estimated glomerular filtration rate  $<60$  mL/min/1.73 m<sup>2</sup> should be evaluated for the presence of anaemia by measuring haemoglobin periodically (pg 57).

**Grade B, Level III**

**B** Further evaluation of anaemia should be initiated in patients with glomerulonephritis and renal dysfunction when:

- Hemoglobin is  $<11$  g/dL in pre-menopausal females and prepubertal patients
- Hemoglobin  $<12$  g/dL in adult males and post-menopausal females (pg 58).

**Grade B, Level III**

**B** Evaluation of anaemia should include

- Red cell indices
- Reticulocyte count
- Iron parameters (serum iron, Total Iron Binding Capacity, percent transferrin saturation and serum ferritin)
- Tests for occult blood in stools (pg 58).

**Grade B, Level III**

**A** Patients with anaemia due to renal dysfunction should be treated with supplemental iron to maintain percent transferrin saturation  $>20\%$  and serum ferritin level  $>100$  ng/mL (pg 58).

**Grade A, Level Ib**

**A** Anaemia due to renal dysfunction should be treated with erythropoietin therapy (pg 58).

**Grade A, Level Ia**

**A** Target for haemoglobin for patients with renal dysfunction should be 12 g/dL. Target range for haemoglobin are for erythropoietin therapy and are not an indication for blood transfusion (pg 59).

**Grade A, Level Ia**



**B** Adverse effects of erythropoietin therapy including hypertension should be monitored in patients with glomerulonephritis and renal dysfunction (pg 59).

**Grade B, Level III**

**B** Serum levels of calcium, phosphorus and intact plasma parathyroid hormone levels should be measured in patients with glomerulonephritis and eGFR <60 mL/min/1.73 m<sup>2</sup> (pg 60).

**Grade B, Level III**

**B** Patients with glomerulonephritis and chronic renal dysfunction should receive therapy to control serum phosphate, calcium and parathyroid hormone levels, so as to reduce onset of bone disease due to secondary hyperparathyroidism (pg 60).

**Grade B, Level III**

**C** Serum calcium, phosphate and parathyroid hormone levels should be monitored at 3-12 monthly intervals in patients with glomerulonephritis and chronic renal dysfunction (pg 60).

**Grade C, Level IV**

**C** Phosphate levels should be maintained between 2.7 and 4.6 mg/dL (0.87 and 1.49 mmol/L) in patients with chronic renal dysfunction (pg 61).

**Grade C, Level IV**

**B** Dietary phosphate should be restricted to 800-1000 mg/day (adjusted for dietary protein needs) when serum phosphate levels are elevated above 4.6 mg/dL or when parathyroid hormone levels are elevated (pg 61).

**Grade B, Level III**

**C** If serum phosphate level cannot be controlled despite dietary phosphate restriction, phosphate-binders should be prescribed (pg 61).

**Grade C, Level IV**

**C** Calcium-based phosphate binders can be used to lower serum phosphate levels (pg 61).

**Grade C, Level IV**

**C** The total dose of elemental calcium provided by calcium-based phosphate binders should not exceed 1,500 mg/day and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/day (pg 61).

**Grade C, Level IV**

**C** Serum calcium levels should be maintained within the range of 8.4 to 9.5 mg/dL (2.10 to 2.37 mmol/L), so as to avoid hypercalcaemia (pg 62).

**Grade C, Level IV**

**C** The calcium-phosphate product should be calculated periodically, from values of serum calcium and phosphate, in patients with glomerulonephritis and chronic renal dysfunction (pg 62).

**Grade C, Level IV**

**C** The target calculated calcium-phosphate product is 55 (in  $\text{mg}^2/\text{dL}^2$ ) in patients with chronic renal dysfunction. Doses of calcium and Vitamin D analogs should be reduced if the calcium-phosphate product exceeds the target range (pg 62).

**Grade C, Level IV**

**GPP** Target range of Intact parathyroid hormone level in patients with chronic renal dysfunction should be as listed below (pg 62):

GFR (mL/min/1.73 m<sup>2</sup>)  
30-59  
15-29

Target intact PTH (pmol/L)  
3.85-7.70  
7.70-12.10

**GPP**

**A** Patients with chronic renal dysfunction and elevated parathyroid hormone levels above the target ranges should be treated with active vitamin D sterols (pg 62).

**Grade A, Level Ib**

**C** Treatment with active vitamin D sterols for elevated parathyroid hormone levels in patients with chronic renal dysfunction should be undertaken only in patients with levels of corrected serum total calcium < 9.5 mg/dL and serum phosphate < 4.6 mg/dL (pg 63).

**Grade C, Level IV**

**C** Patients with glomerulonephritis and renal dysfunction should be evaluated for dyslipidaemia. They should have a complete lipid profile including triglycerides, total, low-density lipoprotein and high-density lipoprotein cholesterol (pg 63).

**Grade C, Level IV**

**A** Patients with elevated cholesterol levels should be treated so as to reduce their risk for cardiovascular disease as for patients in the general population. These patients should be treated with cholesterol-reducing diet and statins (pg 64).

**Grade A, Level Ia**

**A** Patients with elevated cholesterol levels should be treated with statins so as to reduce their risk for progression of renal disease (pg 64).

**Grade A, Level Ia**

**C** Targets for LDL cholesterol with therapy in patients with glomerulonephritis and renal dysfunction is <100 mg/dL (pg 65).

**Grade C, Level IV**

**C** Serum bicarbonate level should be measured in patients with glomerulonephritis and renal dysfunction so as to detect acidosis (pg 65).

**Grade C, Level IV**

**B** Patients with acidosis (serum bicarbonate level < 15 mmol/L) should be treated with an alkali such as sodium bicarbonate. Target serum bicarbonate level with therapy is >22 mmol/L (pg 65).

**Grade B, Level III**

## **Management of Minimal Change Disease in Adults**

**B** Patients with nephrotic syndrome due to minimal change disease should be treated so as to induce remission of proteinuria (pg 67).

**Grade B, Level III**

**A** High dose prednisolone is recommended for initial treatment of nephrotic syndrome due to minimal change disease (pg 69).

**Grade A, Level Ib**

**B** Daily oral prednisolone at 1 mg/kg/day is recommended for initial treatment of nephrotic syndrome due to minimal change disease (pg 69).

**Grade B, Level III**

**B** Alternate-day oral prednisolone at 2 mg/kg/day can be used for initial treatment of nephrotic syndrome due to minimal change disease (pg 70).

**Grade B, Level III**

**B** Steroid resistance should be considered if there is failure to achieve remission of nephrotic syndrome due to minimal change disease by 16 weeks after initiation of corticosteroid therapy (pg 70).

**Grade B, Level III**

**GPP** High dose prednisolone dose should be continued until remission is achieved unless steroid toxicity or steroid resistance is diagnosed (pg 71).

**GPP**

**A** Prednisolone dose should be tapered after remission in nephrotic syndrome is achieved and subsequently discontinued. Tapering of prednisolone should be performed over 6 months (pg 71).

**Grade A, Level Ib**

**B** During taper, alternate-day prednisolone can be used to minimize the side effects of therapy (pg 71).

**Grade B, Level III**

**B** Patients undergoing prednisolone taper should be monitored for relapse of nephrotic syndrome (pg 71).

**Grade B, Level III**

**B** Patients who experience a relapse of nephrotic syndrome following a remission should be treated with a second course of corticosteroids (pg 71).

**Grade B, Level III**

**GPP** Patients with nephrotic syndrome due to minimal change disease should be monitored for side effects of corticosteroids. Prednisolone doses should be reduced and alternative treatment considered if there is unacceptable steroid toxicity or if steroid resistance is diagnosed (pg 72).

**GPP**

**B** Cytotoxic therapy with cyclophosphamide can be used for treatment of frequently relapsing or steroid-dependent nephrotic syndrome due to minimal change disease (pg 72).

**Grade B, Level III**

**GPP** Patients in whom cyclophosphamide therapy is planned should be informed of the potential risk for sterility and malignancy. Male patients should be advised to consider sperm storage (pg 73).

**GPP**

**A** Cyclosporin A can be used in the treatment of frequently-relapsing or steroid-dependent nephrotic syndrome due to minimal change disease (pg 74).

**Grade A, Level Ib**

**B** Cyclosporin A can be started at a dose of up to 5 mg/kg/day in the treatment of frequently-relapsing or steroid-dependent nephrotic syndrome due to minimal change disease. Cyclosporin A should be administered at these doses for 1 year after which doses should be tapered. Cyclosporin A should be discontinued after 3 years (pg 74).

**Grade B, Level III**

**B** Cyclosporin A should be administered together with corticosteroids for treatment of nephrotic syndrome due to minimal change disease (pg 75).

**Grade B, Level III**

**B** Patients on cyclosporin A therapy for treatment of nephrotic syndrome due to minimal change disease should have periodic monitoring of renal function. A repeat renal biopsy should be considered after a year of cyclosporin A therapy to detect histological evidence of nephrotoxicity (pg 75).

**Grade B, Level III**

**B** Mycophenolate mofetil can be used for treatment of frequently-relapsing or steroid-dependent nephrotic syndrome due to minimal change disease (pg 76).

**Grade B, Level III**

**B** Cyclophosphamide, cyclosporin A, mycophenolate mofetil or tacrolimus can be used in the treatment of steroid-resistant nephrotic syndrome due to minimal change disease (pg 76).

**Grade B, Level III**

## **Focal and Segmental Glomerulosclerosis**

**B** Patients with nephrotic syndrome due to focal and segmental glomerulosclerosis should be treated with immunosuppression so as to induce remission of proteinuria (pg 79).

**Grade B, Level IIb**

**B** Patients with nephrotic syndrome due to focal and segmental glomerulosclerosis should be treated with steroids (pg 79).

**Grade B, Level III**

**B** Patients with nephrotic syndrome due to focal and segmental glomerulosclerosis should receive high dose prednisolone at 1 mg/kg/day as initial therapy. High dose steroids should be continued for 1 to 2 weeks after remission is achieved and then tapered slowly (pg 80).

**Grade B, Level III**

**B** Total treatment duration with steroids for patients with nephrotic syndrome due to focal and segmental glomerulosclerosis should be for at least 6 months (pg 80).

**Grade B, Level III**

**B** Patients with nephrotic syndrome due to focal and segmental glomerulosclerosis may be treated with alternative-day steroids to minimise corticosteroid toxicity (pg 81).

**Grade B, Level IIb**

**B** Failure to achieve remission of nephrotic syndrome due to focal and segmental glomerulosclerosis by 6 months after initiation of corticosteroid therapy is defined as steroid resistance (pg 81).

**Grade B, Level III**

**B** Cytotoxic therapy with cyclophosphamide can be considered for patients with steroid-dependent nephrotic syndrome due to focal and segmental glomerulosclerosis or those with steroid-related side effects (pg 82).

**Grade B, Level III**

**B** Cytotoxic therapy with cyclophosphamide can be considered as alternative therapy for patients with steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis (pg 82).

**Grade B, Level III**

**B** Patients in whom cyclophosphamide therapy is planned should be informed of the potential risk for sterility; male patients should be advised sperm storage (pg 83).

**Grade B, Level III**

**B** Cyclosporin A should be considered for patients with steroid-dependent nephrotic syndrome due to focal and segmental glomerulosclerosis or those with steroid-related side effects. As a lasting remission may not be achieved, long-term use may be necessary to maintain remission (pg 83).

**Grade B, Level III**

**A** Cyclosporin A at starting doses of 3 to 5 mg/kg/day should be considered for patients with steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis. As a lasting remission may not be achieved, long-term use may be necessary to maintain remission (pg 84).

**Grade A, Level Ib**

**B** Cyclosporin A should be administered together with steroids for patients with steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis until remission is achieved. Steroid doses may be tapered subsequently (pg 84).

**Grade B, Level III**

**B** Patients receiving cyclosporin A for treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis should have renal function monitored (pg 85).

**Grade B, Level III**

**A** Patients with steroid-responsive nephrotic syndrome due to focal and segmental glomerulosclerosis, who are considered for alternative therapy, may be treated with either cyclosporin A or cyclophosphamide (pg 85).

**Grade A, Level Ib**

**B** Patients with steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis are preferentially treated with cyclosporin A (pg 85).

**Grade B, Level III**

**B** Mycophenolate mofetil may be used in the treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis (pg 86).

**Grade B, Level II**

**B** Tacrolimus may be used as alternative therapy in treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis (pg 86).

**Grade B, Level III**

**C** Plasmapheresis may be used as alternative therapy in treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis (pg 87).

**Grade C, Level IV**

## **IgA Nephropathy**

**C** No specific therapy is recommended for patients with IgA nephropathy and isolated haematuria without proteinuria (pg 89).

**Grade C, Level IV**

**C** Patients with IgA nephropathy and isolated haematuria should be monitored regularly (every 3-12 months) for the development of hypertension, renal impairment and proteinuria (pg 89).

**Grade C, Level IV**



**C** No specific therapy is recommended for patients with IgA nephropathy and asymptomatic haematuria and proteinuria of 0.15 g/day to 1 g/day and no other adverse clinical or histological indicators (pg 90).

**Grade C, Level IV**

**C** Patients with IgA nephropathy and haematuria and proteinuria should be monitored regularly (every 3-12 months) for the level of proteinuria and the development of hypertension and renal impairment (pg 90).

**Grade C, Level IV**

**A** Patients with IgA nephropathy and proteinuria  $\geq 1$  g/day should be treated so as to reduce the risk of progression of renal failure (pg 90).

**Grade A, Level Ib**

**B** Angiotensin converting enzyme inhibitor therapy is recommended for treatment of hypertension in patients with IgA nephropathy (pg 91).

**Grade B, Level IIa**

**A** Angiotensin converting enzyme inhibitor therapy is recommended in normotensive patients with IgA nephropathy and proteinuria  $\geq 1$  g/day (pg 91).

**Grade A, Level Ib**

**A** Angiotensin II receptor blockers can be used as alternatives to angiotensin converting enzyme inhibitors in patients with IgA nephropathy for similar indications (pg 92).

**Grade A, Level Ib**

**A** Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers can be used in combination to reduce proteinuria in patients with IgA nephropathy and proteinuria  $\geq 1$  g/day (pg 92).

**Grade A, Level Ib**

**A** Dipyridamole and low-dose warfarin combination therapy is recommended in patients with IgA nephropathy and proteinuria  $\geq 1$  g/day. Its use is not contraindicated in patients with abnormal renal function (pg 93).

**Grade A, Level Ib**

**B** Fish oil supplementation can be used in patients with IgA nephropathy and proteinuria >3 g/day (pg 94).

**Grade B, Level III**

**A** Corticosteroids can be used for treatment in selected patients with IgA nephropathy (pg 94).

**Grade A, Level Ia**

**GPP** Immunosuppression is not without risk of toxicity and should only be considered in patients with persistent proteinuria  $\geq 1$  g/day or in those with evidence of progressive renal damage despite adequate blood pressure control at 130/80 mm Hg or lower with an ACEI or ARB (pg 95).

**GPP**

**B** Treatment for patients with nephrotic syndrome due to IgA nephropathy should be based on findings on renal biopsy (pg 96).

**Grade B, Level IIa**

**B** Nephrotic patients with IgA nephropathy and mild histological changes on renal biopsy should be treated with prednisolone at an initial dose of 1 mg/kg/day with subsequent tapering after 4-6 weeks for a total treatment period of 3-4 months (pg 96).

**Grade B, Level IIa**

**B** Nephrotic patients with IgA nephropathy and mild histological changes who have relapses, steroid resistance or steroid dependence should be treated with cyclophosphamide at a dose of 1.5-2.0 mg/kg/day for 2-3 months together with low-dose prednisolone (pg 97).

**Grade B, Level IIa**

**C** Cyclosporin A at an initial dose of 5 mg/kg/day can be used in nephrotic IgA patients with mild histological changes who fail steroid and cyclophosphamide therapy. The recommended treatment period is 6-12 months and low-dose prednisolone should be given concomitantly (pg 97).

**Grade C, Level IV**

**C** Nephrotic IgA patients with histological changes that are not mild can be treated with prednisolone, cyclophosphamide or cyclosporin A, similar to those with mild histological changes (pg 97).

**Grade C, Level IV**

**GPP** As response to immunosuppressive therapy is less favourable in patients with IgA nephropathy and more severe histological changes, over-immunosuppression should be avoided in non-responders (pg 98).

**GPP**

**C** Patients with IgA nephropathy and acute renal failure should undergo renal biopsy to determine treatment (pg 98).

**Grade C, Level IV**

**C** Patients with acute renal failure due to crescentic IgA nephropathy should be treated as for other forms of crescentic glomerulonephritis. Treatment with methylprednisolone pulse should be followed by oral prednisolone, cyclophosphamide, dipyridamole and warfarin (pg 98).

**Grade C, Level IV**

**GPP** Plasma exchange and intravenous immunoglobulins can be instituted in some patients with crescentic IgA nephropathy (pg 99).

**GPP**

**C** No specific treatment is recommended for patients with IgA nephropathy and acute renal failure in the presence of mild glomerular changes on renal biopsy (pg 99).

**Grade C, Level IV**

# 1 Introduction

## 1.1 Aim and scope of guideline

The first edition of the MOH clinical practice guideline on Glomerulonephritis was published in 2001. Since that time, more facts have emerged with regard to the diagnosis and management of glomerulonephritis and its complications.

This second edition of the guidelines aim to address some of the complex issues wherever evidence-based information pertaining to these is available and to help doctors in clinical decision making by providing balanced information on the management of patients with glomerulonephritis, without restricting the physician's individual clinical judgement.

## 1.2 Target group

The guidelines are developed for all healthcare professionals, in particular, primary care physicians, who are involved in the care of patients with Glomerulonephritis.

## 1.3 Guideline development

These guidelines have been produced by a Workgroup comprised of members of the National Committee on Renal Care appointed by the Ministry of Health. The guidelines were developed using the best available current evidence and expert opinion.

## 1.4 What's new in the revised guidelines?

The following is a list of major changes or additions to the guidelines:

- 1) Chapter 2 on overview of glomerulonephritis has been updated and information on histological pattern of glomerulonephritis in patients with end stage renal failure has been included. This has given insight to the types of glomerulonephritis that could progress to ESRF and emphasized the need of early diagnosis to delay the progression of glomerulonephritis to ESRF.
- 2) Chapter 3 has been updated and diagnosis and management of haematuria and proteinuria has been revised.

- 3) Chapter 4 has been revised to define the target proteinuria that is to be attained with therapy in patients with glomerulonephritis to accrue maximal benefit in renoprotection.
- 4) Chapter 5 on management of hypertension in glomerulonephritis has been revised with more emphasis on regular monitoring and life-style modifications.
- 5) Chapter 6 on management of renal dysfunction in glomerulonephritis has been added to deal with the complications of renal dysfunction, including anaemia and bone disease.
- 6) Chapter 7-9 have updated information on the management of specific types of glomerulonephritis.

## **1.5 Review of guidelines**

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supercede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review five years after publication, or if new evidence appears that requires substantive changes to the recommendations.

## 2 Overview of Glomerulonephritis

### 2.1 Introduction

While there has been no population survey on the incidence of glomerulonephritis in Singapore, there is direct evidence from renal registry data that glomerulonephritis is the second leading cause of end stage renal failure, contributing to approximately a third of end stage renal failure in the country.<sup>1</sup> Of 624 new incident patients starting dialysis in 2000, and reported to the Singapore Renal Registry, glomerulonephritis was diagnosed as the underlying cause in 35.7%.<sup>1</sup> The following provides an overview of glomerulonephritis, as reported in the largest systematic survey from Singapore in terms of its clinical presentation, histopathology and management.<sup>2</sup>

### 2.2 Clinical syndromes

Haematuria and proteinuria are the hallmarks of glomerular disease; in addition, hypertension, impaired renal function and fluid retention can be present to varying extents. The nature and severity of the underlying glomerular injury often dictate the nature and severity of these symptoms. Whereas some glomerular diseases tend to produce particular groups of symptoms that can be classified as a syndrome, the mode of clinical presentation can often give clues to the underlying glomerular pathology. Apart from the clinical syndromes, glomerulonephritis is also classified into primary or secondary types; in the former, the pathology is limited to the kidney whereas in the latter, a systemic condition is associated with renal involvement. The major clinical syndromes of glomerulonephritis are as listed below in Table 1.

**Table 1 Major clinical syndromes of glomerulonephritis**

- |    |                                          |
|----|------------------------------------------|
| 1. | Isolated microscopic or gross haematuria |
| 2. | Isolated proteinuria                     |
| 3. | Asymptomatic haematuria and proteinuria  |
| 4. | Acute nephritic syndrome                 |
| 5. | Nephrotic syndrome                       |
| 6. | Nephritic-nephrotic syndrome             |
| 7. | Rapidly progressive GN                   |

Among these clinical syndromes, **haematuria** and **proteinuria**, in isolation or in combination, are very common and may afflict as many as 2% of the general population. As only a small proportion of patients with these symptoms or signs have significant glomerular disease, the vast majority of these patients would not be subjected to a renal biopsy. Patients with these abnormalities should thus undergo evaluation as described in Chapter 3 so as to identify those with significant renal disease.

In contrast, patients presenting with the other clinical syndromes have significant glomerular disease and further characterisation of their glomerular lesions frequently requires a renal biopsy.

Patients with **acute nephritic syndrome** present with oedema associated with gross haematuria (smoky urine) and hypertension. Often the aetiology is post-infectious glomerulonephritis; Streptococci, other bacteria, viruses and parasites can all cause this entity. Recovery is the rule and generally patients have a good prognosis with 95% renal survival at 5 years and 90% at 10 years.<sup>3</sup> Treatment is often symptomatic and includes salt and fluid restriction, diuretics, treatment of sepsis, hypertension and heart failure. A secondary glomerulonephritis due to systemic lupus erythematosus (SLE) or rapidly progressive glomerulonephritis should also be kept in mind.

Patients with the **nephrotic syndrome** present with the classical triad of oedema, proteinuria (>3 g/day) and hypo-albuminaemia (serum albumin <30 g/L). While primary glomerulonephritis is the most common cause of this condition, other conditions such as diabetes, drugs (e.g., gold, penicillamine, captopril and non-steroidal anti-inflammatory drugs) should be excluded. Secondary glomerulonephritis can also cause nephrotic syndrome as a result of kidney involvement from autoimmune diseases like systemic lupus erythematosus, cryoglobulinaemia and thyrotoxicosis. Finally, rarer causes such as infections including hepatitis B and C, malaria and human immunodeficiency virus; amyloidosis; and malignancies such as those of the lung, gastrointestinal tract, lymphoma and myeloma should also be considered in the evaluation.

Patients presenting with the **nephritic-nephrotic syndrome** have clinical features of both conditions and systemic lupus erythematosus often needs to be considered in this context. **Rapidly progressive glomerulonephritis** (RPGN) is a term applied for acute nephritis that results in rapid loss of kidney function over a period of weeks to months. Goodpasture's syndrome and Wegener's granulomatosis are some conditions associated with this very severe form of glomerular inflammation.

In the largest survey of patients undergoing renal biopsies at a single institution in Singapore between 1987 and 1997, the leading clinical presentations that prompted a renal biopsy were nephrotic syndrome and asymptomatic haematuria and proteinuria (ASHP) (Table 2).<sup>2</sup>

**Table 2 Primary glomerulonephritis: clinical presentation (1987-1997)\***

Clinical presentation	No. of cases	%
Nephrotic syndrome	238	36
Asymptomatic haematuria & proteinuria	236	35
Hypertension	93	14
Acute nephritis	44	6
Gross haematuria	26	4
Others	26	4
Chronic renal failure	3	<1
Total	666	100%

\* Adapted with permission from Woo KT and Chiang GSC.<sup>2</sup>

### 2.3 Histopathological pattern at initial presentation

Although the clinical presentation can often provide clues to the underlying glomerular pathology, a renal biopsy is often necessary as several glomerular conditions can result in the same clinical syndrome. Thus biopsy is necessary to help determine the nature and severity of the underlying glomerulonephritis, to prognosticate and to guide treatment.

The histological pattern of glomerulonephritis from the largest series from Singapore is shown in Table 3.<sup>2</sup> The commonest diagnoses were Mesangial proliferative glomerulonephritis (diffuse and focal) and Focal global sclerosis or Minimal change disease (29%). Among



those with Mesangial proliferative glomerulonephritis, 68% were due to IgA nephritis. After analysing the various types of glomerular disease from biopsies of patients from this series, IgA nephritis, comprising 45% of glomerulonephritis, is likely the commonest glomerulonephritis in Singapore. Of note is that ASHP is the commonest mode of presentation of this condition.

Detailed guidelines on the management of these glomerular diseases are suggested in the following specific chapters.

**Table 3            Histopathological pattern of primary glomerulonephritis at presentation and at end stage renal failure**

<b>Histology</b>	<b>% at initial presentation, 1987-1997<sup>2</sup></b>	<b>% among prevalent patients on dialysis as of 31 December 1998*</b>
Mesangial proliferative glomerulonephritis	53	81
Focal global sclerosis	15	0
Minimal change	14	0
Focal and segmental glomerulosclerosis	9	10
Membranous glomerulonephritis	6	4
Crescentic glomerulonephritis	<1	2
Others	2	3
<b>Total</b>	<b>100</b>	<b>100</b>

<sup>2</sup> Adapted with permission from Woo KT and Chiang GSC.

\* Adapted with permission from Second Report of the Singapore Renal Registry 1998.

The histopathological profile among those with the nephrotic syndrome is shown in Table 4.<sup>2</sup>

**Table 4 Causes of nephrotic syndrome (1987-1997)\***

Histology	No. of cases	%
Minimal change	72	30
Focal global sclerosis	49	21
Mesangial proliferative glomerulonephritis	59	25
Focal and segmental glomerulosclerosis	21	9
Membranous glomerulonephritis	29	12
Crescentic glomerulonephritis	2	1
Others	6	2
Total	238	100

\* Adapted with permission from Woo KT and Chiang GSC.<sup>2</sup>

## 2.4 Histopathological pattern of patients with end stage renal failure

However, the histological pattern of glomerulonephritis for patients with end stage renal failure, as reported to the Singapore Renal Registry is significantly different (Table 3).<sup>1</sup> Of the 2,080 prevalent patients treated with dialysis and reported to the Singapore Renal Registry as of 31 December 1998, 1,040 or 50% had underlying glomerulonephritis.<sup>1</sup> Of these, the majority were primary glomerulonephritis (n = 950), while the remainder (n = 90) had systemic conditions such as systemic lupus erythematosus causing end stage renal failure. Unfortunately, a significant number of those with end stage renal failure due to glomerulonephritis had been diagnosed based on clinical and other laboratory criteria without benefit of biopsy (n = 778, 74.8%) or had advanced glomerulosclerosis at biopsy (n = 44, 4.2%). Of the remainder, 135 (13%) had biopsy-proven primary glomerulonephritis, predominately mesangial proliferative glomerulonephritis, 6 (0.6%) had other secondary glomerulonephritis while 77 (7.4%) had lupus nephritis.

Important findings from the Singapore Renal Registry data suggest that the majority of end stage renal failure patients with underlying glomerulonephritis, do not have biopsy diagnosis or have their biopsy performed only at an advanced stage of glomerulosclerosis. Furthermore, it is apparent that while focal global sclerosis and minimal change disease do not progress to end stage renal failure, the

other types of glomerulonephritis do progress to end stage renal failure and their early diagnosis and treatment may ameliorate progression to end stage renal failure. Indeed, as nearly 50% of those with nephrotic syndrome had glomerulonephritis that could potentially lead to end stage renal failure, biopsy diagnosis of patients with nephrotic syndrome is also needed for optimal management of patients. As late diagnosis precludes appropriate biopsy-based treatment, early diagnosis, as recommended by these guidelines, is crucial in delaying progression of glomerulonephritis to end stage renal failure.

## **2.5 Principles of treatment of glomerulonephritis**

The management of glomerulonephritis is often targeted at treating several phases of the condition. Often the glomerular pathology can be considered as progressing in two phases: in the acute or early immunological phase, antibodies, immune complexes or cytokine mediated mechanisms initiate glomerular injury.<sup>4</sup> These immune mediated mechanisms can be ameliorated by immunosuppressive drugs like prednisolone, cyclophosphamide, cyclosporin A and mycophenolate mofetil (MMF).<sup>5,6</sup>

With progression of glomerulosclerosis, a chronic or late phase occurs due to injury resulting from glomerular hyperfiltration.<sup>7</sup> Glomerular hyperfiltration is associated with increasing proteinuria or renal deterioration (elevated serum creatinine) and hypertension. Therapy with angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) ameliorates angiotensin II mediated vasoconstriction at the efferent glomerular arteriole or blocks angiotensin II receptors respectively.<sup>7-11</sup> Whereas treatment of hypertension reduces systemic and glomerular hypertension, dietary protein restriction reduces macromolecular traffic and the afferent glomerular vasodilatation associated with hyperfiltration.<sup>7-9,11,12</sup> Hyperfiltration-associated endothelial cell and platelet damage is reduced with reduction in intra-glomerular hypertension and glomerular hyperfiltration.<sup>13</sup> Agents such as dipyridamole and low dose warfarin may also ameliorate endothelial and platelet injury resulting from intra-glomerular hypertension.<sup>14,15</sup>

With a combination of measures directed at the underlying glomerular pathology, progression to end stage renal failure can be ameliorated.<sup>16,17</sup>

## 3 Management of Haematuria and Proteinuria

### 3.1 Introduction

As glomerulonephritis is the second leading cause of end stage renal failure in Singapore, its early detection and treatment is likely to reduce the incidence of end stage renal failure. Haematuria, generally microscopic, and proteinuria are hallmarks of glomerular disease and can be detected by urinalysis. In general, as dipstick analysis for haemoglobin and protein in asymptomatic populations has yielded very low incidence of significant renal disease, population screening is not recommended.<sup>18</sup> On the other hand, opportunistic screening, and screening of individuals at risk for kidney disease is recommended.<sup>2</sup> To date, there have been no prospective, randomised, controlled studies on urinalysis interpretation and renal outcome assessment. The following discussion deals with the interpretation and further diagnostic steps required in the presence of haematuria and/or proteinuria on urinalysis.

**C** Screening to detect microscopic haematuria and proteinuria in asymptomatic population is not recommended. However, screening using dipstick analysis should be done for individuals at risk for kidney disease.

**Grade C, Level IV**

### 3.2 Microscopic haematuria

**B** Patients with microscopic haematuria ( $\geq 3$  RBCs/hpf) should undergo evaluation to exclude renal/urinary tract disease.<sup>18-20</sup>

**Grade B, Level III**

**B** Urine phase contrast microscopy under standard conditions is useful in differentiating glomerular from non-glomerular sources of haematuria.<sup>21-23</sup>

**Grade B, Level III**

**B** Patients with microhaematuria should be evaluated for the presence of hypertension, proteinuria and renal impairment.<sup>21,24</sup>

**Grade B, Level III**

**B** Patients with isolated glomerular microhaematuria should remain on follow-up at 6-12 month intervals to monitor blood pressure, proteinuria and renal function.<sup>21,24</sup>

**Grade B, Level III**

**B** Patients with microhaematuria of non-glomerular origin should undergo evaluation to exclude urinary tract disease.<sup>25-28</sup>

**Grade B, Level III**

Microscopic haematuria is defined as the presence of  $\geq 3$  erythrocytes per high power field (RBCs/hpf) on urinary microscopy of unspun urine.<sup>20</sup> As concomitant urinary tract infections, trauma or menstruation in women can also cause haematuria, urine examination should be performed under appropriate conditions. Those with exercise-induced haematuria or myoglobinuria should also be re-evaluated with a repeat urinalysis at least 48 hours after the last strenuous exercise. The primary evaluation should begin with the history and physical examination and clues to the presence of glomerular disease can be elicited on history and physical examination (Table 5).<sup>21</sup>

**Table 5****C History, physical examination and laboratory evaluation for patients with haematuria<sup>21</sup>****History**

## Urinary Symptoms:

- Dysuria, frequency
- Previous gross haematuria
- Ureteric or renal colic
- Symptoms suggestive of bladder outlet obstruction such as poor stream and dribbling

## Past Medical History:

- Autoimmune diseases
- Pelvic oncological radiotherapy
- Sexually transmitted diseases pre-disposing to urethritis and urethral stricture
- Renal trauma
- Previous renal or extra-renal tuberculosis
- Lower or upper urinary tract infections

## Drug History:

- Warfarin
- Non-steroidal anti inflammatory drugs
- Previous cytotoxic/immunosuppressive therapy
- Exposure to chemicals (benzene, aromatic amines, leather dyes, chemicals in rubber or tyre manufacture)
- Cigarette smoking
- History of consuming herbal slimming remedies (example: those containing aristocholic acid)
- Drugs that may cause a false positive dipstick reaction such as certain antiseptic solutions

## Family History of:

- Primary renal disease
- Hypertension
- Adult polycystic kidney disease (APCKD)
- Deafness suggestive of Alport's syndrome
- Urolithiasis
- Microscopic haematuria

## Other:

- Recent upper respiratory tract infection (URTI) or tonsillitis suggesting post-infectious glomerulonephritis
- Ongoing URTI and/or gastroenteritis (GE), suggesting IgA nephropathy
- Constitutional symptoms such as myalgia, arthralgia and cutaneous rash, suggesting Henoch-Schonlein purpura or crescentic glomerulonephritis
- Diabetes mellitus and diabetic nephropathy
- Evidence of a bleeding diathesis

**Table 5 (con't)**

<b>Physical Examination for Patients with Haematuria</b> Blood pressure Skin examination for purpura, digital vasculitis Throat/tonsil inspection Cardiac auscultation for murmurs Signs of fluid overload Abdominal examination for enlarged, ballotable kidneys or other organomegaly Digital rectal examination of the prostate in males
<b>Initial Laboratory Investigations for Patients with Haematuria</b> Full blood count Renal function tests: serum urea, creatinine and electrolytes Urine culture <ul style="list-style-type: none"><li>• microbiologically proven urinary tract infections should first be treated and urinalysis re-checked before further tests are done</li></ul> Urine phase contrast microscopy Urine protein measurement (24-hour urinary protein or urine protein / creatinine ratio)

**Grade C, Level IV**

Urine phase contrast microscopy under standard conditions (urine osmolality  $\geq 700$  mOsm/kg + urine pH  $< 7.0$ ) is recommended to identify the source of haematuria.<sup>22-24</sup> Figure 1 (on page 40) provides a flow-chart on the management of haematuria. In subjects with predominantly dysmorphic urinary RBCs ( $\geq 80$  %), i.e., glomerular bleeding, the underlying pathology is likely to be reno-parenchymal.<sup>22</sup> Histopathologically, the commonest diagnoses in these patients are IgA nephropathy and Thin Basement Membrane Disease in one series.<sup>29</sup> Patients with glomerular bleeding should be evaluated for the presence of hypertension, proteinuria or renal insufficiency.<sup>25,30</sup> In the absence of these adverse risk factors, patients with glomerular haematuria can be followed up at 6 to 12 monthly intervals, as 9.5 % of those with persistent isolated microhaematuria, will develop concomitant proteinuria during the course of follow-up.<sup>25</sup> There is no evidence to support routine diagnostic renal biopsy solely on the basis of isolated microhaematuria and in the absence of other clinical findings such as hypertension and/or significant proteinuria as the overall incidence of significant glomerular disease is low.<sup>25</sup>

Those with predominantly isomorphic or mixed isomorphic and dysmorphic haematuria should be evaluated for urological disease as they have non-glomerular bleeding.<sup>21,26</sup> Complete urological evaluation is performed to exclude stones, infections and renal or bladder tumours and consists of upper urinary tract imaging, cystoscopic examination of the bladder and urine cytology.

**C** In the absence of contraindications, intravenous urography (IVU) is the recommended initial imaging of choice for investigation of non-glomerular bleeding and may be complemented by ultrasonography.<sup>31,32</sup>

**Grade C, Level IV**

With a negative result, additional investigations such as flexible cystourethroscopy and cystoscopy may be still required to definitively exclude a small bladder or lower urinary tract urothelial tumours. However, the cost effectiveness of complete urologic evaluation of every patient with non-glomerular asymptomatic microscopic haematuria is likely to be low as the incidence of malignancy is <3%.<sup>27</sup> In other series, it was found that the incidence of urological malignancies ranged from 0.09 to 0.1% in subjects with isolated asymptomatic microhaematuria.<sup>28</sup> Guidelines from the American Urological Association suggest that patients over 40 years of age, those with history of cigarette smoking or exposure to pelvic irradiation, phenacetin or other industrial agents should undergo full urological evaluation.<sup>21,22</sup> On the other hand, any male patient with a first episode of microscopic haematuria in the context of urinary symptoms should still be referred for urological assessment.

### 3.3 Proteinuria

**B** Patients with orthostatic proteinuria have a good renal prognosis and do not require follow-up.<sup>18,33</sup>

**Grade B, Level III**

**B** Patients with proteinuria should be evaluated for the presence of microhaematuria, hypertension and renal impairment.<sup>18,20,21,24</sup>

**Grade B, Level III**



**B** Patients with intermittent isolated proteinuria have a favourable renal prognosis but should be followed up until resolution of proteinuria.<sup>25,33,34</sup>

**Grade B, Level III**

**B** Patients with persistent isolated proteinuria should be followed-up indefinitely with monitoring of blood pressure and renal function since the risk of subsequently developing renal insufficiency is higher.<sup>34</sup>

**Grade B, Level III**

**B** Patients with persistent proteinuria  $\geq 1$  g/day should undergo renal biopsy as they are at risk for adverse renal histopathology and therefore worse renal outcome.<sup>35-38</sup>

**Grade B, Level III**

Patients who are dipstick positive for protein should undergo a repeat evaluation to confirm if the finding is orthostatic, intermittent or persistent. Orthostatic proteinuria is that associated with an upright posture and can be excluded by testing the first urine sample after an overnight rest. In orthostatic proteinuria, this overnight sample will be negative for protein while samples taken during the day will be positive. Orthostatic proteinuria is associated with a good prognosis and the patient does not require further follow-up.<sup>33</sup> Patients with urine dipstick positive for proteinuria on only *one of two* dipstick tests performed on early morning urine samples collected one week apart have intermittent proteinuria. It is commonly associated with stress or exercise.<sup>34</sup> Patients with persistent dipstick proteinuria should have blood pressure measurement and quantitative assessment of proteinuria and renal function (Table 6). In the presence of isolated intermittent proteinuria, patients should be followed up to confirm resolution of proteinuria.<sup>33</sup>

Patients with positive dipstick test for proteinuria on *two* separate early morning urine samples collected one week apart have persistent proteinuria. These patients need to undergo further diagnostic investigations as outlined in Table 6 since they have a significant risk for glomerular disease and may develop hypertension or renal insufficiency upon follow-up.<sup>25,35,36</sup> Follow-up of such patients should include blood pressure measurement and assessment of urine protein excretion and renal function at regular intervals. Various guidelines recommend the use of spot urine protein/creatinine or urine

albumin/creatinine ratios to quantitate proteinuria and formulas to assess GFR or renal function, as an alternative to 24-hour urine protein and creatinine clearances.<sup>39-42</sup> While these have not been validated in Asian populations, they are gaining increasing acceptance in clinical practice. Figure 2 (on page 41) provides an algorithmic approach to management of patients with proteinuria.

**Table 6** **GPP** History, physical examination and laboratory evaluation for patients with proteinuria<sup>43</sup>

<p><b>History:</b></p> <p>Urinary Symptoms:</p> <ul style="list-style-type: none"> <li>• dysuria, frequency to exclude urinary tract infection</li> </ul> <p>Past Medical History of:</p> <ul style="list-style-type: none"> <li>• childhood glomerulonephritis</li> <li>• pre-eclampsia in women</li> <li>• autoimmune conditions</li> <li>• diabetes</li> <li>• cardiac failure</li> </ul> <p>Drug History:</p> <ul style="list-style-type: none"> <li>• gold, penicillamine and captopril in relation to secondary membranous nephropathy</li> <li>• Non-steroidal anti-inflammatory drugs (NSAIDS) or penicillins in relation to (allergic) interstitial nephritis</li> </ul>
<p><b>Physical Examination:</b></p> <p>Blood pressure</p> <p>Signs of end organ damage due to hypertension</p> <p>Signs of renal failure</p> <p>Signs of diabetes or auto-immune disease</p> <p>Oedema</p>

**Table 6 (con't)**

<p><b>Initial Laboratory Investigations:</b></p> <p>Urinalysis for haematuria and glycosuria (if not already performed)</p> <p>Fresh mid-stream urine specimen for culture</p> <p>Serum urea, creatinine and fasting glucose (in the presence of glycosuria)</p> <p>Serum albumin</p> <p>24-hour urine collection for quantification (24-hour UTP)</p> <p><u>or</u></p> <p>Random or spot urinary protein and creatinine measurement to derive the urinary protein/creatinine ratio (PCR). PCR <math>\geq</math>200 mg/g indicates elevated urine protein content.</p> <p>Exclusion of monoclonal gammopathy in subjects &gt;45 years of age</p> <p>Ultrasound of the kidneys to evaluate structure and size</p> <p>Urine phase contrast microscopy</p> <p>24-hour urinary creatinine clearance (CCT)</p> <p><u>or</u></p> <p>Glomerular Filtration Rate (GFR) Calculation</p>
<p><b>Nephrological Evaluation:</b></p> <p>Renal biopsy if proteinuria <math>\geq</math> 1 g/day and/or rapidly worsening renal dysfunction in the absence of other causes (both renal and systemic causes)</p>

(Source: SIGN. Investigations of asymptomatic proteinuria in adults: A quick reference guide. Edinburg: SIGN 1997; 18:1-19).

**GPP**

Increasing proteinuria is associated with a higher risk for progression to renal insufficiency.<sup>35,36</sup> Data from Lim et al suggest that 24-hour UTP >1 g/day correlates with adverse renal histology and therefore, would represent a useful threshold for biopsy.<sup>36</sup>

### **3.4 Microhaematuria and proteinuria**

**B** Patients with microhaematuria and either proteinuria or hypertension or renal impairment should be referred to a nephrologist for further evaluation.<sup>37,38,44</sup>

**Grade B, Level III**

Combined microhaematuria and proteinuria is the commonest mode of presentation of glomerulonephritis, with primary glomerulonephritis accounting for 91% of cases in one series.<sup>37</sup> Among the different primary glomerulonephritides, the commonest histopathological type associated with microhaematuria and proteinuria is IgA nephropathy.<sup>29,37,38</sup> In one series, unfavourable prognostic indices included hypertension, severe proteinuria >2 g/day and histological changes such as crescents in the renal biopsy.<sup>37</sup> Prognostically, the severity of proteinuria had a more important correlation than microscopic haematuria with the histopathological type and grade and thus ultimate renal prognosis. In addition, there was no correlation between the severity of haematuria and severity of the histopathological changes. In contrast, proteinuria >1 g/day was significantly associated with the concomitant presence of granular casts ( $p < 0.001$ ) which in turn correlated with the presence of glomerular sclerosis ( $p = 0.005$ ).

As with isolated proteinuria, haematuria with proteinuria >1 g/day is a useful predictive index of glomerular sclerosis.<sup>36</sup> This also represents the threshold for diagnostic renal biopsy in the course of nephrological follow-up. In addition to its association with adverse histology, proteinuria *per se* is an important adverse risk factor for renal disease progression.<sup>35,36,45</sup> Thus patients with haematuria and proteinuria should be evaluated by a nephrologist to exclude significant glomerular disease. Those with these adverse factors should undergo renal biopsy to help prognosticate and guide therapy, so as to retard progression of renal failure.<sup>44</sup>

### 3.5 Gross haematuria

**B** All patients with gross haematuria should be evaluated for urological pathology with a combination of ultrasound, intravenous urography and flexible cystourethroscopy.<sup>46,47</sup>

**Grade B, Level III**

All patients with gross haematuria have to be evaluated for pathology of the urinary tract. Regardless of the age or sex, a complete work-up to exclude urinary tract sepsis, urolithiasis as well as urological malignancies should be undertaken. To this end, initial screening ultrasonography, followed up by intravenous urography and flexible cystourethroscopy, is recommended.<sup>31,32</sup> Ultrasonography is more sensitive than intravenous urography in detecting bladder

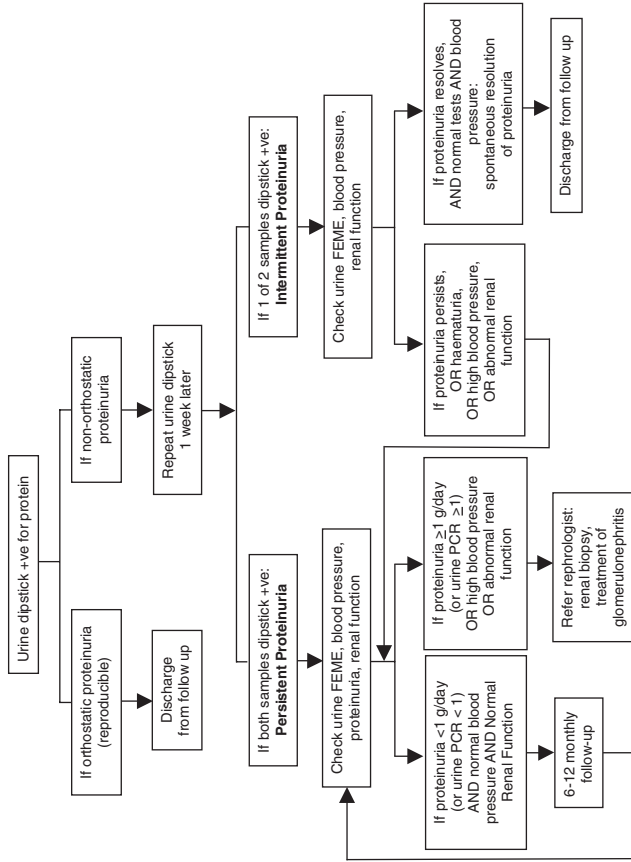
malignancies in subjects presenting with painless gross haematuria; in those with sonographic evidence of bladder tumours as well as those with a negative or inconclusive sonographic result, cystourethroscopy should then be performed.<sup>46,47</sup> Other imaging modalities such as CT scan or angiography may also be required to identify the etiology.

### **3.6 Summary**

An algorithmic approach to the management of haematuria and proteinuria is given in Figures 1 and 2 (pages 40 and 41). With appropriate screening and investigation, early diagnosis and management of glomerulonephritis can be initiated.



**Figure 2: Approach to Proteinuria**



## 4 General Measures in Management of Patients with Glomerulonephritis

### 4.1 Evaluation and followup

**A** Patients with glomerulonephritis should be evaluated to establish the type of glomerulonephritis and identify its severity.<sup>1,39,48,49</sup>

**Grade A, Level Ib**

Haematuria and proteinuria are hallmarks of glomerulonephritis. There are several types of glomerulonephritis, many of which can be treated with specific measures to ameliorate progression to end stage renal failure. Indeed, as evident from renal registry data, glomerulonephritis was the cause of end stage renal failure in 50% of prevalent patients on dialysis in Singapore in 1998. Unfortunately, only 13% of these patients had undergone renal biopsy to identify the underlying type of glomerulonephritis.<sup>1</sup> Specific measures to treat the underlying glomerulonephritis may have prevented progression of renal failure in many of these patients if the diagnosis on type and severity of glomerulonephritis had been made early.<sup>48,49</sup> Thus patients with glomerulonephritis should be evaluated to assess type and severity of glomerulonephritis.<sup>39</sup>

**A** Testing for level of renal function, degree of proteinuria, renal biopsy and other investigations should be performed as indicated.<sup>39</sup>

**Grade A, Level Ib**

**C** Patients should be followed up to assess progression of glomerulonephritis. Renal function, proteinuria and other markers should be monitored on follow up, as indicated by type of glomerulonephritis and severity of condition. The severity of kidney disease should be identified based on these markers.<sup>39</sup>

**Grade C, Level IV**

The level of renal function and degree of proteinuria often determine the severity of underlying glomerulonephritis and its rate of progression to end stage renal failure. These parameters should be assessed initially and followed up periodically to assess the efficacy of general and specific measures in halting progression of



glomerulonephritis and to assess the rate of progression of renal disease.<sup>39</sup>

**Renal function** is traditionally evaluated by measurement of serum creatinine (SCr) and urea. However, SCr varies with age, gender, diet and body mass and may not reflect renal function accurately. Other measures of renal function include measured 24-hour creatinine clearance with its own inaccuracies, and the more expensive but more accurate radionuclide assessments of glomerular filtration rate (GFR). Based on large correlation studies, several guidelines now advocate the routine use of estimated GFR to assess renal function, rather than measured creatinine clearance or GFR, especially in the range below 60 mL/min.<sup>39,50</sup> Estimated GFR is calculated with various formulae which take into account the serum creatinine, age, gender and body size of the individuals.<sup>39</sup> One such formula is the Cockcroft-Gault equation<sup>51</sup>:

$$\text{Creatinine Clearance (mL/minute)} = \frac{(140 - \text{Age}^a) \times \text{Weight}^b}{72 \times \text{Serum Creatinine}^c} \quad (\times 0.85 \text{ if female})$$

<sup>a</sup> Age in years, <sup>b</sup> Weight in Kg, <sup>c</sup> Serum Creatinine in mg/dL

Other formulae take into account the individual's race as race also impacts on correlation of estimated to measured GFR and normalizes these estimates to body surface area of 1.73 m<sup>2</sup>; unfortunately, there are no correlation studies of actual GFR with these formulae in large Asian populations.<sup>39</sup> Further studies are clearly required before any existing formulae can be routinely applied in clinical practice in the Asian population; however and until these studies are performed, a combination of SCr, estimated GFR, measured GFR or creatinine clearance should be used to assess renal function in patients with glomerulonephritis.

Though **proteinuria** can be detected using the standard urine dipstick, quantitation of proteinuria is necessary to identify patients with more severe proteinuria and thus at higher risk for progression to end stage renal failure and to monitor the efficacy of therapy. The traditional method of quantitating proteinuria is a timed (usually 24-hour) urine collection. However, timed collections are inconvenient and may be inaccurate due to collection errors and variations in protein excretion that occur with different levels of physical activity. Assessment of the Urine Protein to Creatinine Ratio or a Urine Albumin to Creatinine

Ratio from a spot urine specimen, preferably a first morning specimen, has been demonstrated to correlate well with timed urine collections.<sup>39</sup> Therefore, patients with glomerulonephritis should be monitored with regular assessments of Urine Protein to Creatinine Ratio (or Albumin to Creatinine Ratios). If urine protein and creatinine are both measured in mg/dL, the derived value is roughly equivalent to proteinuria in g/day; urine Protein to Creatinine Ratios greater than 0.2 are deemed abnormal and indicate the presence of significant proteinuria.<sup>39</sup>

**A** Specific therapy of glomerulonephritis should be instituted as indicated by type and severity of underlying condition.<sup>48,49</sup>

**Grade A, Level Ia**

Patients with glomerulonephritis and more severe proteinuria, renal dysfunction or hypertension are at high risk for progression to end stage renal failure and should undergo evaluation by a nephrologist. Renal biopsy should be performed in these patients to identify the type of glomerulonephritis and specific measures, as discussed in Chapters 7 to 9, instituted to halt progression of renal disease.<sup>48,49</sup> In addition, treatment of hypertension as described in Chapter 5, and general measures, as described below, should be initiated to retard the progression of renal disease.<sup>52,53</sup>

## **4.2 General measures to retard progression of renal disease**

### **4.2.1 Reduction of proteinuria**

**A** As the level of proteinuria predicts the rate of progression of renal disease, general measures should be instituted to reduce proteinuria in patients with glomerulonephritis.<sup>54</sup>

**Grade A, Level Ia**

Patients with glomerulonephritis have kidney damage which may progress to chronic renal failure and eventually end stage renal failure. Proteinuria is recognized as an independent risk factor for progression of renal disease. In a meta-analysis of patient level data, Jafar et al demonstrated that patients with non-diabetic renal disease with higher levels of proteinuria at baseline or followup had a greater risk of

progression (relative risk 5.56, 95% CI 3.87 to 7.98 for each 1.0 g/day higher protein excretion).<sup>54</sup>

**A** Angiotensin converting enzyme inhibitors should be used to reduce proteinuria and retard progression, in the absence of hypertension, in patients with glomerulonephritis.<sup>54</sup>

**Grade A, Level Ia**

Angiotensin II is believed to play a central role in mediating progression of kidney damage in patients with underlying renal disease. Following renal injury, it increases single-nephron GFR in the remaining nephrons through elevation of systemic blood pressure and vasoconstriction of the glomerular efferent arteriole. Glomerular hypertension in turn causes damage to the structural integrity of the glomerular capillary wall, leading to proteinuria in renal disease. In addition, Angiotensin II stimulates transforming growth factor beta and glomerular mesangial cell proliferation, thereby contributing to progression of kidney damage.

Many studies have demonstrated the efficacy of Angiotensin converting enzyme inhibitors (ACEI) to reduce proteinuria in patients with glomerular disease. In the meta-analysis by Jafar et al, the benefit of ACEI in reducing proteinuria was demonstrated; after controlling for level of proteinuria, the relative risk for renal failure with ACE inhibition versus control was 0.66 (95% CI 0.52 to 0.83).<sup>54</sup> Indeed, the level of proteinuria after treatment was begun was a better predictor of risk than the proteinuria at baseline, implying the need to control proteinuria *per se* in patients with glomerulonephritis.

**B** Angiotensin receptor blockers can be used as an alternative to Angiotensin converting enzyme inhibitors to reduce proteinuria and retard progression in patients with glomerulonephritis.<sup>11,55</sup>

**Grade B, Level IIb**

**A** Angiotensin converting enzyme inhibitors can be combined with Angiotensin receptor blockers to reduce proteinuria and retard progression in patients with glomerulonephritis.<sup>56</sup>

**Grade A, Level Ib**

**B** Proteinuria should be reduced to  $<0.5$  g/day with therapy in patients with glomerulonephritis.<sup>57</sup>

**Grade B, Level III**

A few studies likewise suggest benefit with Angiotensin Receptor Blockers (ARB) in reducing proteinuria and ameliorating renal progression in glomerulonephritis.<sup>11,55</sup> Combined therapy with ACEI and ARBs may likewise be beneficial in reducing proteinuria and retarding progression of renal disease.<sup>56</sup> Target level of proteinuria with therapy has been recommended to be less than 0.5 g/day so as to accrue maximal benefit in renoprotection.<sup>57</sup>

#### **4.2.2 Dietary protein restriction**

**GPP** Patients with glomerulonephritis and renal failure (GFR  $<25$  mL/min), who are not on maintenance dialysis and have no evidence of malnutrition, should be considered for a low-protein diet providing 0.8 g protein/kg body weight/day. At least 50% of dietary protein should be of high biologic value.

**GPP**

Dietary protein restriction has also been suggested to retard progression of renal disease. The Modification of Diet in Renal Disease (MDRD) Study which had been designed to address this issue was inconclusive on the benefit of a low protein diet in retarding progression of renal disease.<sup>58</sup> The secondary analysis of this study appears to suggest some benefit in the group randomized to a low protein diet (0.58 g/kg body weight/day),<sup>59</sup> although the magnitude of benefit was suggested to be low in a meta-analysis.<sup>60</sup> On the other hand, protein energy malnutrition can develop as a result of protein restriction and lead to adverse outcomes.

Thus, recommendations for dietary protein restriction (to 0.8 g/kg body weight/day) attempt to strike a balance between the goal to slow progression versus that to preserve protein nutritional status. Patients with an estimated GFR of  $<25$  mL/min (approximate SCr of 265  $\mu$ mol/L in a 50-year old male of weight 60 kg) may benefit from such protein restriction. Protein restriction will also reduce the generation of nitrogenous wastes and inorganic ions, thereby ameliorating many of the clinical and metabolic disturbances characteristic of renal failure.

**C** A diet providing 35 kcal/kg body weight/day is recommended in patients with renal failure (GFR <25 mL/min) to maintain neutral nitrogen balance, to promote higher serum albumin concentrations and more normal anthropometric parameters.<sup>61</sup>

**Grade C, Level IV**

Dietary energy intake of 35 kcal/kg/day is recommended as nitrogen utilization is more efficient at higher energy intakes.<sup>61</sup>

### **4.3 Summary**

Renal function and proteinuria should be evaluated in patients with glomerulonephritis to assess the type and severity of renal disease. Apart from measures to control blood pressure, general measures to reduce proteinuria should also be instituted. ACEI and /or ARBs have been shown to be beneficial in this regard. Dietary protein restriction may also retard progression of renal disease in selected patients.

## 5 Management of Hypertension in Patients with Glomerulonephritis

### 5.1 Introduction

Many types of glomerulonephritis are associated with a progressive course culminating in end stage renal failure.<sup>62</sup> The rate of progression varies widely among patients and between diseases. The level of renal function at the time of diagnosis, magnitude of proteinuria, the severity of hypertension and its control, and the extent of tubular atrophy and interstitial fibrosis on histology are major predictors of eventual onset of end stage renal failure. This chapter addresses measures to control blood pressure in patients with underlying glomerulonephritis.

### 5.2 Goals of blood pressure management

**A** Hypertension, defined as blood pressure  $\geq 140/90$  mm Hg, should be treated in patients with glomerulonephritis in order to retard the rate of deterioration of renal function.<sup>53</sup>

**Grade A, Level Ia**

The prevalence of hypertension in patients with chronic glomerulonephritis is reported as 15 to 80%.<sup>63</sup> The Multiple Risk Factor Intervention Trial (MRFIT) demonstrated increasing risk of developing end stage renal failure with higher levels of blood pressure.<sup>64</sup> As compared with men with an optimal blood pressure level (systolic pressure  $< 120$  mm Hg and diastolic pressure  $< 80$  mm Hg), the relative risk of end stage renal failure for those with systolic pressure  $\geq 210$  mm Hg or diastolic pressure  $\geq 120$  mm Hg was 22.1 ( $P < 0.001$ ).<sup>64</sup> On the other hand, control of blood pressure has been demonstrated to retard the progression of renal failure in virtually all forms of renal disease.<sup>65-68</sup> In a meta-analysis of 1,860 non-diabetic patients, of whom 33% had glomerulonephritis, decreasing levels of systolic blood pressure with therapy were associated with decreased risks for progression of renal dysfunction.<sup>53</sup>

**C** Hypertension should be treated in patients with glomerulonephritis so as to reduce the risk for cardiovascular disease.<sup>69</sup>

**Grade C, Level IV**

In addition to being exposed to a higher risk for end stage renal failure, patients with glomerulonephritis have an increased risk for cardiovascular disease.<sup>70</sup> There is an increased prevalence of both traditional and non-traditional risk factors for cardiovascular disease in patients with early chronic kidney disease. Among the traditional risk factors, the prevalence of both hypertension and hyperlipidaemia is increased in patients with glomerulonephritis. Indeed, each 1-mm Hg increase in follow-up systolic blood pressure has been shown to be associated with a 1.35-times greater risk of hospitalization for cardiovascular or cerebrovascular disease.<sup>71</sup> Thus the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) recommends that the choice of antihypertensive therapy in patients with glomerulonephritis should also be dictated by the need to ameliorate the risk of cardiovascular disease.<sup>69</sup>

### 5.3 Target blood pressure

**A** A target blood pressure less than 130/80 mm Hg (Mean arterial pressure <98 mm Hg) is recommended for patients with glomerulonephritis and proteinuria  $\leq$ 1 g/day.<sup>72</sup>

**Grade A, Level Ia**

**A** A target blood pressure less than 125/75 mm Hg (Mean arterial pressure <92 mm Hg) is recommended for patients with glomerulonephritis and proteinuria >1 g/day.<sup>54</sup>

**Grade A, Level Ia**

The Modification of Diet in Renal Disease (MDRD) study, a randomised controlled trial, was designed to examine the impact of different target blood pressure on renal disease progression in non-diabetic patients with kidney disease.<sup>72,73</sup> In the overall study, there were no differences in the decline in glomerular filtration rate (GFR) in the usual blood pressure (Mean arterial pressure, (MAP), 107 mm Hg) versus low blood pressure (MAP 92 mm Hg) groups. However, in the extension phase of the trial, GFR declined faster in patients with higher achieved blood pressure and the decline was greater in persons with higher baseline proteinuria; hazard ratio for renal failure in the low blood pressure group was 0.68, 95% CI 0.57 to 0.82.<sup>72</sup> In a meta-analysis, Jafar et al showed that non diabetic patients with proteinuria >1 g/day who attained a systolic blood pressure between 110 and 129 mm Hg had the lowest risk of progression of renal disease.<sup>54</sup> Thus,

these studies suggested that more aggressive blood pressure control should be instituted in patients with higher degrees of proteinuria. Current guidelines by World Health Organisation – International Society of Hypertension likewise recommend lower targets for blood pressure control in patients with proteinuria >1 g/day.<sup>74</sup>

**A** More than one anti-hypertensive drug may be required to achieve target blood pressure in patients with glomerulonephritis.<sup>72</sup>

**Grade A, Level Ib**

Multiple anti-hypertensive agents are generally needed to achieve target blood pressures in patients with renal disease. In the MDRD study, 2.1 anti-hypertensive drugs were needed to achieve a blood pressure target of 125/75 mm Hg in patients with renal disease while 1.5 drugs were required to reach the target of 140/90 mm Hg.<sup>72</sup>

## 5.4 Treatment of hypertension

**A** Any anti-hypertensive agent may be used to control blood pressure in patients with glomerulonephritis.

**Grade A, Level Ia**

**A** Angiotensin converting enzyme inhibitors are recommended as preferred treatment of hypertension in patients with glomerulonephritis as they confer greater renoprotection.

**Grade A, Level Ia**

Any antihypertensive agent may be used to control blood pressure in patients with renal disease.<sup>52,69,75</sup> In a meta-analysis and systematic review that examined the impact of inhibitors of the renin-angiotensin system (RAS) on renal outcomes, Casas et al demonstrated no significant advantage to the former in comparison to other anti-hypertensives (relative risk for doubling of creatinine, 0.71 (95% CI 0.49-1.04); relative risk for end stage renal failure, 0.87, (95% CI 0.75-0.99). However, as RAS inhibitors were superior to placebo, they suggested that any anti-hypertensive therapy could be beneficial in ameliorating renal progression. Nevertheless, other studies suggest additional benefits with Angiotensin converting enzyme inhibitors (ACEI) in patients with renal disease. Angiotensin converting enzyme inhibitors retard progression of renal disease by promoting preferential glomerular efferent arteriolar vasodilatation and reducing intraglomerular pressures, thereby ameliorating the disordered



autoregulation in chronic kidney disease.<sup>76</sup> In clinical trials, the Ramipril Efficacy in Nephropathy (REIN) study compared Ramipril, an ACEI, to placebo, in non-diabetic patients with chronic kidney disease. Both groups also received conventional antihypertensive therapy to achieve similar blood pressure control. Patients with proteinuria >3 g/day who were assigned to ramipril experienced a significantly lower rate of decline in GFR than the placebo group.<sup>77</sup> Jafar et al in their meta-analysis involving 1,860 patients with non diabetic proteinuric chronic kidney disease, demonstrated that regimens that included ACEI were more effective in slowing progression of kidney disease.<sup>53</sup> The relative risk for doubling of serum creatinine or progression to end stage renal failure with ACEI therapy was 0.67 (95% CI 0.53 to 0.84).<sup>53</sup>

**B** Angiotensin receptor blockers can be used as an alternative to Angiotensin converting enzyme inhibitors to treat hypertension in patients with glomerulonephritis.<sup>11,78</sup>

**Grade B, Level IIa**

Angiotensin receptor blockers (ARB) have also been demonstrated to prevent progression of renal injury in some, but not all experimental models of renal damage.<sup>79</sup> Though several randomized controlled trials have demonstrated the efficacy of ARBs in reducing progression in diabetic renal disease,<sup>80,81</sup> there are no such trials on the renoprotective effects of ARBs in nondiabetic renal disease. Some studies have nevertheless demonstrated their benefits in reducing proteinuria and ameliorating progression in patients with IgA nephropathy.<sup>11,78</sup>

Due to their similarity of action and their favourable effects in non-diabetic and diabetic renal disease, the JNC VII and National Kidney Foundation Kidney Disease Outcomes Initiative (NKF/DOQI) recommends these drugs as preferred therapy of hypertension in this group.<sup>69,52</sup> Therapy with ARB is thus recommended as an alternative to ACE inhibitor and is especially useful in patients who are intolerant of ACEI due to hyperkalaemia, cough, angioedema or hypersensitivity.

**B** Angiotensin receptor blockers may be used in combination with Angiotensin converting enzyme inhibitors to treat hypertension in patients with glomerulonephritis.<sup>56</sup>

**Grade B, Level IIa**

Since ACEI and ARBs are independently effective in treating hypertension and ameliorating progression of renal disease, combined therapy with these classes of agents has been considered a therapeutic option. In a randomized controlled trial in 263 patients with non-diabetic renal disease, only 11% of patients receiving the combination (versus over 20% of patients on monotherapy) reached the combined end point of end stage renal failure or doubling of serum creatinine.<sup>56</sup> Though some studies suggest increased mortality with combined use of both classes of agents, in a meta-analysis, Dimopoulos et al found no increase in mortality when ACEI and ARBs were combined in patients with heart failure even with concomitant use of beta blockers.<sup>82</sup>

**A** Diuretics are preferred 2<sup>nd</sup> line antihypertensive agents in patients with glomerulonephritis as they reduce the risk for cardiovascular disease.<sup>83</sup>

**Grade A, Level 1b**

Diuretics have been recommended by JNC VII and NKF/DOQI as preferred agents for second line therapy of hypertension in patients with renal disease for several reasons.<sup>52,69</sup> On the one hand, more than one antihypertensive drug may be required to achieve target blood pressure in patients with renal disease. Diuretics reduce fluid overload, an important cause of hypertension in patients with glomerular disease, and may also help reduce hyperkalaemia in patients with renal insufficiency or those receiving ACEI or ARB therapy. Moreover, cardiovascular disease is a common cause of death in patients with renal disease. In a large randomized trial comparing the impact of initial antihypertensive therapy on cardiovascular disease, thiazide type diuretics were superior to both amlodipine or lisinopril in preventing one or more major forms of cardiovascular disease.<sup>84</sup> A subanalysis of 2,492 with chronic kidney disease and GFR 30 to 59 mL/min/1.73 m<sup>2</sup> from this study revealed similar benefits with diuretics with respect to cardiovascular disease, in comparison to the other agents.<sup>52</sup> A post hoc analysis of cardiovascular outcomes in hypertensive subjects randomised to three different anti-hypertensive regimens documented a lower incidence of heart failure in diuretic-treated patients with reduced GFR, in comparison to lisinopril or amlodipine.<sup>83</sup> Diuretics should thus be used as second line anti-hypertensive therapy in patients with glomerulonephritis. While for patients with GFR  $\geq 30$  mL/min/1.73 m<sup>2</sup> thiazide diuretics are

recommended, loop diuretics are recommended for those with GFR <30 mL/min/1.73 m<sup>2</sup>.

**B** Beta blockers and calcium channel blockers can be used alternatively to control blood pressure in patients with glomerulonephritis.<sup>85,86</sup>

**Grade B, Level IIa**

If blood pressure is uncontrolled with the use of ACEI/ARBs and diuretics, a third agent is often required to achieve target blood pressure. Other anti-hypertensive medications have been demonstrated to be effective in controlling blood pressure in patients with renal disease. In a study of 158 patients with non-diabetic renal disease receiving an ACEI or a calcium antagonist or both, those receiving the combination achieved better blood pressure control and had slower progression in renal disease than the other two groups.<sup>85</sup> The African American Study of Kidney Disease and Hypertension Study demonstrated that in comparison to amlodipine, both ramipril and metoprolol reduced the risk of renal failure and renal failure and death combined.<sup>86</sup> As proteinuria was exacerbated in patients receiving amlodipine in proteinuric patients in this study, the NKF/DOQI recommends that dihydropyridine calcium channel blockers not be used alone in patients with proteinuric renal disease, but be preferentially used in combination with an ACEI or ARB.<sup>52</sup>

**C** Lifestyle modifications should be begun simultaneously as part of a comprehensive strategy to lower blood pressure and cardiovascular risk.<sup>52</sup>

**Grade C, Level IV**

Dietary and other lifestyle modifications have been demonstrated to reduce blood pressure and should thus be a part of a comprehensive strategy to retard progression of renal disease and lower cardiovascular risk in chronic kidney disease.<sup>52</sup> Key lifestyle modifications include:

- Maintaining ideal body weight
- Aerobic physical activity
- Eating abundant fruits and vegetables and low fat dairy products
- Reducing intake of saturated and total fats
- Limiting sodium intake to less than 100 mmol/day
- Maintaining adequate intake of dietary calcium and magnesium

- Limiting alcohol intake
- Smoking cessation.

## 5.5 Monitoring in patients with hypertension and glomerular disease

**C** Patients with hypertension and glomerulonephritis should be monitored regularly for blood pressure, renal function and level of proteinuria.<sup>52,69</sup>

**Grade C, Level IV**

General principles in management of hypertension are applicable in patients with glomerulonephritis.<sup>52,69</sup> Patients should be educated on the benefits of anti-hypertensive therapy, the potential side effects and the need for compliance to therapy. Long acting, once daily medication should be used preferentially to encourage compliance. Upon initiation of therapy, patients should be monitored regularly for blood pressure, renal function and proteinuria to ensure optimal control and to monitor progression of renal disease. On follow-up, doses of antihypertensive medications should be optimized so as to achieve target blood pressure. In the absence of side effects, the dose of each anti-hypertensive agent should be maximized before adding another agent. As much as possible, doses should not be escalated more often than once in 4 weeks.

**C** Patients receiving an Angiotensin converting enzyme inhibitor or Angiotensin receptor blocker should be monitored for decrease in renal function and hyperkalaemia.<sup>52</sup>

**Grade C, Level IV**

**C** Angiotensin converting enzyme inhibitors or Angiotensin receptor blockers can be continued in patients with decrease in renal function of <30% over 4 months or serum potassium  $\leq 5.5$  mmol/L.<sup>52</sup>

**Grade C, Level IV**

**C** Angiotensin converting enzyme inhibitors or Angiotensin receptor blockers should not be used in pregnant patients or in those with drug-induced angioedema or allergy. They should also be used with caution in patients with renal artery stenosis or severe hyperkalaemia.<sup>52</sup>

**Grade C, Level IV**

Use of ACEI or ARBs is associated with a decline in renal function and hyperkalaemia due to the intrinsic effects of these drugs in reducing glomerular hyperfiltration. If these effects supervene, the drugs need not be discontinued and only careful monitoring is required. If, over a period of <4 months, decline in renal function of  $\geq 30\%$  or hyperkalaemia (Serum Potassium  $>5.5$  mmol/L) are diagnosed, ACEI or ARBs should be discontinued and renal artery stenosis should be suspected and investigated for. Furthermore, initiation of ACEI or ARBs should be postponed in patients with hyperkalaemia until it is corrected. If hyperkalaemia occurs, diuretics may be added to promote kaliuresis (and control blood pressure); if severe hyperkalaemia persists, doses of ACEI and/or ARBs should be reduced. Pregnancy is a contraindication for the use of these drugs as they may impair placental blood flow and cause fetal kidney and lung abnormalities.<sup>52</sup>

## **5.6 Summary**

Lowering of blood pressure is associated with a reduced risk for progression of glomerular disease. ACEI and ARBs have been demonstrated to control blood pressure; together with diuretics and other antihypertensive agents, they can be used to retard progression of renal disease and reduce cardiovascular disease in patients with glomerulonephritis.

## 6 Management of Renal Dysfunction in Patients with Glomerulonephritis

### 6.1 Evaluation and followup

**B** Patients with glomerulonephritis and estimated glomerular filtration rate  $<60$  mL/min/1.73 m<sup>2</sup> should be assessed for complications of renal failure, including anaemia and bone disease.<sup>39,87</sup>

**Grade B, Level III**

**C** Patients with glomerulonephritis should be monitored for complications of the underlying condition, risk factors for cardiovascular disease and side effects of therapy.<sup>52,70</sup>

**Grade C, Level IV**

Patients with glomerulonephritis have chronic kidney disease as manifested by haematuria and/or proteinuria; furthermore, they may have different levels of renal dysfunction. The level of renal dysfunction and degree of proteinuria often determine the severity of underlying glomerulonephritis and the rate of progression to end stage renal failure. To optimally manage patients with glomerulonephritis, the severity of kidney disease should be assessed based on the level of renal function and other markers of renal damage. The National Kidney Foundation, USA has recommended staging chronic kidney disease, based on estimated glomerular filtration rate (eGFR) (Table 7).<sup>39</sup> GFR can be estimated using various formulae, for example the Cockcroft-Gault formula, as described in Chapter 4.

**Table 7 Stages of chronic kidney disease**

Description	Stage
eGFR $> 90$ mL/min/1.73 m <sup>2</sup> with pathologic abnormalities or other markers of kidney damage	1
eGFR 60 - 89 mL/min/1.73 m <sup>2</sup>	2
eGFR 30 - 59 mL/min/1.73 m <sup>2</sup>	3
eGFR 15 - 29 mL/min/1.73 m <sup>2</sup>	4
End Stage Renal Failure, eGFR $< 15$ mL/min/1.73 m <sup>2</sup>	5

Adapted from National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification.<sup>39</sup>

As increasing severity of chronic kidney disease is associated with an increasing incidence of complications of anaemia, bone disease, malnutrition, neuropathy and impairment in indices of functioning and well-being, staging of the severity of chronic kidney disease in patients with glomerulonephritis will facilitate early detection of these associated complications.<sup>39</sup> In general, patients with chronic kidney disease have a higher incidence of complications of renal failure when their eGFR is less than 60 mL/min/1.73 m<sup>2</sup>. As such, patients with glomerulonephritis and renal dysfunction and eGFR <60 mL/min/1.73 m<sup>2</sup> should be evaluated and treated for the complications of renal failure, as described below. Due to the high risk for cardiovascular disease in those with chronic kidney disease, patients with glomerulonephritis should also be assessed for these risk factors as well as side effects of therapy.<sup>52,70</sup>

**B** Patients with renal dysfunction should be initiated on renal replacement therapy when indicated by symptoms of renal failure and/or biochemical investigations.<sup>88</sup>

**Grade B, Level III**

In due course, many patients with glomerulonephritis do progress to end stage renal failure. Timely initiation of renal replacement therapy reduces morbidity and mortality from renal failure.<sup>88</sup> While, in general, symptoms of uraemia increase with severity of renal dysfunction, the correlation is not absolute. Nevertheless, those with eGFR < 6 mL/min/1.73 m<sup>2</sup> would develop symptoms of uraemia and should be considered for initiation of dialysis. Those with symptoms of uraemia at higher levels of GFR should also be considered for early initiation of dialysis. Thus the decision to initiate dialysis is based on the presence of symptoms of uraemia or fluid overload, presence of hyperkalaemia or acidosis as well as the level of eGFR.

## 6.2 Complications of chronic kidney disease

### 6.2.1 Anaemia

**B** Patients with glomerulonephritis and estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup> should be evaluated for the presence of anaemia by measuring haemoglobin periodically.<sup>89</sup>

**Grade B, Level III**

Anaemia, as measured by low haemoglobin levels, develops in patients with more severe chronic kidney disease and is inversely correlated with GFR.<sup>39,89-91</sup> In general, anaemia is more severe when eGFR is <60 mL/min/1.73 m<sup>2</sup> and is associated with higher rates of hospitalization, cardiovascular disease, cognitive impairment and other adverse patient outcomes including mortality.<sup>39,89-91</sup> Evaluation of anaemia should generally be initiated when haemoglobin levels fall below 80% of that for healthy normals.

**B** Further evaluation of anaemia should be initiated in patients with glomerulonephritis and renal dysfunction when:

- Hemoglobin is <11 g/dL in pre-menopausal females and prepubertal patients
- Hemoglobin <12 g/dL in adult males and post-menopausal females.<sup>89</sup>

**Grade B, Level III**

**B** Evaluation of anaemia should include

- Red cell indices
- Reticulocyte count
- Iron parameters (serum iron, Total Iron Binding Capacity, percent transferrin saturation and serum ferritin)
- Tests for occult blood in stools.<sup>89</sup>

**Grade B, Level III**

In addition to a search for iron deficiency and blood loss, in the Asian context, Thalassemia trait should be considered if the investigations suggest microcytic indices. If no cause for anaemia other than renal dysfunction is detected, anaemia is most likely due to erythropoietin deficiency from chronic kidney disease.<sup>89</sup>

**A** Patients with anaemia due to renal dysfunction should be treated with supplemental iron to maintain percent transferrin saturation >20% and serum ferritin level >100 ng/mL.<sup>92</sup>

**Grade A, Level Ib**

**A** Anaemia due to renal dysfunction should be treated with erythropoietin therapy.<sup>93</sup>

**Grade A, Level Ia**



The anaemia of chronic kidney disease should be treated initially with iron supplementation, after which erythropoietin therapy should be administered.<sup>89,91-95</sup> In a Cochrane database review of 15 trials, erythropoietin administration in pre-dialysis patients was associated with correction of anaemia and improvements in work capacity and quality of life, without adverse consequences on progression of renal disease.<sup>11</sup> In pre-dialysis patients, erythropoietin is administered more conveniently via the subcutaneous approach.<sup>96</sup>

**A** Target for haemoglobin for patients with renal dysfunction should be 12 g/dL. Target range for haemoglobin are for erythropoietin therapy and are not an indication for blood transfusion.<sup>97</sup>

**Grade A, Level Ia**

In a meta-analysis of trials examining target haemoglobin levels with erythropoietin therapy in pre-dialysis and dialysis patients, Strippoli et al demonstrated lower all cause mortality with haemoglobin targets less than 12 g/dL in patients with chronic kidney disease and cardiovascular disease.<sup>97</sup> These haemoglobin targets can therefore be applied in patients with glomerulonephritis without cardiovascular disease.

**B** Adverse effects of erythropoietin therapy including hypertension should be monitored in patients with glomerulonephritis and renal dysfunction.<sup>89</sup>

**Grade B, Level III**

Erythropoietin therapy has been associated with an increased incidence of hypertension in approximately 23% of treated patients.<sup>89</sup> Hypertension if exacerbated should be treated with increase in anti-hypertensive therapy. However, early concerns over a higher incidence of seizures, increased clotting tendency or hyperkalaemia in relation to erythropoietin use have not been substantiated with its long term use. On the other hand, recent reports of pure red cell aplasia (PRCA), due to the development of anti-erythropoietin antibodies following the use of some formulations of erythropoietin, suggest the need for continued vigilance and followup for complications of erythropoietin use.<sup>98</sup>

## 6.2.2 Bone disease

**B** Serum levels of calcium, phosphorus and intact plasma parathyroid hormone levels should be measured in patients with glomerulonephritis and eGFR <60 mL/min/1.73 m<sup>2</sup>.<sup>87,99</sup>

**Grade B, Level III**

**B** Patients with glomerulonephritis and chronic renal dysfunction should receive therapy to control serum phosphate, calcium and parathyroid hormone levels, so as to reduce onset of bone disease due to secondary hyperparathyroidism.<sup>100-102</sup>

**Grade B, Level III**

Chronic renal dysfunction is associated with a variety of disorders of calcium and phosphorus metabolism. Reduced activity of 1 alpha hydroxylase activity in the diseased kidney results in diminished 1, 25-dihydroxyvitamin D<sub>3</sub> levels, leading in turn to reduced intestinal calcium absorption and hypocalcaemia. Phosphorous retention in renal dysfunction also contributes to hypocalcaemia. Finally, inadequate Vitamin D intake by patients with chronic kidney disease may also contribute to hypocalcaemia in these patients.<sup>103</sup>

Hypocalcaemia in turn stimulates increased Parathyroid Hormone (PTH) secretion, which then enhances calcium reabsorption from the kidney and mobilizes calcium from bone. Skeletal resistance to the calcaemic action of PTH may further contribute to a rise in PTH levels in chronic kidney disease patients. Indeed, more severe chronic kidney disease is associated with more severe disturbances in calcium and phosphate metabolism.<sup>87,103</sup>

Thus patients with glomerulonephritis and chronic renal dysfunction may have bone pains, increased incidence of bone fractures and deformity, myopathy and muscle pain, and tendon rupture. Moreover, excess phosphate levels leads to a high calcium-phosphate product and soft tissue calcification which can cause lung, cardiac or other vascular calcification, leading to considerable morbidity and mortality in chronic kidney disease patients.<sup>103</sup>

**C** Serum calcium, phosphate and parathyroid hormone levels should be monitored at 3-12 monthly intervals in patients with glomerulonephritis and chronic renal dysfunction.<sup>87</sup>

**Grade C, Level IV**

Severity of abnormalities of calcium, phosphate and PTH appear to correlate with worsening GFR.<sup>87,99</sup> The National Kidney Foundation, USA, recommends monitoring of these parameters 3 to 12 monthly, depending on the severity of the renal dysfunction.<sup>87</sup> These parameters should be monitored more frequently in patients with more severe chronic kidney disease so as to minimize the development of parathyroid hyperplasia and its associated bone disease.<sup>87</sup>

**C** Phosphate levels should be maintained between 2.7 and 4.6 mg/dL (0.87 and 1.49 mmol/L) in patients with chronic renal dysfunction.<sup>87</sup>

**Grade C, Level IV**

**B** Dietary phosphate should be restricted to 800-1000 mg/day (adjusted for dietary protein needs) when serum phosphate levels are elevated above 4.6 mg/dL or when parathyroid hormone levels are elevated.<sup>100</sup>

**Grade B, Level III**

**C** If serum phosphate level cannot be controlled despite dietary phosphate restriction, phosphate-binders should be prescribed.<sup>87</sup>

**Grade C, Level IV**

**C** Calcium-based phosphate binders can be used to lower serum phosphate levels.<sup>87</sup>

**Grade C, Level IV**

**C** The total dose of elemental calcium provided by calcium-based phosphate binders should not exceed 1,500 mg/day and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg/day.<sup>87</sup>

**Grade C, Level IV**

Given that phosphate retention is a key factor in the development of renal bone disease, its restriction can ameliorate the severity of parathyroid hyperplasia.<sup>100</sup> Though ideal targets for serum phosphate in pre-dialysis patients are not established, various expert committees have recommended target phosphate levels based on studies in dialysis populations; it would be reasonable to adopt these targets for patients with chronic renal dysfunction.<sup>87</sup> Phosphate binders such as calcium carbonate or calcium acetate should be administered to those

patients in whom dietary phosphate restriction fails to normalize the phosphate level.<sup>87,101</sup>

**C** Serum calcium levels should be maintained within the range of 8.4 to 9.5 mg/dL (2.10 to 2.37 mmol/L), so as to avoid hypercalcaemia.<sup>87</sup>

**Grade C, Level IV**

**C** The calcium-phosphate product should be calculated periodically, from values of serum calcium and phosphate, in patients with glomerulonephritis and chronic renal dysfunction.<sup>87</sup>

**Grade C, Level IV**

**C** The target calculated calcium-phosphate product is 55 (in mg<sup>2</sup>/dL<sup>2</sup>) in patients with chronic renal dysfunction. Doses of calcium and Vitamin D analogs should be reduced if the calcium-phosphate product exceeds the target range.<sup>87</sup>

**Grade C, Level IV**

Hypercalcaemia, together with hyperphosphataemia, leads to an elevated calcium phosphate product which has been held responsible for metastatic calcification in patients with end stage renal failure.<sup>20</sup> Calcium-containing phosphate binders may, when given to patients with the hyperphosphataemia of chronic renal dysfunction, lead to an elevated calcium-phosphate product, thereby leading to metastatic calcification with its associated morbidities.<sup>87,102</sup> Thus, calcium intake including that from calcium-based phosphate binders and dietary intake should be restricted so as to maintain serum calcium within the normal range.

**GPP** Target range of Intact parathyroid hormone level in patients with chronic renal dysfunction should be as listed below:<sup>87</sup>

<u>GFR (mL/min/1.73 m<sup>2</sup>)</u>	<u>Target intact PTH (pmol/L)</u>
30-59	3.85-7.70
15-29	7.70-12.10

**GPP**

**A** Patients with chronic renal dysfunction and elevated parathyroid hormone levels above the target ranges should be treated with active vitamin D sterols.<sup>104,105</sup>

**Grade A, Level Ib**

**C** Treatment with active vitamin D sterols for elevated parathyroid hormone levels in patients with chronic renal dysfunction should be undertaken only in patients with levels of corrected serum total calcium < 9.5 mg/dL and serum phosphate < 4.6 mg/dL.<sup>87</sup>

**Grade C, Level IV**

As suggested earlier, hyperphosphataemia and hypocalcaemia, as found in chronic kidney disease, stimulate PTH secretion from the parathyroid glands, which in turn leads to renal osteodystrophy and its associated morbidity. If PTH levels are elevated despite phosphate control and regulation of calcium, Vitamin D sterols should be given so as to achieve target PTH levels.<sup>87,104,105</sup> However, as Vitamin D sterols can predispose to hypercalcaemia, these drugs should be discontinued in the presence of either hypercalcaemia, hyperphosphataemia or an elevated calcium-phosphate product, so as to avoid metastatic calcification. Thus careful monitoring of calcium, phosphate and PTH is necessary to minimize the complications of hyperparathyroidism. Vitamin D sterols should be discontinued in patients with PTH levels below the target ranges listed above and in patients with elevated calcium, phosphate or a calcium-phosphate product.<sup>87</sup>

### **6.2.3 Dyslipidaemia**

**C** Patients with glomerulonephritis and renal dysfunction should be evaluated for dyslipidaemia. They should have a complete lipid profile including triglycerides, total, low-density lipoprotein and high-density lipoprotein cholesterol.<sup>106,107</sup>

**Grade C, Level IV**

Patients with glomerulonephritis and renal dysfunction are at high risk for dyslipidaemia and atherosclerotic vascular disease.<sup>108</sup> It has been estimated that patients with chronic kidney disease have a 10-year risk of coronary heart disease events greater than or equal to 20%, placing them in the highest risk category according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines.<sup>106,107</sup>

**A** Patients with elevated cholesterol levels should be treated so as to reduce their risk for cardiovascular disease as for patients in the general population. These patients should be treated with cholesterol-reducing diet and statins.<sup>106-109</sup>

**Grade A, Level Ia**

Treatment with diet and statins in patients with elevated cholesterol levels has been demonstrated to reduce risk for cardiovascular events in the general population.<sup>109</sup> Thus, the National Kidney Foundation K/DOQI guidelines for managing dyslipidaemia suggest that chronic kidney disease patients with LDL greater than or equal to 100 mg/dL (2.59 mmol/L) should be treated with diet and a statin.<sup>107</sup>

**A** Patients with elevated cholesterol levels should be treated with statins so as to reduce their risk for progression of renal disease.<sup>110-112</sup>

**Grade A, Level Ia**

Proteinuria, especially in the nephrotic range, is associated with an increased risk for hyperlipidaemia. On the other hand, experimental studies have demonstrated that lipids may induce glomerular and tubulointerstitial injury, and that lipid-lowering treatments may ameliorate renal injury.<sup>110-113</sup> Thus, it is likely that dyslipidaemia is both a consequence and cause of renal dysfunction. In a randomized controlled trial of treatment with statin versus placebo in patients with renal disease, Bianchi et al demonstrated stabilization of renal function and proteinuria in patients with renal disease and hyperlipidaemia.<sup>110</sup> In a randomized controlled trial of cerivastatin versus placebo in patients with proteinuria and glomerulonephritis, Nakamura et al demonstrated decrease in proteinuria at 6 months in statin-treated patients 1.8+/-0.6 to 0.8+/-0.4 g/day, pre versus post, P<0.01).<sup>111</sup> In a meta-analysis of the impact of lipid reduction on progression of renal disease, the rate of decline in GFR was lower in patients treated with a lipid lowering agent as compared to placebo (0.156 mL/min/month; 95% CI, 0.026 to 0. 285 mL/min/month, P = 0.008).<sup>112</sup> Thus lipid lowering therapy should be initiated in glomerulonephritis patients with elevated cholesterol levels, not only to ameliorate their risk for cardiovascular disease, but also to reduce the risk of progression of renal disease.

**C** Targets for LDL cholesterol with therapy in patients with glomerulonephritis and renal dysfunction is <100 mg/dL.<sup>106,107</sup>

**Grade C, Level IV**

The expert panel on cholesterol management recommends LDL cholesterol as the primary target measure for lipid lowering therapy.<sup>107</sup> As patients with chronic kidney disease are at the highest risk category for developing cardiovascular disease, the NCEP guidelines and the National Kidney Foundation recommends target LDL levels of <100 mg/dL (2.59 mmol/L), with statin therapy for patients with glomerulonephritis and renal dysfunction.

## 6.2.4 Acidosis

**C** Serum bicarbonate level should be measured in patients with glomerulonephritis and renal dysfunction so as to detect acidosis.<sup>114</sup>

**Grade C, Level IV**

In renal dysfunction, organic acids accumulate in the serum due to impairment in urinary acidification mechanisms. As renal dysfunction progresses, net acid excretion fails to keep pace with dietary net acid production and metabolic acidosis ensues. The incidence of metabolic acidosis increases with increasing severity of renal dysfunction; indeed, the majority of patients with GFR < 30 mL/min have metabolic acidosis.<sup>114</sup> Acidosis has a variety of adverse clinical effects, ranging from dramatic and life-threatening cardiovascular collapse and arrhythmias to non-specific symptoms such as lethargy, mental confusion and disorientation. Chronic acidosis also affects calcium-phosphate metabolism and contributes towards renal bone disease. In addition, acidosis is associated with decreased protein synthesis, and a negative protein balance that improves after bicarbonate supplementation.<sup>115</sup>

**B** Patients with acidosis (serum bicarbonate level < 15 mmol/L) should be treated with an alkali such as sodium bicarbonate. Target serum bicarbonate level with therapy is >22 mmol/L.<sup>87,116</sup>

**Grade B, Level III**

Therapy of acidosis with administration of alkali such as sodium bicarbonate is effective in correcting acidosis. While target serum bicarbonate level with therapy has not been clearly established, studies suggest that maintaining a bicarbonate level  $>22$  mmol/L ameliorates the adverse consequences of acidosis on renal bone disease.<sup>116</sup> Thus, guidelines from the National Kidney Foundation, USA recommend a target serum bicarbonate of 22 mmol/L with alkali therapy.<sup>87</sup>

### **6.3 Summary**

Patients with glomerulonephritis should be evaluated to determine the severity of renal dysfunction. Those with GFR  $<60$  mL/min/1.73 m<sup>2</sup> should be evaluated for the complications of anaemia, bone disease, dyslipidaemia and acidosis. These complications should be appropriately treated so as reduce the morbidity and mortality from renal dysfunction.



## 7 Management of Minimal Change Disease in Adults

### 7.1 Introduction

Minimal change disease is an idiopathic glomerulonephritis that occurs in up to 30% of cases of adult nephrotic syndrome in Singapore.<sup>117</sup> It has rarely been associated with systemic diseases such as malignant thymomas, Graves disease or may occur following exposure to drugs such as non-steroidal anti inflammatory agents or rifampicin.<sup>118,119</sup> It is characterized by an acute onset of symptomatic nephrotic syndrome, with oedema, proteinuria >3 g/day and hypoalbuminaemia. Mild renal dysfunction and hypertension may be present in a significant proportion of adults. In the series reported by Mak et al, elevated serum creatinine occurred in 55% at presentation but returned to normal upon remission of nephrotic syndrome.<sup>120</sup> Hypertension was likewise present at presentation in 47%, but persisted in 25%, long after remission.<sup>120</sup>

Albumin is the predominant form of urinary protein excreted, microhaematuria is rare and red cell casts are absent. The histological hallmark is the relative paucity of glomerular or tubular abnormalities on renal biopsy. The glomeruli on microscopy are well preserved except for the non-specific finding of podocyte effacement; the tubules commonly demonstrate lipid deposits.

### 7.2 Course and prognosis

**B** Patients with nephrotic syndrome due to minimal change disease should be treated so as to induce remission of proteinuria.<sup>120</sup>

**Grade B, Level III**

Minimal change disease is associated with an excellent long-term renal outcome, with less than 5% of cases going into end stage renal failure.<sup>120-123</sup> Spontaneous resolution of nephrotic syndrome in minimal change disease has been estimated to occur in 10% to 75% of cases; however, awaiting this spontaneous resolution is impractical as the interval to remission may be months to years. Thus, therapy is expected to induce remission earlier, although different studies quote different remission rates in older versus younger patients. Tse et al, in

their study demonstrated remission rates of 90% versus 87% at 8 weeks of therapy and 100% versus 93% at 16 weeks of therapy, respectively, for patients over 50 years versus those younger.<sup>124</sup> Korbet et al reported a response rate of 73% by 8 weeks for patients younger than 40 years versus 32% for patients older than 40 years.<sup>125</sup>

Multiple relapses and remissions of the nephrotic syndrome, as well as a marked sensitivity to steroid therapy characterize the clinical course. Relapses have been described to occur at a lower frequency in adults than in children; further, relapses occur less frequently with increasing age.<sup>123,124</sup> Untreated, the disease appears to be associated with the risk of thrombo-embolism and a predisposition to infection.

### **7.3 Disease patterns**

The disease is classified based on its response to steroid therapy.<sup>121,124</sup> Disease patterns are listed below.

Complete Remission: Absence of proteinuria with normal serum albumin levels

Partial Remission: Proteinuria of 0.5 to 3 g/day

Relapse: Reappearance of proteinuria >3 g/day with hypoalbuminaemia

Frequently Relapsing: Initially steroid-responsive but with 2 or more relapses within 6 months or 4 or more relapses within 1 year

Steroid Dependent: Initially steroid-responsive but relapses during tapering of corticosteroids or within 4 weeks of discontinuing corticosteroids and the need for maintenance

Steroid Resistant: No remission after 16 weeks of appropriate corticosteroid therapy.

## 7.4 Specific therapy

Several immunosuppressive therapies have been used in the treatment of nephrotic syndrome due to minimal change disease, to achieve remission. These include:

- Corticosteroids
- Alkylating agents
- Cyclosporin A
- Mycophenolate Mofetil
- Tacrolimus

Though corticosteroids are used at initial presentation, subsequent choice of therapy is based on the occurrence of steroid resistance and relapses and the frequency of relapse.

### 7.4.1 Initial presentation

**A** High dose prednisolone is recommended for initial treatment of nephrotic syndrome due to minimal change disease.<sup>126</sup>

**Grade A, Level Ib**

Corticosteroid therapy is the *initial agent* of choice for the treatment of nephrotic syndrome due to minimal change disease, unless there are contraindications to its use. Black, in a prospective controlled trial reported a complete remission rate of 80% following the use of corticosteroids.<sup>126</sup> Most series report a remission rate ranging from 60-77% at 8 weeks and 73-97% at 16 weeks of therapy, with complete remission rates ranging from 65% to 92%.<sup>124-127</sup>

**B** Daily oral prednisolone at 1 mg/kg/day is recommended for initial treatment of nephrotic syndrome due to minimal change disease.<sup>125</sup>

**Grade B, Level III**

However, there is considerable variation in the actual dosing regimen for corticosteroids. Nolasco et al used prednisolone at 60 mg/day for 1 week and then 45 mg/day for 4 weeks before tapering this off over 3 to 15 weeks.<sup>120</sup> They reported complete remission in 77%, with 60% responding by the 8<sup>th</sup> week of therapy. Korbet used prednisone at  $\geq 60$  mg/day for 1-3 months before tapering this off over a mean of 8 months, while Fujimoto used prednisolone of 1 mg/kg/day for 4-8

weeks before tapering this off over 9 months.<sup>122,124</sup> Korbet and Fujimoto achieved complete remission in 91% and 97% respectively, using high dose steroids.<sup>123,125</sup> In a controlled trial of intravenous methylprednisolone pulses versus high dose oral prednisone, Imbasciati et al demonstrated both regimens to be equally effective in inducing remission of nephrotic syndrome due to minimal change disease.<sup>127</sup> There were no significant differences, between the two regimens, in complete remission rates (94% vs. 97%) or in relapse rates (68% vs. 64%). Thus 1 mg/kg/day is recommended as the initial dosing regimen for treatment of nephrotic syndrome due to minimal change disease.

**B** Alternate-day oral prednisolone at 2 mg/kg/day can be used for initial treatment of nephrotic syndrome due to minimal change disease.<sup>128,129</sup>

**Grade B, Level III**

In order to reduce the incidence of steroid complications, alternate-day corticosteroids have also been used to induce remission in nephrotic syndrome due to minimal change disease. Wang used prednisolone initially at 60 mg/day for 1 week then 120 mg on alternate days until remission, tapering this off over the next 10 to 16 months.<sup>128</sup> Nair used prednisolone at 2 mg/kg/day on alternate days for 6 to 12 weeks, tapering this off over 13 weeks.<sup>129</sup> Both studies reported complete remission rates (83% and 93%), comparable to that of daily steroid therapy, and reported a low incidence of side effects. The total amount of corticosteroids used was however not lower in comparison to daily corticosteroid therapy.

**B** Steroid resistance should be considered if there is failure to achieve remission of nephrotic syndrome due to minimal change disease by 16 weeks after initiation of corticosteroid therapy.<sup>122,125</sup>

**Grade B, Level III**

In most studies in adults, remission appears to be achieved by 16 weeks following initiation of high dose corticosteroids. Nolasco et al reported a remission rate of 60% by 8 weeks, but a 73% response by 16 weeks.<sup>122</sup> Korbet et al likewise reported remission in 77% by 16 weeks.<sup>125</sup> Thus, corticosteroid resistance is defined as failure to achieve remission of nephrotic syndrome by 16 weeks and is an indication for alternative therapy for minimal change disease.

**GPP** High dose prednisolone dose should be continued until remission is achieved unless steroid toxicity or steroid resistance is diagnosed.

**GPP**

The duration of high-dose corticosteroid therapy is not clearly established in adults. Although studies in children suggest that shorter courses of corticosteroids, in which steroids are tapered rapidly after remission is induced, are associated with an increased risk of relapse, similar studies in adults are lacking.<sup>130</sup> In clinical practice, high dose prednisolone is continued for 1 week after remission is achieved.

**A** Prednisolone dose should be tapered after remission in nephrotic syndrome is achieved and subsequently discontinued. Tapering of prednisolone should be performed over 6 months.<sup>127</sup>

**Grade A, Level Ib**

**B** During taper, alternate-day prednisolone can be used to minimize the side effects of therapy.<sup>128,129</sup>

**Grade B, Level III**

Once remission of nephrotic syndrome has been achieved, corticosteroid doses can be reduced; the duration of the subsequent taper has ranged from 15 weeks<sup>122</sup> to 16 months<sup>128</sup>. In a controlled trial, Imbisciati achieved excellent remission with high doses of prednisolone for 4 weeks followed by a taper over the next 5 months.<sup>127</sup> Thus a total duration of therapy of 6 months is recommended. As suggested by Wang and Nair, alternate day prednisolone can be continued during the taper so as to minimize steroid-related side effects.<sup>128,129</sup>

**B** Patients undergoing prednisolone taper should be monitored for relapse of nephrotic syndrome.<sup>122,125</sup>

**Grade B, Level III**

**B** Patients who experience a relapse of nephrotic syndrome following a remission should be treated with a second course of corticosteroids.<sup>122,123</sup>

**Grade B, Level III**

A high incidence of relapse following withdrawal of prednisolone has been reported. Korbet et al reported a 70% incidence of relapse occurring within 3 months of attaining a complete remission.<sup>125</sup> Nolasco et al likewise reported a 58.6% incidence of relapse.<sup>122</sup> Thus patients should be monitored for relapse of nephrotic syndrome during and after the prednisolone taper. If patients relapse (infrequently) after having achieved a remission, a second course of corticosteroids can be initiated.<sup>118,131</sup> On the other hand, frequent relapsers should be treated as described below.

**GPP** Patients with nephrotic syndrome due to minimal change disease should be monitored for side effects of corticosteroids. Prednisolone doses should be reduced and alternative treatment considered if there is unacceptable steroid toxicity or if steroid resistance is diagnosed.

**GPP**

Patients on treatment with corticosteroids should be monitored for its side effects. These include acne, striae, central obesity and features of Cushing's syndrome, steroid induced diabetes, cataracts and avascular necrosis of bone and osteopenia. Steroid toxicity is cumulative and is an indication to switch to alternative treatments for nephrotic syndrome due to minimal change disease. Likewise, the diagnosis of steroid resistance is an indication to switch to alternative treatments (*vide infra*).

#### **7.4.2 Frequently relapsing or steroid-dependent nephritic syndrome**

Although an infrequent relapse of the nephrotic syndrome due to minimal change disease can be treated with a repeat course of prednisolone, treatment of repeated relapses with corticosteroids is associated with toxicity. Alternative choices for therapy are cyclophosphamide or cyclosporin A (CyA).<sup>120,122,132</sup>

**B** Cytotoxic therapy with cyclophosphamide can be used for treatment of frequently relapsing or steroid-dependent nephrotic syndrome due to minimal change disease.<sup>132</sup>

**Grade B, Level III**

Therapy with an alkylating agent, specifically cyclophosphamide, in steroid-dependent or frequently relapsing patients can produce a sustained remission in the majority.<sup>120,122,132</sup> Al Khader treated 8 adult minimal change disease patients with cyclophosphamide alone and compared the outcome to that in 8 patients not treated with immunosuppressive therapy.<sup>132</sup> Seven of those treated with cyclophosphamide achieved remission, whereas only 2 of the controls went into spontaneous remission. There was no relapse in the cyclophosphamide-treated group at 6 years of follow-up. Mak et al reported remission in 63% at 5 years for patients with multiple relapses treated with cyclophosphamide.<sup>120</sup> Nolasco reviewed the use of cyclophosphamide with prednisolone in patients with frequently relapsing disease, steroid dependence or steroid resistance. 69% achieved complete remission. 58% remitted within 8 weeks of therapy, and the duration of remission was longer (compared with studies using steroids alone), with 2/3 of those who had responded to cyclophosphamide continuing to remain in remission at the end of 4 years.<sup>122</sup>

In local practice, cyclophosphamide is given at 2 mg/kg/day for 8 to 12 weeks and is administered with low dose prednisolone. While on therapy, a high fluid intake should be encouraged. The leucocyte count should be monitored and therapy adjusted to prevent leucopaenia of less than 3,000 cells per mm<sup>3</sup>.

The need for use of prednisolone together with cyclophosphamide is not established. Although Al Khader reported response with cyclophosphamide alone,<sup>132</sup> other studies have used prednisolone together with cyclophosphamide.<sup>122</sup>

**GPP** Patients in whom cyclophosphamide therapy is planned should be informed of the potential risk for sterility and malignancy. Male patients should be advised to consider sperm storage.

**GPP**

Cyclophosphamide however is associated with an increased risk of gonadal toxicity and malignancy with prolonged treatment.<sup>133,134</sup> Thus, patients should be advised of these potential complications prior to starting therapy. Male patients should be given an opportunity for sperm storage. Furthermore, in view of these risks, and as minimal change disease is a benign condition, repeat courses of

cyclophosphamide should be avoided in patients with minimal change disease.

**A** Cyclosporin A can be used in the treatment of frequently-relapsing or steroid-dependent nephrotic syndrome due to minimal change disease.<sup>135</sup>

**Grade A, Level Ib**

Ponticelli, in a randomised controlled trial, treated frequent relapsers or steroid-dependent patients with nephrotic syndrome due to minimal change disease with either cyclosporin A, at 5 mg/kg/day for 9 months or cyclophosphamide for 8 weeks.<sup>135</sup> Cyclosporin A therapy resulted in a better remission rate (88% versus 68%,  $p>0.05$ ). The remission however was unsustainable after discontinuation of therapy and relapse was more common in the cyclosporin A group (75% versus 37%).

**B** Cyclosporin A can be started at a dose of up to 5 mg/kg/day in the treatment of frequently-relapsing or steroid-dependent nephrotic syndrome due to minimal change disease. Cyclosporin A should be administered at these doses for 1 year after which doses should be tapered. Cyclosporin A should be discontinued after 3 years.<sup>136</sup>

**Grade B, Level III**

The optimal duration of cyclosporin A therapy has been varied between studies. Meyrier, in an uncontrolled study, treated 41 steroid-dependent and steroid-resistant nephrotics with either minimal change disease or focal and segmental glomerulosclerosis with cyclosporin A for a mean of 19.6 months.<sup>137</sup> This regimen was associated with complete remission in 86%; the remission was sustained only in 10 patients after cyclosporin A withdrawal.<sup>137</sup> Ittel treated frequent relapsers, steroid-dependent and steroid-resistant nephrotics (a mixed group of minimal change disease and focal and segmental glomerulosclerosis) for a longer median time of 32 months, and achieved only 60% complete remission; none had a sustained remission on cyclosporin A withdrawal.<sup>138</sup> As the majority respond to cyclosporin A within 8 weeks, therapy should be discontinued if there has been no response after 3 months.<sup>137</sup> Longer duration of therapy however appears to be associated with fewer relapses.<sup>137</sup>

The optimal dose of cyclosporin A is likewise not established. Cyclosporin A doses used in the studies of Meyrier and Ittel ranged from 4 to 6 mg/kg/day.<sup>137,138</sup> Matsumoto et al, on the other hand,



demonstrated remission in 8 of 11 Japanese patients (73%) with an average dose of 2.4 mg/kg/day.<sup>139</sup> Following a pooled analysis of outcomes with cyclosporin A therapy in adult nephrotic syndrome patients with minimal change disease, Meyrier recommended a starting dose of cyclosporin A of 5 mg/kg/day for 1 year, followed by the lowest dose that sustains a remission for a total duration of 3 years.<sup>136</sup> In local practice, a starting dose of 4 mg/kg/day is used in treatment; cyclosporin A doses should be increased to 5 mg/kg/day if remission is not achieved.

**B** Cyclosporin A should be administered together with corticosteroids for treatment of nephrotic syndrome due to minimal change disease.<sup>140</sup>

**Grade B, Level III**

In a non-randomised controlled study, Matsumoto et al demonstrated superior remission rates when cyclosporin A was administered together with corticosteroids (complete remission 100%) than when cyclosporin A was administered alone (complete remission 75%).<sup>140</sup>

**B** Patients on cyclosporin A therapy for treatment of nephrotic syndrome due to minimal change disease should have periodic monitoring of renal function. A repeat renal biopsy should be considered after a year of cyclosporin A therapy to detect histological evidence of nephrotoxicity.<sup>137</sup>

**Grade B, Level III**

Dose-related calcineurin inhibitor nephrotoxicity has been the major complication in the use of cyclosporin A.<sup>137</sup> Meyrier, who studied serial renal biopsies of adults with minimal change disease on treatment for up to 78 months with cyclosporin A, demonstrated more cyclosporin A related histological lesions on renal biopsy at doses in excess of 5.5 mg/kg/day.<sup>137</sup> Although cyclosporin A level monitoring and targeting trough cyclosporin A levels may ameliorate the risk of cyclosporin A nephrotoxicity, the optimal cyclosporin A levels required to achieve and sustain remission are also largely unknown. Matsumoto et al targeted for cyclosporin A trough levels of 150 ng/mL in their study.<sup>140</sup> Given the risks, Meyrier recommended a routine biopsy to identify cyclosporin A nephrotoxicity.<sup>137</sup> Presence of cyclosporin A nephrotoxicity is an indication for reduction and / or discontinuation of cyclosporin A.

**B** Mycophenolate mofetil can be used for treatment of frequently-relapsing or steroid-dependent nephrotic syndrome due to minimal change disease.<sup>141,142</sup>

**Grade B, Level III**

Anecdotal studies report the efficacy of mycophenolate mofetil (MMF) in inducing remission of nephrotic syndrome due to minimal change disease. Pesavento reported successful remission in 4 patients with steroid responsive nephrotic syndrome with MMF 2 g/day<sup>141</sup> Choi et al likewise reported successful remission in 5 of 6 patients after 3 months of therapy.<sup>142</sup> Thus, failure to respond within 3 months is an indication to switch to alternative therapies.<sup>142</sup> Some studies have reported that corticosteroids may be tapered off following remission with MMF therapy. There is however no data on the optimal duration of MMF therapy required to prevent relapse after a successful remission has been achieved. As MMF is not nephrotoxic, it may have some advantages over cyclosporin A in long-term use. Until controlled trials suggest otherwise, a minimum duration of 6 months to 1 year may be acceptable in patients in whom MMF is used.

### 7.4.3 Steroid-resistant nephrotic syndrome

The majority of patients with apparently steroid-resistant nephrotic syndrome due to minimal change disease actually have other underlying conditions such as focal and global segmental sclerosis (see Chapter 8) or have received an inadequate trial of corticosteroid therapy. For those patients with true corticosteroid resistance, as defined by failure to respond within 16 weeks of therapy, repeat renal biopsy should be considered to identify these lesions.

**B** Cyclophosphamide, cyclosporin A, mycophenolate mofetil or tacrolimus can be used in the treatment of steroid-resistant nephrotic syndrome due to minimal change disease.<sup>122,143,144</sup>

**Grade B, Level III**

Patients with true steroid resistance can receive alternative therapies such as cyclophosphamide, cyclosporin A, mycophenolate mofetil (MMF) or tacrolimus.<sup>122,136,143,144</sup> There is no randomized trial comparing the efficacy of these agents. Nolasco reported remission in 69% of patients with cyclophosphamide therapy.<sup>122</sup> In a pooled analysis, Meyrier reported 56% remission rates following cyclosporin

A therapy in patients with steroid resistance.<sup>136</sup> Six of 7 patients with steroid-resistant nephrotic syndrome due to MCN sustained remission following therapy with MMF and corticosteroids.<sup>143</sup>

Tacrolimus, a calcineurin inhibitor with a mechanism of action similar to that of cyclosporin A, has also been reported to be successful in inducing remission in steroid-resistant cases.<sup>144</sup> The optimal duration of therapy with tacrolimus is unknown, although protocols similar to that for cyclosporin A are likely to be needed so as to minimize calcineurin inhibitor nephrotoxicity. As shown above, response rates to these therapies are in general lower than that reported in steroid-responsive cases.

## **7.5 Summary**

Nephrotic syndrome due to minimal change disease should be initially treated with high dose corticosteroids. Those who are frequently relapsing or steroid-dependent or steroid-resistant course should be treated with alternative therapies such as cyclophosphamide, cyclosporin A, MMF or tacrolimus. Although response rates are high, patients should be monitored for complications of the disease or of the therapy. Those with unacceptable toxicity due to one drug should be considered for a switch in therapies so as to reduce overall morbidity from the disease.

## 8 Focal and Segmental Glomerulosclerosis

### 8.1 Introduction

Focal and segmental glomerulosclerosis is a glomerular disease that commonly presents with the nephrotic syndrome. Two major forms have been identified: an idiopathic variety where no aetiology can be ascertained and a secondary one with underlying causes such as morbid obesity, obstruction or vesico-ureteric reflux, loss of renal mass as in hypoplasia or ablation, ageing, malignancy, HIV infection, heroin and consumption of other drugs.<sup>145</sup> In Singapore, idiopathic or primary focal and segmental glomerulosclerosis accounts for about 9% of all biopsies performed for nephrotic syndrome.<sup>117</sup> Males are affected twice as often as women. The following discussion focuses mainly on idiopathic or primary focal and segmental glomerulosclerosis in the adult population presenting with nephrotic syndrome.

### 8.2 Course and prognosis

The spectrum of presentation is varied; primary focal and segmental glomerulosclerosis often presents with nephrotic syndrome, as manifested by severe proteinuria and hypoalbuminaemia. Presentation with asymptomatic proteinuria also occurs, most often with secondary focal and segmental glomerulosclerosis. Up to 40% to 60% of patients have associated microhaematuria. Hypertension is present in about 50% of adults and impaired glomerular filtration rate in 20% to 40%. The prognosis depends on the degree of proteinuria, the presence of renal impairment, severity of tubulo-interstitial lesions on biopsy and response to initial therapy. Untreated, focal and segmental glomerulosclerosis often progresses to end stage renal failure. However, those achieving remission of the nephrotic syndrome with immunosuppressive therapy have a better prognosis than those not achieving such remission. Although definition of remission has been different with various studies, the Toronto Glomerulonephritis Registry defines complete remission as proteinuria less than 300 mg/day, partial remission as a 50% reduction in peak proteinuria and attainment of proteinuria less than 3.5 g/day and relapse as recurrence of proteinuria of greater than 3.5 g/day among those who had undergone remission.<sup>146</sup>

## 8.3 Treatment of focal and segmental glomerulosclerosis

**B** Patients with nephrotic syndrome due to focal and segmental glomerulosclerosis should be treated with immunosuppression so as to induce remission of proteinuria.<sup>147-153</sup>

**Grade B, Level IIb**

Although in the past it was thought the course of focal and segmental glomerulosclerosis to end stage renal failure was unaltered by immunosuppressive treatment, more recent data suggests that response rates range from 30% to 50%.<sup>147-153</sup> Whereas, renal survival of patients who achieve remission has been reported as high as 100% at 10 years<sup>147,152</sup>, non responders had a high chance of renal impairment on follow-up, ranging from 45% to 67%.<sup>150,151</sup> Rydel et al reported 5 and 10-year renal survival of 100% for patients with remission and 66% and 41% respectively for nephrotic patients not in remission.<sup>147</sup> Stirling et al reported a 5-year survival rate off dialysis of 94%, compared with 53% if remission was not achieved, among 136 adult patients with focal and segmental glomerulosclerosis.<sup>153</sup> Even attaining a partial remission reduces the risk of developing end stage renal failure.<sup>146</sup> Thus patients with focal and segmental glomerulosclerosis should be treated with immunosuppression so as to induce remission. Treatment choices for focal and segmental glomerulosclerosis are:

- Corticosteroids
- Cytotoxic agents such as cyclophosphamide
- Cyclosporin A
- Mycophenolate mofetil
- Tacrolimus
- Plasmapheresis

In addition, patients with both nephrotic and non-nephrotic proteinuria should be treated with non-immunosuppressive therapy as suggested in the chapter on “General Measures” (Chapter 4).

### 8.3.1 Corticosteroids

**B** Patients with nephrotic syndrome due to focal and segmental glomerulosclerosis should be treated with steroids.<sup>147,151-154</sup>

**Grade B, Level III**

**B** Patients with nephrotic syndrome due to focal and segmental glomerulosclerosis should receive high dose prednisolone at 1 mg/kg/day as initial therapy. High dose steroids should be continued for 1 to 2 weeks after remission is achieved and then tapered slowly.<sup>154</sup>

**Grade B, Level III**

**B** Total treatment duration with steroids for patients with nephrotic syndrome due to focal and segmental glomerulosclerosis should be for at least 6 months.<sup>147,151-154</sup>

**Grade B, Level III**

Corticosteroids are considered the mainstay of treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis. 33% to 94% of patients in reported studies used initial doses of about 60 mg/day. Ponticelli et al gave either prednisolone 1 mg/kg body weight/day for 8 weeks, tapered by 5-10 mg/week to a maintenance dose of 10-15 mg/day or methylprednisolone pulses (3 pulses, 1 g/day) followed by oral prednisolone 0.5 mg/kg/day for 8 weeks.<sup>154</sup> Median treatment time was 16 weeks (range 8 to 125 weeks with oral prednisolone alone, 50 weeks with methylprednisolone pulse therapy). The authors recorded complete remission in 36% and partial remission in 19% in this series. Rydel et al used prednisolone  $\geq$  60 mg/day (upper limit of dose not stated) for one to 2 months while Shiiki used 40-60 mg/day.<sup>147,151</sup> Response rates using prednisolone alone ranged from 0% to 94% but majority of the studies reported rates between 40% to 60%. Mean time to remission was 3.7 months but range was wide and patients have been reported to remit as late as 9 months in Rydel's series. In Cattran's series, remission occurred at a mean of 4 months and as late as 6 months.<sup>152</sup>

Some studies have suggested variable response rates to corticosteroids and thus worse prognosis with some histological variants of focal and segmental glomerulosclerosis. Patients with the glomerular tip lesion on histology are suggested to be steroid responsive<sup>155</sup> and those with the collapsing variant are more likely to progress to end stage renal failure.<sup>156,157</sup> While Franceschini et al suggest that patients with the collapsing variant of focal and segmental glomerulosclerosis may not benefit from corticosteroid therapy<sup>158</sup>, Chun et al demonstrated that response to corticosteroids was independent of the underlying histological variant of focal and segmental glomerulosclerosis.<sup>159</sup>

It is thus recommended that patients with nephrotic syndrome due to primary focal and segmental glomerulosclerosis should be initiated on high dose oral prednisolone starting at doses of 1 mg/kg/day. In local practice, this rarely exceeds 60 mg/day, even for patients heavier than 60 kg. High dose prednisolone should be given for at least 8-12 weeks, continued for 1-2 weeks after remission has been induced then tapered slowly. As prolonged corticosteroids therapy is associated with higher remission rates, minimum duration of therapy for 6 months is recommended.

**B** Patients with nephrotic syndrome due to focal and segmental glomerulosclerosis may be treated with alternative-day steroids to minimise corticosteroid toxicity.<sup>160</sup>

**Grade B, Level IIb**

Nagai et al treated elderly patients with nephrotic syndrome due to focal and segmental glomerulosclerosis with 1.0 to 1.6 mg/kg on alternative days for 3 to 5 months; over 37 months of follow-up, no relapses occurred and no patient with a complete remission progressed to end stage renal failure, compared to 47% of untreated or non-responsive patients.<sup>160</sup> This suggests that in steroid-responsive patients with nephrotic syndrome due to focal and segmental glomerulosclerosis, alternate-day corticosteroids can be used so as to reduce steroid-related toxicity.

**B** Failure to achieve remission of nephrotic syndrome due to focal and segmental glomerulosclerosis by 6 months after initiation of corticosteroid therapy is defined as steroid resistance.<sup>152</sup>

**Grade B, Level III**

Steroid resistance, as defined by the failure of nephrotic syndrome to remit despite 6 months of corticosteroid therapy, is considered an indication for alternative therapy.<sup>152</sup> Nevertheless, the majority of patients who will eventually respond to corticosteroids will manifest reduction of proteinuria within 16 weeks after starting high dose steroids.

These patients should be considered for alternative therapy as described below. Poor response or poor tolerance of prolonged, high dose steroids, relapse in nephrotic syndrome occurring during the

steroid reduction or withdrawal are also indications for alternative therapy as listed below.

### 8.3.2 Cytotoxic therapy

**B** Cytotoxic therapy with cyclophosphamide can be considered for patients with steroid-dependent nephrotic syndrome due to focal and segmental glomerulosclerosis or those with steroid-related side effects.<sup>161</sup>

**Grade B, Level III**

To date, there has been no controlled trial comparing steroids alone versus steroids with cytotoxic agents as first line therapy for nephrotic syndrome due to focal and segmental glomerulosclerosis. In fact a significant proportion of patients may have been treated with a course of empiric high dose steroids while awaiting renal biopsy, making such a study difficult to conduct. Ponticelli's series showed remission (complete or partial) in 58% with steroids as the first agent compared with 41% with cytotoxics (cyclophosphamide and azathioprine either alone or in combination with each other and low dose prednisolone) as the first agent.<sup>154</sup> Thus cytotoxic therapy, primarily with cyclophosphamide, has been used as second-line therapy in inducing remission of nephrotic syndrome in focal and segmental glomerulosclerosis. Korbet concluded that steroid-sensitive patients have a remission rate of 74% (either complete or partial) with cytotoxic therapy.<sup>161</sup>

**B** Cytotoxic therapy with cyclophosphamide can be considered as alternative therapy for patients with steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis.<sup>149,151,161,162</sup>

**Grade B, Level III**

Banfi et al gave cytotoxics in 32 steroid-resistant nephrotic syndrome and obtained 50% response.<sup>149</sup> Shiiki's experience of cyclophosphamide (1-2 mg/kg/day) or Mizoribine 150 mg for 3-6 months in steroid-resistant patients increased remission by another 37%.<sup>151</sup> In Korbet's study, 32% with steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis had a remission rate of 32% (either complete or partial) with cytotoxic therapy.<sup>161</sup> In a series by Martinelli et al, of the 24 steroid-resistant patients treated with steroids (prednisone, 1.0 to 2.0 mg/kg/day), in



combination with cyclophosphamide (2.0 to 3.0 mg/kg body weight for 12 weeks), 33.3% obtained a complete/partial response.<sup>162</sup> At the time of final evaluation, 25% of the patients treated with prednisone and 10% of those treated with prednisone in combination with cyclophosphamide had reached end stage renal failure.

**B** Patients in whom cyclophosphamide therapy is planned should be informed of the potential risk for sterility; male patients should be advised sperm storage.<sup>163</sup>

**Grade B, Level III**

As cyclophosphamide use is associated with the potential for sterility, patients in whom such therapy is considered should be informed of the risk and sperm storage offered to male patients.<sup>163</sup>

### 8.3.3 Cyclosporin A

**B** Cyclosporin A should be considered for patients with steroid-dependent nephrotic syndrome due to focal and segmental glomerulosclerosis or those with steroid-related side effects. As a lasting remission may not be achieved, long-term use may be necessary to maintain remission.<sup>161</sup>

**Grade B, Level III**

Cyclosporin A is an immunosuppressant that has been used to induce remission in nephrotic syndrome due to focal and segmental glomerulosclerosis.<sup>136,138,161,164-166</sup> In addition to its immunosuppressive effects, cyclosporin A may reduce proteinuria in focal and segmental glomerulosclerosis through its non-immunosuppressive action on renal arteriolar blood flow.<sup>136</sup> Korbet reported that 80% of steroid-sensitive patients remitted (either complete or partial) with cyclosporin A therapy.<sup>161</sup> Although, there are no controlled studies in steroid-dependent patients with nephrotic syndrome due to focal and segmental glomerulosclerosis, cyclosporin A doses and duration as used in steroid-resistant cases are likely to be effective in steroid-responsive cases (*vide infra*).

**A** Cyclosporin A at starting doses of 3 to 5 mg/kg/day should be considered for patients with steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis. As a lasting remission may not be achieved, long-term use may be necessary to maintain remission.<sup>136,138,164-166</sup>

**Grade A, Level Ib**

Among 49 steroid-resistant patients treated for 26 weeks in the randomized controlled trial by Cattran et al, 69% responded to cyclosporin A therapy (12% had complete remission, 57% had partial remission).<sup>164</sup> Mean interval to complete remission was 7 weeks (range 1-15 weeks). Six of seven patients (86%) in Ittel's series responded (1 complete, 3 partial remission, 2 reduction in proteinuria) at 6 months.<sup>138</sup> In the latter series all but one relapsed after stopping cyclosporin A, suggesting that cyclosporin A dependency may be a problem with the use of this drug. Similar to steroid responsiveness, cyclosporin A responsiveness correlates with better renal preservation. In a study in 55 patients receiving cyclosporin A for steroid-resistant nephrotic syndrome, although only 36% were cyclosporin A-responsive, progression to end stage renal failure occurred in only 10% of cyclosporin A-responsive patients versus in 60% of cyclosporin A-resistant patients.<sup>165</sup> Ponticelli likewise demonstrated response in about 60% of patients with steroid-resistant nephrotic syndrome.<sup>166</sup> Therefore, cyclosporin A at starting doses of 3 to 5 mg/kg/day is recommended for treatment of steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis. Although the optimal duration of therapy is unknown, minimum duration of therapy with cyclosporin A is for 6 months.

**B** Cyclosporin A should be administered together with steroids for patients with steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis until remission is achieved. Steroid doses may be tapered subsequently.<sup>138,164,166-168</sup>

**Grade B, Level III**

Cyclosporin A has been administered either alone or in combination with low dose prednisolone (up to 15 mg/day) or high dose prednisolone (60 mg/day).<sup>138,164,166-168</sup> Although prednisolone has been successfully stopped by 6-8 weeks in some studies<sup>167</sup>, Meyrier recommends its continuation as alternate-day therapy in steroid-resistant patients as cyclosporin A may increase the sensitivity to steroids.<sup>168</sup>

**B** Patients receiving cyclosporin A for treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis should have renal function monitored.<sup>169</sup>

**Grade B, Level III**

While an increase in tubulo-interstitial lesions and fibrosis has been shown with prolonged use of cyclosporin A<sup>169</sup>, Ghigheri et al suggests that cyclosporin A for a duration of >2 years in cyclosporin A-responsive patients is not associated with renal functional deterioration.<sup>165</sup> Nevertheless, optimization of cyclosporin A therapy with the use of cyclosporin A level monitoring may help ameliorate risk of cyclosporin A nephrotoxicity. A cyclosporin A trough value of between 125 and 225 ng/mL has been suggested.<sup>170</sup> After remission has been achieved, low cyclosporin A dose of 1-2 mg/kg/day can be used for maintenance therapy.<sup>171</sup>

**A** Patients with steroid-responsive nephrotic syndrome due to focal and segmental glomerulosclerosis, who are considered for alternative therapy, may be treated with either cyclosporin A or cyclophosphamide.<sup>135</sup>

**Grade A, Level Ib**

In a randomised controlled trial of cyclosporin A at 2.5 mg/kg/day for 8 weeks versus cyclophosphamide at 5 mg/kg/day for 9 months in 66 steroid-responsive patients with nephrotic syndrome due to focal and segmental glomerulosclerosis, Ponticelli demonstrated similar remission rates (74.3% vs. 67.9% for cyclophosphamide versus cyclosporin A,  $p =$  nephrotic syndrome) and similar relapse rates with either therapy.<sup>135</sup> Thus either treatment can be used as alternative therapy in patients with steroid-sensitive nephrotic syndrome due to focal and segmental glomerulosclerosis.

**B** Patients with steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis are preferentially treated with cyclosporin A.<sup>161,164</sup>

**Grade B, Level III**

There are no controlled trials comparing cyclosporin A versus cyclophosphamide in steroid-resistant focal and segmental glomerulosclerosis. In Cattrans's controlled trial of cyclosporin A versus steroids, 69% of cyclosporin A treated patients had either complete or partial remission of proteinuria and only 10% of the

cyclosporin A treated group had progressed to end stage renal failure by 4 years after randomisation.<sup>164</sup> On the other hand, steroid-resistant patients with focal and segmental glomerulosclerosis treated with cyclophosphamide, experienced lower remission rates of only 32%.<sup>161</sup> Thus patients with steroid-resistant nephrotic syndrome due to focal and segmental glomerulosclerosis are preferentially treated with cyclosporin A, rather than with cyclophosphamide.

### 8.3.4 Mycophenolate mofetil

**B** Mycophenolate mofetil may be used in the treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis.<sup>142,172,173</sup>

**Grade B, Level II**

Mycophenolate mofetil (MMF) has been reported in the treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis in a few series.<sup>142,172,173</sup> Among 18 patients with steroid-resistant or steroid-dependent focal and segmental glomerulosclerosis, MMF resulted in stabilisation of renal function and reduced proteinuria.<sup>142</sup> In some cases, steroids were withdrawn totally without relapse. A report by Radhakrishnan et al showed reduction in proteinuria and unchanged serum creatinine over 1 year in 11 steroid and cyclosporin A-resistant patients, but there was a lack of complete remission.<sup>172</sup> In an open-labeled trial of MMF in 18 patients with steroid-resistant focal and segmental glomerulosclerosis, MMF reduced proteinuria in 44% by 6 months; the reduction was sustained for up to 1 year post treatment in 50%.<sup>173</sup> However, no patient had complete remission and relapses were common suggesting that its role in treatment of focal and segmental glomerulosclerosis is as yet not clearly defined.

### 8.3.5 Other alternative therapies

**B** Tacrolimus may be used as alternative therapy in treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis.<sup>174,175</sup>

**Grade B, Level III**

Duncan et al demonstrated partial remission of nephrotic syndrome and improvement of renal function in all 6 patients treated with a mean tacrolimus dose of  $0.07 \pm 0.03$  mg/kg/day.<sup>174</sup> Tacrolimus is a calcineurin inhibitor similar to cyclosporin A and may thus have

similar effects as cyclosporin A in focal and segmental glomerulosclerosis. In another study in 25 adults with cyclosporin A-resistant or cyclosporin A-dependent idiopathic focal and segmental glomerulosclerosis, tacrolimus at 0.15 mg/kg/day, together with corticosteroids, induced remission in 68% of patients.<sup>175</sup> However, relapse was common after withdrawal of tacrolimus. Furthermore, these studies were small and additional studies are needed to support its routine use as alternative therapy in focal and segmental glomerulosclerosis. Optimal tacrolimus doses and levels and duration of therapy are yet to be determined.

**C** Plasmapheresis may be used as alternative therapy in treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis.

**Grade C, Level IV**

A circulating glomerular capillary albumin permeability factor has been implicated in the pathogenesis of focal and segmental glomerulosclerosis.<sup>176</sup> As plasmapheresis may remove the putative factor, it has been tried in the treatment of focal and segmental glomerulosclerosis; however results have been disappointing. Among 8 patients with focal and segmental glomerulosclerosis treated with plasmapheresis, only 2 patients responded with reduction in proteinuria after 6 sessions of plasmapheresis.<sup>176</sup> Use of plasmapheresis in combination with cyclophosphamide may yield a better response as suggested by Mitwalli.<sup>177</sup>

## 8.4 Summary

Patients with nephrotic syndrome due to focal and segmental glomerulosclerosis should be treated with corticosteroids as initial therapy. Treatment needs to be prolonged so as to sustain remission; patients with steroid related toxicity or steroid dependency may need treatment with cyclophosphamide or cyclosporin A. Those with steroid-resistant focal and segmental glomerulosclerosis should be treated with cyclosporin A.

## 9 IgA Nephropathy

### 9.1 Introduction

IgA nephropathy is the commonest glomerulonephritis in Singapore accounting for 52% of all renal biopsies.<sup>2</sup> It typically presents in children and young adults and is seldom seen in infancy or after the age of 50 years.<sup>178</sup> The clinical presentation is varied with the commonest being asymptomatic haematuria and proteinuria (52%); the other presentations are nephrotic syndrome (15%), hypertension (15%), acute renal failure (9%), gross haematuria (6%) and chronic renal failure (1%).

### 9.2 Course and prognosis

IgA nephropathy pursues a highly variable course. It is not a benign disease as 30-50% of patients develop end stage renal failure after 25 years of follow-up.<sup>178</sup> There are clinical and histological factors that predict the likelihood of progression to end stage renal failure and these prognostic factors can be used to select patients for therapy (Table 8).<sup>179-182</sup>

**Table 8 Risk factors for progression of IgA nephropathy**

Clinical factors	Histological factors
– Magnitude and character of proteinuria	– Chronic tubulo-interstitial infiltration/fibrosis
– Impaired renal function	– Extensive crescents (>30-50%)
– Hypertension	– Advanced glomerulosclerosis (>20%)
	– Medial hypertrophy of arterioles

A recent study correlating prognostic factors with the rate of progression of renal impairment showed that mean arterial pressure and severity of proteinuria over time were the most important prognostic indicators in IgA nephropathy.<sup>182</sup> Polymorphism of the Angiotensin Converting Enzyme (ACE) gene has also been an area of interest in recent years and some investigators have suggested that the ACE DD genotype is a marker of upregulation of the renin-

angiotensin system that may cause more rapid progression of renal disease in IgA nephropathy.<sup>183-185</sup> These findings have not been consistently shown in other studies.

### 9.3 Pathogenesis

IgA nephropathy is generally believed to be an immune complex disease arising as a result of an abnormal IgA immune response to either environmental or autologous antigens leading to subsequent deposition of IgA immune complexes in the glomerular mesangium.<sup>186,187</sup> As the understanding of its pathogenesis is incomplete, most treatment options for IgA nephropathy remain empirical. Furthermore, the long interval from onset of the condition to renal failure has made it difficult to establish the most effective treatment regimen.

### 9.4 Treatment of IgA nephropathy

There have been several reviews of treatment of IgA nephropathy over the years.<sup>179,188-193</sup> Therapeutic efforts have been directed at either (1) reducing or preventing antigen entry and (2) altering the abnormal immune response and its consequences. Therapeutic recommendations for the following clinical syndromes are discussed:

- Isolated haematuria
- Haematuria and proteinuria
  - Proteinuria 0.15 to 1 g/day
  - Proteinuria  $\geq 1$  g/day
- Nephrotic syndrome
- Acute renal failure

### 9.5 Isolated haematuria

**C** No specific therapy is recommended for patients with IgA nephropathy and isolated haematuria without proteinuria.<sup>180</sup>

**Grade C, Level IV**

**C** Patients with IgA nephropathy and isolated haematuria should be monitored regularly (every 3-12 months) for the development of hypertension, renal impairment and proteinuria.<sup>194</sup>

**Grade C, Level IV**

There are no therapeutic trials on progression to renal failure in patients with IgA nephropathy and isolated haematuria without proteinuria. However, clinico-pathological studies suggest a benign course in patients with recurrent isolated episodes of gross haematuria without adverse histological features.<sup>180</sup> In fact, in local practice, a diagnosis of IgA nephropathy may not even have been made in the majority of patients with isolated haematuria as biopsy in patients with isolated haematuria is generally not carried out as there is little impact on treatment. Thus no specific therapy is recommended for patients with IgA nephropathy and isolated haematuria. Long-term monitoring is important however, as patients with isolated haematuria may develop proteinuria (33%), hypertension (26%) or renal impairment (7%) after a median follow-up of 84 months.<sup>194</sup>

## 9.6 Haematuria and proteinuria

**C** No specific therapy is recommended for patients with IgA nephropathy and asymptomatic haematuria and proteinuria of 0.15 g/day to 1 g/day and no other adverse clinical or histological indicators.<sup>188</sup>

**Grade C, Level IV**

**C** Patients with IgA nephropathy and haematuria and proteinuria should be monitored regularly (every 3-12 months) for the level of proteinuria and the development of hypertension and renal impairment.<sup>188</sup>

**Grade C, Level IV**

There is no data to date suggesting benefit from treating patients with IgA nephropathy and mild proteinuria (0.15 g/day to 1 g/day) in the absence of other adverse clinical or histological features. These patients are best left untreated although they should be monitored at regular intervals, every 3-6 months initially, then 6-12 monthly if the proteinuria remains stable.<sup>188</sup>

**A** Patients with IgA nephropathy and proteinuria  $\geq 1$  g/day should be treated so as to reduce the risk of progression of renal failure.<sup>195-197</sup>

**Grade A, Level Ib**

Therapy should be reserved for patients with one or more adverse prognostic features, especially those with proteinuria  $\geq 1$  g/day.<sup>195-197</sup>



The five categories of therapy that have been used in the treatment of patients with IgA nephropathy and proteinuria  $\geq 1$  g/day are:

- A) Angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB)
- B) Dipyridamole and warfarin combination therapy
- C) Dietary supplementation with fish oil
- D) Steroid therapy
- E) Other therapies

### 9.6.1 Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers

In addition to their anti-hypertensive effects, ACEI and ARB have been shown to reduce proteinuria and slow the rate of decline of renal function in different forms of glomerulonephritis including IgA nephropathy. These effects appear independent of their blood pressure lowering ability. ACEI and ARB exert their effects through a number of mechanisms including alteration of the haemodynamics in the kidney resulting in reduction in intra-glomerular pressure and at the cellular level by reducing mesangial cell proliferation and matrix production. Recent studies have further shown that ACEI and ARB improve glomerular permselectivity.<sup>11,78</sup>

**B** Angiotensin converting enzyme inhibitor therapy is recommended for treatment of hypertension in patients with IgA nephropathy.<sup>198</sup>

**Grade B, Level IIa**

Blood pressure control remains the cornerstone in therapy to retard the progression of disease in virtually all forms of glomerular disease including IgA nephropathy. Although any agent, singly or in combination, that satisfactorily controls blood pressure can be used, an ACEI is the preferred drug of choice.<sup>198-200</sup> Other treatment measures, including sodium restriction, (see Chapter 5) are also recommended.

**A** Angiotensin converting enzyme inhibitor therapy is recommended in normotensive patients with IgA nephropathy and proteinuria  $\geq 1$  g/day.<sup>8</sup>

**Grade A, Level Ib**

Several studies have been conducted using ACEI in IgA nephropathy for retardation of progression of renal failure. These studies have looked at various end-points including reduction in proteinuria and stabilization of renal function (serum creatinine and creatinine clearance). Almost all the studies enrolled patients with proteinuria  $\geq 1$  g/day<sup>8,198-201</sup> with the exception of two randomized trials that enrolled patients with  $\geq 0.5$  g/day.<sup>78,195</sup> Maschio, in a multicentre, randomized, placebo-controlled trial (cross-over study) using the ACEI fosinopril, in 39 patients with normal blood pressures and creatinines demonstrated a significant reduction in proteinuria in the fosinopril treated arm.<sup>8</sup> Some studies suggest that the deletion ACE DD genotype is linked with more rapid progression and it is in this group of patients that ACEI may be more effective.<sup>11,78</sup> As these latter findings have not been confirmed, it is recommended that all patients with significant proteinuria be started on ACEI therapy.

Thus, treatment with an ACEI is recommended in hypertensive or normotensive patients with IgA nephropathy and significant proteinuria ( $\geq 1.0$  g/day). Renal impairment or chronic renal failure is not a contraindication for use of ACEI although caution should be exercised when initiating and maintaining ACEI in patients with abnormal renal function as hyperkalaemia and acute deterioration of renal function can ensue (see Chapter 5).

**A** Angiotensin II receptor blockers can be used as alternatives to angiotensin converting enzyme inhibitors in patients with IgA nephropathy for similar indications.<sup>11,202</sup>

**Grade A, Level Ib**

**A** Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers can be used in combination to reduce proteinuria in patients with IgA nephropathy and proteinuria  $\geq 1$  g/day.<sup>203</sup>

**Grade A, Level Ib**

Recent trials using the newer ARB have shown similar beneficial effects on proteinuria and progression of disease when compared with ACEI.<sup>11,202</sup> Therapy with either an ACEI or ARB was found to have similar anti-proteinuric effects in a trial by Perico et al<sup>204</sup> and improve renal function in some patients in another trial by Woo et al.<sup>11</sup> In a double-blind, randomized controlled trial, Li et al demonstrated that the ARB valsartan significantly reduced the mean rate of glomerular

filtration rate decrease over a 2-year period.<sup>202</sup> Furthermore, a combination of ACEI and ARB was found to have an additive anti-proteinuric effect in one study by Russo et al.<sup>203</sup>

## **9.6.2 Dipyridamole and warfarin combination therapy**

**A** Dipyridamole and low-dose warfarin combination therapy is recommended in patients with IgA nephropathy and proteinuria  $\geq 1$  g/day. Its use is not contraindicated in patients with abnormal renal function.<sup>197</sup>

**Grade A, Level Ib**

Increased platelet aggregation and activation of the coagulation pathway, in part as a result of endothelial cell damage occurring from the intra-glomerular hypertension, are features of IgA nephropathy. These observations formed the rationale for the use of dipyridamole and warfarin in IgA nephropathy. The initial trials included six months of cyclophosphamide, together with dipyridamole and warfarin<sup>14,205</sup> but the most recent trial used only dipyridamole and warfarin in patients with renal impairment<sup>197</sup> in order to avoid the hematological and gonadal toxicity of cyclophosphamide. The trials showed that treatment reduced proteinuria (in patients with normal renal function) and stabilised renal function in patients with normal and abnormal renal function (creatinine 1.6-3.0 mg/dl).

Dipyridamole (75 mg - 10 mg thrice daily) and low dose warfarin (1-3 mg/day to keep the International Normalised Ratio (INR) between 1.2 to 1.5) is recommended in patients with proteinuria  $\geq 1$  g/day. Abnormal renal function is not a contraindication to treatment. The INR has to be monitored at regular intervals during treatment.

## **9.6.3 Dietary supplementation with fish oil**

Fish oil supplementation is not beneficial in every patient with IgA nephropathy.<sup>206</sup>

Fish oil, composed mainly of omega-3 fatty acids, produces trienoic eicosanoids that may reduce glomerular and interstitial inflammation, platelet aggregation and vasoconstriction, thus reducing renal damage.<sup>207</sup> There are five studies (three randomized controlled trials)

using fish oil in IgA nephropathy and the results have been conflicting.<sup>208-213</sup> Two had positive results while the other three had negative results. A meta-analysis by Dillon failed to demonstrate a statistically significant benefit of fish oil in most patients with IgA nephropathy.<sup>206</sup>

**B** Fish oil supplementation can be used in patients with IgA nephropathy and proteinuria >3 g/day.<sup>206,214</sup>

**Grade B, Level III**

However, Dillon noted there was a 75% probability of at least a minor beneficial effect, and that mixed-effects regression suggested that this therapy may be more effective among individuals with more proteinuria.<sup>206</sup> Donadio et al demonstrated lower progression to end stage renal failure at 3 years in high-risk patients with renal impairment and heavy proteinuria treated with fish oil therapy than a placebo-treated retrospective control.<sup>214</sup> They further compared low-dose with high-dose fish oil and found no difference in preservation of renal function between the two groups.<sup>214</sup> The low-dose regimen included 12 g of fish oil containing 1.88 g of eicosapentaenoic acid and 1.47 g of docosahexaenoic acid, while the high dose regimen contained twice the amount of these omega-3 fatty acids. Thus low-dose fish oil can be used in patients with IgA nephropathy and heavy proteinuria.

#### 9.6.4 Steroid therapy

**A** Corticosteroids can be used for treatment in selected patients with IgA nephropathy.<sup>215</sup>

**Grade A, Level Ia**

Steroids were one of the first agents used in the treatment of IgA nephropathy but to date, there is no consensus on the dose, duration of therapy and the indications for the use of steroid therapy. There are, however, two situations where there are definite indications for the use of steroid therapy and they are (1) in patients with the nephrotic syndrome and minimal change lesions on renal biopsy and (2) in patients with crescentic glomerulonephritis (*vide infra*).

In recent years, there have been four randomised controlled trials<sup>196,216-218</sup> using steroids and/or cytotoxic agents in patients with IgA nephropathy who were either at high risk of progressive disease

or with documented renal insufficiency. All the studies showed benefit in the treated groups with two showing reduction in the rate of decline of renal function (Ballardie et al, Pozzi et al) and the other two demonstrated reduction in proteinuria. Ballardie et al<sup>216</sup> used a combination of oral prednisolone and cytotoxics (cyclophosphamide followed by azathioprine) for a period of at least 2 years in patients with abnormal serum creatinine at presentation while Pozzi et al<sup>196</sup> used a combination of methylprednisolone pulses and oral prednisolone for a period of 6 months. The dose of prednisolone varied between different study protocols but in general, the prednisolone was initiated at a dose of 0.5 mg/kg/day and was tapered to 10 mg/day or alternate day. The recommended duration of treatment is 6 months. In a meta-analysis of seven trials comparing steroids with no treatment in IgA nephropathy, steroids were associated with a lower risk of progression to end stage renal failure (Relative Risk 0.44, 95% CI 0.25 to 0.80) and lower urinary protein excretion (Weighed Mean Difference -0.49 g/24h, 95% CI -0.72 to -0.12).<sup>215</sup>

**GPP** Immunosuppression is not without risk of toxicity and should only be considered in patients with persistent proteinuria  $\geq 1$  g/day or in those with evidence of progressive renal damage despite adequate blood pressure control at 130/80 mm Hg or lower with an ACEI or ARB.<sup>219</sup>

**GPP**

However, at this point, it is prudent to be aware that the studies mentioned above were designed in the early 1990's where target blood pressures were higher and different from the current recommended target of 130/80 mm Hg in patients with proteinuria  $\geq 1$  g/day, and the usage of ACEI was not optimal as judged by current standards. It is therefore unknown if the immunosuppressive regimens would still be beneficial if optimal blood pressure control is achieved with the use of ACEI and/or ARBs. Hence, it is recommended that steroid therapy be considered only after the patient has received full optimal supportive care (achieves target blood pressure with ACEI and/or ARBs) and still remains heavily proteinuric.<sup>219,220</sup>

### **9.6.5 Other therapeutic options**

Many other treatment regimens have been used in IgA nephropathy and there are large trials in progress comparing the effects of steroids against various therapies including fish oil, ACEI and azathioprine.

Other treatment options<sup>179</sup> include azathioprine, mycophenolate mofetil, cyclosporin A, intravenous immunoglobulin and non-immunosuppressive options such as phenytoin, danazol, a gluten-free diet, tonsillectomy, sodium cromoglycate and urokinase. A recent 3-year, placebo-controlled randomized trial showed disappointing results with mycophenolate mofetil with no demonstrated benefit on renal function and proteinuria in patients with IgA nephropathy and bad prognostic indicators.<sup>221</sup>

## 9.7 IgA nephropathy and nephrotic syndrome

**B** Treatment for patients with nephrotic syndrome due to IgA nephropathy should be based on findings on renal biopsy.<sup>222</sup>

**Grade B, Level IIa**

Nephrotic syndrome is an uncommon presentation of IgA nephropathy and treatment for these patients should be based on severity of histological changes on renal biopsy.

### 9.7.1 Mild histological changes

**B** Nephrotic patients with IgA nephropathy and mild histological changes on renal biopsy should be treated with prednisolone at an initial dose of 1 mg/kg/day with subsequent tapering after 4-6 weeks for a total treatment period of 3-4 months.<sup>222</sup>

**Grade B, Level IIa**

There is only one controlled study by Lai et al using steroids in patients with IgA nephropathy and the nephrotic syndrome.<sup>222</sup> There was an *overall* lack of benefit of steroid therapy in the group. However, there was excellent remission in 80% of patients with mild histological changes suggesting that patients who respond frequently have mild histological changes on renal biopsy and behave like minimal change disease. Thus, patients with mild histological changes and nephrotic syndrome should be treated with prednisolone at an initial dose of 40-60 mg/day (1 mg/kg/day) with tapering of the dose after 4-6 weeks for a total treatment period of 3-4 months.

**B** Nephrotic patients with IgA nephropathy and mild histological changes who have relapses, steroid resistance or steroid dependence should be treated with cyclophosphamide at a dose of 1.5-2.0 mg/kg/day for 2-3 months together with low-dose prednisolone.<sup>223</sup>

**Grade B, Level IIa**

There are only few anecdotal reports on the management of relapses of nephrotic syndrome in patients with IgA nephropathy and mild histological changes; some have responded to a second course of steroids or to cyclophosphamide at a dose of 1.5-2.0 mg/kg/day given for 8-12 weeks<sup>224,225</sup> Support for the use of cyclophosphamide comes from a meta-analysis by Schena et al which suggested that corticosteroids and/or cytotoxic drugs are beneficial in patients with heavy proteinuria whether or not associated with the nephrotic syndrome.<sup>223</sup>

**C** Cyclosporin A at an initial dose of 5 mg/kg/day can be used in nephrotic IgA patients with mild histological changes who fail steroid and cyclophosphamide therapy. The recommended treatment period is 6-12 months and low-dose prednisolone should be given concomitantly.<sup>226</sup>

**Grade C, Level IV**

A single short-term controlled trial using cyclosporin A in patients with heavy proteinuria showed reduction in proteinuria but there was also a more rapid decline in renal function.<sup>227</sup> However, cyclosporin A has been used in other forms of glomerular disease with the nephrotic syndrome and found to be beneficial in inducing and maintaining remission.<sup>137,228</sup> However, continuous therapy of up to 12 months or more is often required. Cyclosporin A may be considered in non-responders, frequent relapsers<sup>226</sup> and those who are steroid-dependent. An initial dose of 5 mg/kg/day with tapering to 2-3 mg/kg/day at 5-6 months for a total period of 6-12 months has been suggested for use. Concomitant low-dose prednisolone is also recommended with cyclosporin A therapy (30 mg tapering to 10 mg).

### **9.7.2 Other histological changes**

**C** Nephrotic IgA patients with histological changes that are not mild can be treated with prednisolone, cyclophosphamide or cyclosporin A, similar to those with mild histological changes.<sup>223,229</sup>

**Grade C, Level IV**

**GPP** As response to immunosuppressive therapy is less favourable in patients with IgA nephropathy and more severe histological changes, over-immunosuppression should be avoided in non-responders.

**GPP**

A meta-analysis by Schena et al suggested that corticosteroids and/or cytotoxic drugs are beneficial in patients with IgA nephropathy and heavy proteinuria whether or not associated with the nephrotic syndrome.<sup>223</sup> As patients with selective proteinuria are likely to respond to therapy irrespective of histology, Woo et al suggest that patients with nephrotic syndrome should undergo further evaluation of proteinuria with studies of protein selectivity.<sup>229</sup> Thus, a similar treatment approach as for those with mild histological changes is suggested for the group of patients with more severe histological changes. Nevertheless, patients with IgA nephropathy and more severe histological changes are less likely to respond to immunosuppressive therapy<sup>223</sup> Thus care should be taken to avoid over aggressive therapy in non-responders to immunosuppression.

## 9.8 IgA nephropathy and acute renal failure

**C** Patients with IgA nephropathy and acute renal failure should undergo renal biopsy to determine treatment.<sup>179</sup>

**Grade C, Level IV**

Acute renal failure (ARF) is also an uncommon presentation in IgA nephropathy and occurs in approximately 9-10% of patients, 20-25% of whom require dialysis. It occurs in two situations: (1) in patients with crescentic glomerulonephritis and (2) after an episode of gross haematuria where the renal biopsy reveals mild glomerular changes but marked acute tubular necrosis. As treatment differs for the two histologies, patients with IgA nephropathy and ARF should undergo renal biopsy to determine treatment strategy.

### 9.8.1 Crescentic IgA nephropathy

**C** Patients with acute renal failure due to crescentic IgA nephropathy should be treated as for other forms of crescentic glomerulonephritis. Treatment with methylprednisolone pulse should



be followed by oral prednisolone, cyclophosphamide, dipyridamole and warfarin.<sup>179</sup>

**Grade C, Level IV**

**GPP** Plasma exchange and intravenous immunoglobulins can be instituted in some patients with crescentic IgA nephropathy.<sup>179</sup>

**GPP**

The diagnosis of crescentic IgA nephropathy is made in patients presenting with ARF in the presence of crescents with underlying IgA nephropathy on renal biopsy. As the proportion of patients with crescentic IgA nephropathy is small, there have been no controlled studies on therapy. General consensus recommends standard treatment as for other forms of rapidly progressive glomerulonephritis (RPGN), with prednisolone at an initial dose of 1 mg/kg/day (with subsequent taper over 3-4 months and total treatment period for 6 months) and cyclophosphamide at 2 mg/kg/day (total treatment period for 3-4 months).<sup>179</sup> A methylprednisolone pulse of 500 mg to 1 g/day for three days can be given prior to initiation of oral prednisolone. Dipyridamole (75-100 mg thrice daily) and warfarin (low dose to keep the INR between 1.2 to 1.5) can be added.

Plasma exchange and intravenous immunoglobulin therapy can also be considered for patients not responding to above therapy. However, there is no standard regimen for plasma exchange and if required, it should be tailored to the patient's clinical progress.

### **9.8.2 IgA nephropathy with mild glomerular changes on renal biopsy**

**C** No specific treatment is recommended for patients with IgA nephropathy and acute renal failure in the presence of mild glomerular changes on renal biopsy.<sup>230</sup>

**Grade C, Level IV**

Patients with IgA nephropathy presenting with ARF may have had a preceding episode of gross haematuria associated with flank pain. Renal biopsy in these patients reveals mild glomerular changes with predominantly marked acute tubular necrosis. The ARF is thought to be the result of glomerular bleeding leading to tubular damage (and thus tubular necrosis) from local production of toxic haemoglobin degradation products and/or toxic oxygen radicals.<sup>230</sup> Thus, no definitive

treatment is recommended. Dialysis may be required in some patients. Although certain patients have recurrent ARF following episodes of gross haematuria, the ARF is reversible and all patients eventually recover.

## 9.9 Summary

IgA nephropathy is a glomerulonephritis with a varied spectrum of presentation. Patients with IgA nephropathy and isolated haematuria with no or minimal proteinuria do not require any specific treatment in the absence of other clinical or histological adverse prognostic factors. However, those with proteinuria  $\geq 1$  g/day should receive treatment with ACEI or ARB or both. Patients should also receive dipyridamole and warfarin at anti-thrombotic doses to reduce intraglomerular coagulation. Patients with hypertension should also preferably receive ACEI and/or ARB to achieve target blood pressure goals as for other glomerulonephritis. High-risk patients not responding to ACEI/ARB should be considered for steroids or fish oil supplementation. Those with IgA nephropathy and the nephrotic syndrome or ARF should be treated based on renal biopsy changes.

## 10 Cost-benefit Issues

End stage renal disease due to chronic kidney disease is a growing public health problem. Kidney disease causes premature morbidity and mortality and lowers quality of life; it is also expensive. In the United States, people with kidney failure represent less than 1% of the Medicare population (individuals with kidney failure, regardless of age, are eligible for Medicare funding), yet their care consumes 6.4% of the health care expenditures by the Centers for Medicare and Medicaid Services.<sup>231</sup> According to the United States Renal Data system, 2001 Medicare spending for end stage renal disease was \$15.4 billion and non-Medicare cost was \$7.4 billion. By 2010, it has been estimated that the expenditure related to ESRD will increase to \$28 billion in United States.<sup>232</sup> In Singapore, glomerulonephritis is the second leading cause of end stage renal disease. In view of the enormous economic and health burden due to this disease, it is important that health care professionals adopt evidence-based and cost-effective practices to manage the disease. This section presents evidence from the scientific literature on the cost-effectiveness of some aspects in the management of glomerulonephritis.

In a study on US adults, mass screening for proteinuria, as a preventive strategy for end stage renal disease, was not cost-effective. The cost-effectiveness ratio for mass screening versus no screening (usual care) was unfavourable (\$282,818 per QALY saved). However, cost-effectiveness ratio was favourable for those who were at risk of kidney disease e.g. patient  $\geq 60$  years (\$53,372 per QALY) or patients with hypertension (\$18,621 per QALY).<sup>233</sup>

An economic analysis comparing an ACE inhibitor, ramipril, with conventional therapy for treatment of hypertension in chronic kidney disease revealed that ramipril delayed progression to end stage renal disease and prolonged patient survival and also saved \$16,605 to \$23,894 lifetime and \$2,422 to \$4,203 yearly direct cost per patient. This study showed that ACE inhibitors prolonged life while saving money because of its beneficial effect on the course of non-diabetic chronic nephropathies.<sup>234</sup>

## Clinical Quality Improvement

The following clinical quality improvement parameters, based on recommendations in these guidelines, are proposed:

- 1) Percentage of patients with glomerulonephritis and hypertension on ACE inhibitors or ARBs (page 50).
- 2) Percentage of patients with hypertension who have achieved target blood pressure (page 49).
- 3) Percentage of patients with blood pressure checked at least once within the last 3 months (page 54).
- 4) Percentage of patients with glomerulonephritis who have achieved target proteinuria of  $<0.5$  g/day with therapy (page 46).
- 5) Percentage of patients with anaemia workup (page 58).

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## Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category III (Self-Study) of the SMC Online CME System. Before you login to claim the CME point, we encourage you to evaluate whether you have mastered the key points in the Guidelines by completing this set of MCQs. This is an extension of the learning process and is not intended to “judge” your knowledge and is not compulsory. The answers can be found at the end of the questionnaire.

*Instruction: Choose the right answer(s). There may be more than one answer for some question.*

- A patient is said to have persistent proteinuria if

  - his/her dipstick test for proteinuria is positive on one of two early morning urine samples collected 24 hours apart.
  - his/her dipstick test for proteinuria is positive on three separate early morning urine samples collected two weeks apart.
  - his/her dipstick test for proteinuria is positive on two separate early morning urine samples collected one month apart.
  - his/her dipstick test for proteinuria is positive on two separate early morning urine samples collected one week apart.
- Haematuria is diagnosed by the presence of

  - $\geq 2$  RBCs/hpf in unspun urine
  - $\geq 3$  RBCs/hpf in unspun urine
  - $\geq 5$  RBCs/hpf in spun urine
  - $\geq 5$  RBCs/hpf in unspun urine
- Referral to nephrologist is indicated in patients with

  - haematuria and proteinuria  $>1$  g/day
  - haematuria and blood pressure  $\geq 140/90$
  - blood pressure  $\geq 140/90$  mm/Hg and negative urine dipstick for blood and protein
  - gross haematuria
- In patients with glomerulonephritis, proteinuria should be treated with

  - ACE inhibitors till proteinuria  $<1$  g/day
  - ARBs till proteinuria  $<1$  g/day
  - ARB or ACE inhibitors till proteinuria  $<1$  g/day
  - ARB or ACE inhibitors till proteinuria  $<0.5$  g/day

5. Dietary protein in patients with glomerular disease should be restricted to
- A)  $<0.4$  g/kg/day
  - B) 0.4 g/kg/day
  - C) 0.4-0.8 g/kg/day
  - D) 0.8 g/kg/day
6. Hypertension in patients with glomerular disease is defined as blood pressure
- A) 130/80
  - B) 125/75
  - C) 140/80
  - D) 130/85
7. Which of the following statements are true?
- A) Target blood pressure for patients with glomerulonephritis and proteinuria  $<1$  g/day is 140/80
  - B) Target blood pressure for patients with glomerulonephritis and proteinuria  $\leq 1$  g/day is 130/80
  - C) Target blood pressure for patients with glomerulonephritis and proteinuria  $\geq 1$  g/day is 130/75
  - D) Target blood pressure for patients with glomerulonephritis and proteinuria  $>1$  g/day is 125/75
8. Target level of LDL cholesterol with therapy (diet and statins) in patients with glomerulonephritis and renal dysfunction is
- A) 130 mg/dL
  - B) 160 mg/dL
  - C) 100 mg/dL
  - D) 80 mg/dL
9. Recommended initial dosage of prednisolone for initial treatment of nephrotic syndrome due to minimal change disease is
- A) daily oral dose of 1 mg/kg/day
  - B) alternate-day oral dose of 1 mg/kg/day
  - C) daily oral dose of 0.5 mg/kg/day
  - D) alternate-day oral dose of 2 mg/kg/day

10. The following statements are true regarding IgA nephropathy:
- A) IgA nephropathy is commonest glomerulonephritis in Singapore.
  - B) ARB and ACE inhibitors should be used to treat patients with haematuria and proteinuria of 0.15 g/day - 1 g/day.
  - C) Steroids can be considered for treatment of patients with crescentic IgA nephropathy, nephrotic syndrome and minimal change lesions on renal biopsy.
  - D) Steroids should be used as first line therapy in all patients with IgA nephropathy.



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## **Answer**

1. D (Pg 35)
2. B (Pg 30)
3. A,B,D (Pg 38)
4. D (Pgs 45, 46)
5. D (Pg 46)
6. C (Pg 48)
7. B,D (Pg 49)
8. C (Pg 65)
9. A,D (Pgs 69, 70)
10. A,C (Pgs 88, 90, 94)

## Workgroup Members

The members of the workgroup, who were appointed in their personal professional capacity, are:

Chairperson            Prof Woo Keng Thye  
Emerius Consultant  
Dept of Renal Medicine  
SGH

Co-chairman            A/Prof A Vathsala  
Sn Consultant & Dir of Renal Transplantation  
Dept of Renal Medicine  
SGH

### Members

Dr Leong See Odd  
Consultant Nephrologist  
Kidney Medical Centre

Dr Chong Hui Lin Lina  
Senior Consultant  
Renal Medicine  
SGH

A/Prof Evan Lee  
Head  
Division of Nephrology  
NUH

Dr Wong Kok Seng  
Head & Senior Consultant  
Dept of Renal Medicine  
SGH

Prof Yap Hui Kim  
Head  
Dept of Paediatric Nephrology  
NUH

Dr Tan Han Khim  
Consultant  
Dept of Renal Medicine  
SGH

Dr Pary Sivaraman  
Consultant  
Dept of Medicine  
NUH

Dr Tan Seng Hoe  
Consultant  
Dept of General Medicine  
TTSH

Dr Stephen Chew Tec Huan  
Stephen Chew Center for Kidney  
Disease & Hypertension  
Mt Elizabeth Medical Centre

Dr Lee Siew Luan Grace  
Consultant Nephrologist  
Grace Lee Renal & Medical Clinic  
Pte Ltd

Subsidiary editors

Dr Pwee Keng Ho  
Assistant Director (Health Technology Assessment)  
Health Services Research & Evaluation Division  
Ministry of Health

Dr Rajni Gupta  
Executive (Health Technology Assessment)  
Health Services Research & Evaluation Division  
Ministry of Health

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CLINICAL TRIALS  
& EPIDEMIOLOGY  
RESEARCH UNIT

Dr Edwin Chan Shih-Yen  
Head of Evidence-Based Medicine  
and  
Director of the Singapore Branch, Australasian Cochrane Centre  
Clinical Trials & Epidemiology Research Unit

Dr Miny Samuel  
Senior Evidence-Based Medicine Analyst  
and  
Co-Director of the Singapore Branch, Australasian Cochrane Centre  
Clinical Trials & Epidemiology Research Unit



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