



# CLINICAL PRACTICE GUIDELINES

## Glomerulonephritis



**NMRC**  
National Medical  
Research Council

**National Committee  
On Renal Care**

Oct 2001

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# **Glomerulonephritis**

**MOH Clinical Practice Guidelines 6/2001**

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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, nor should they be construed as including all proper methods of care or excluding 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

End-stage renal disease (ESRD) is a severe condition which results in substantial morbidity for those afflicted by it. At the same time, the need for treatment with dialysis imposes a large financial burden on patients and on the country as a whole.

We need to do much more to prevent or retard the progression of early renal disease to ESRD.

Nationally, the Ministry of Health is spearheading the coordination of efforts to identify patients at risk of renal failure early, to adopt best clinical practices to prevent or retard the progression of renal disease and to adopt cost-effective strategies for the management of ESRD.

Glomerulonephritis (GN) is the second leading cause of kidney failure in Singapore after diabetes melitus. In the year 1999, GN accounted for 34% of new ESRD patients starting dialysis in Singapore. As part of the national effort to reduce the incidence of ESRD, a special workgroup of the National Committee on Renal Care was formed to produce clinical practice guidelines on GN to assist doctors in the early detection, assessment and management of such patients. The guidelines were formulated after an extensive literature review of the topics and have been adapted for use under local conditions. They address common issues which are very relevant to both primary care physicians and specialists.

These guidelines offer a comprehensive framework for doctors in all sectors to work together to prevent ESRD in Singapore. I hope that all physicians involved in the care of patients with renal disease will benefit from these guidelines and use them actively in their practice.

Finally, I would like to record the Ministry's gratitude to the workgroup and the National Committee on Renal Care for their hard work and commitment in producing the guidelines.

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# 1 Guidelines development and objectives

## 1.1 Guidelines development

These clinical guidelines were developed by a workgroup appointed by the National Committee on Renal Care. They were developed after a review of the available literature to June 2001 and the recommendations were adapted to local practice. When evidence for therapy was not available, the consensus opinion of the members of the workgroup was accepted as recommendations for best clinical practice.

While every effort has been made to provide the best available evidence in the treatment of glomerular disease, local practice was also taken into consideration when arriving at the recommendations. It must be mentioned that these guidelines may require updating when sufficient new evidence becomes available.

## 1.2 Objectives and target group

These guidelines were developed to provide a practical approach to the management of glomerular disease for all doctors.

Chapter 4 on the overview of glomerulonephritis in Singapore gives a general description of the syndromes and conditions that are commonly seen in the country.

General guidelines on the management of asymptomatic haematuria and proteinuria as well as management of other manifestations of glomerular disease such as hypertension, renal impairment and hyperlipidaemia are outlined in chapters 5 and 6. These are likely to be useful for doctors in the primary health care sector as well as in the hospital services. For the primary care physician, these chapters will serve as a guide to identify patients with significant glomerular disease and in further identifying those who require referral to a nephrologist.

The focus of chapters 7 to 12 is on the treatment of specific forms of glomerulonephritis and these chapters provide a consensus statement for the practising nephrologist on their treatment. Chapter 13 covers

the management of nephrotic syndrome in children in particular as this group presents with unique features and problems.

Although the specific treatment of various glomerulonephritides is generally initiated by nephrologists, general practitioners and specialists from other fields are often called upon to co-manage patients with glomerular disease. Thus, these guidelines may also be used by non-nephrologists as a reference guide. An awareness of the underlying renal disease and its management will permit generalists and other specialists co-managing these patients to be aware of potential complications of the disease or its treatment. Better understanding will permit all physicians participating in the care of the patient to minimise complications and optimise care.

## 2 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 trials.
<b>Ib</b>	Evidence obtained from at least one randomised controlled trial.
<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

Grade	Recommendation
<b>A</b> (evidence levels Ia, Ib)	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 IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation.
<b>C</b> (evidence level IV)	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.

### 3 Executive summary of recommendations

#### Management of haematuria and proteinuria

**B** Patients with microscopic haematuria ( $\geq 5$  RBCs/hpf) should be evaluated to exclude renal/urinary tract disease.

**Grade B, Level III**

**B** Urine phase contrast microscopy under standard conditions is recommended to differentiate glomerular from non-glomerular sources of haematuria.

**Grade B, Level III**

**B** Patients with isolated asymptomatic microhaematuria should remain on follow-up at 6-12 month intervals to monitor renal function and blood pressure.

**Grade B, Level III**

**B** Asymptomatic microhaematuria  $< 5$  RBCs/hpf in patients  $< 40$  years of age does not require full urological evaluation in the absence of other clinical features of malignancy.

**Grade B, Level III**

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

**Grade B, Level III**

**B** Patients with intermittent isolated proteinuria have a favourable renal prognosis but should still be followed up six monthly until its resolution.

**Grade B, Level III**

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

**Grade B, Level III**

**B** Patients with persistent proteinuria  $\geq 1$  g/day have adverse renal histopathology and therefore worse ultimate renal prognosis and should undergo renal biopsy.

**Grade B, Level III**

**B** Patients with microhaematuria and proteinuria, especially in the presence of red cell casts, hypertension and/or renal insufficiency should be referred for further nephrological assessment.

**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.

**Grade B, Level III**

## **Management of glomerular disease – General measures**

**B** Hypertension defined as blood pressure  $\geq 140/90$  mmHg in patients with renal disease should be treated in order to retard the rate of deterioration of renal function.

**Grade B, Level IIIb**

**B** A target blood pressure  $< 125/75$  mmHg (Mean arterial pressure  $< 92$  mmHg) is recommended for patients with serum creatinine  $< 600$   $\mu\text{mol/l}$  and total urinary protein excretion  $\geq 1$  g/day.

**Grade B, Level III**

**C** A target blood pressure < 130/80 mmHg (Mean arterial pressure < 98 mmHg) is recommended for patients with serum creatinine < 600 µmol/l and total urinary protein excretion < 1 g/day.

**Grade C, Level IV**

**A** Angiotensin converting enzyme inhibitor therapy is preferable to conventional therapy for treatment of hypertension in patients with glomerulonephritis as it confers greater renoprotection.

**Grade A, Level Ib**

**B** Angiotensin converting enzyme inhibitor therapy is preferable to calcium channel blockers for treatment of hypertension in patients with glomerulonephritis as it confers greater renoprotection.

**Grade B, Level III**

**B** Angiotensin II receptor antagonists can be used as an alternative to Angiotensin converting enzyme inhibitors to treat hypertension in patients with glomerulonephritis.

**Grade B, Level III**

**GPP** Angiotensin converting enzyme inhibitors or Angiotensin II receptor antagonists can be used to reduce proteinuria in patients with glomerulonephritis in the absence of hypertension.

**GPP** For patients with serum creatinine levels > 265 µmol/l, Angiotensin converting enzyme inhibitors and Angiotensin II receptor antagonists should be used with particular caution, with regular monitoring of serum creatinine and potassium.

**A** Patients with severe renal insufficiency (serum creatinine > 350 µmol/l) should be considered for treatment with low protein diets. However, low protein diets should be used judiciously so as to avoid malnutrition and its potential adverse effects.

**Grade A, Level Ia**

**A** Lipid-lowering therapy does not confer renoprotection in patients with glomerular disease.

**Grade A, Level Ib**

**C** Lipid-lowering therapy is recommended for cardiovascular benefit in patients with glomerular disease.

**Grade C, Level IV**

## **Minimal Change Disease**

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

**Grade A, Level Ib**

**A** Prednisolone dose should be tapered after remission in nephrotic syndrome is achieved and subsequently discontinued.

**Grade A, Level Ib**

**B** Cytotoxic therapy with cyclophosphamide can be used in the treatment of frequently relapsing, steroid dependent or steroid resistant nephrotic syndrome due to minimal change disease.

**Grade B, Level III**

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

**A** Cyclosporin A can be used in the treatment of frequently relapsing, steroid dependent or steroid resistant nephrotic syndrome due to minimal change disease.

**Grade A, Level Ib**

**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.

**Grade B, Level III**

## **Focal and Segmental Glomerulosclerosis**

**B** High dose prednisolone should be given as first line therapy for treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis. Prednisolone dose should be tapered slowly after remission is achieved and total treatment duration should be for at least 6 months.

**Grade B, Level III**

**B** Cytotoxic therapy with cyclophosphamide should be considered for patients with steroid dependent nephrotic syndrome due to focal and segmental glomerulosclerosis, or those with steroid-related side effects.

**Grade B, Level III**

**B** Cytotoxic therapy may be considered as alternative therapy in patients with steroid resistant nephrotic syndrome due to focal and segmental glomerulosclerosis.

**Grade B, Level III**

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

**A** Cyclosporin A at starting doses of 3-5 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.

**Grade A, Level Ib**

**C** There is no firm evidence for benefit from other therapies in the treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis.

**Grade C, Level IV**

## **IgA Nephropathy**

**C** No therapy is recommended for patients with IgA nephropathy and isolated haematuria without proteinuria. These patients should be monitored regularly (every 3-12 months) for the development of proteinuria.

**Grade C, Level IV**

**C** No therapy is recommended for patients with IgA nephropathy and asymptomatic haematuria with proteinuria of 0.15 g/day to 1 g/day and no other adverse clinical or histological indicators. Proteinuria should be monitored at 3-12 month intervals.

**Grade C, Level IV**

**A** Angiotensin converting enzyme inhibitor therapy is recommended for treatment of hypertension in patients with IgA nephropathy.

**Grade A, Level Ib**

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

**Grade A, Level Ib**

**B** Angiotensin II receptor antagonists can be used as alternatives to Angiotensin converting enzyme inhibitors in patients with IgA nephropathy for similar indications.

**Grade B, Level IIa**

**B** Angiotensin converting enzyme inhibitors and Angiotensin II receptor antagonists can be used in combination to reduce proteinuria in patients with IgA nephropathy and proteinuria  $\geq 1$  g/day.

**Grade B, Level IIb**

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

**Grade A, Level Ib**

**A** Fish oil supplementation is not beneficial in every patient with IgA nephropathy.

**Grade A, Level Ia**

**C** Fish oil supplementation can be used in patients with IgA nephropathy and proteinuria  $> 3$  g/day.

**Grade C, Level IV**

**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.

**Grade B, Level IIb**

**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.

**Grade B, Level IIa**

**C** Cyclosporin A at an initial dose of 5 mg/kg/day can be initiated 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.

**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.

**Grade C, Level IV**

**GPP** However, response to therapy in these patients is less favourable and over-immunosuppression should be avoided in non-responders.

**C** Standard treatment as for other forms of crescentic glomerulonephritis is recommended for patients with acute renal failure due to crescentic IgA nephropathy. Treatment with methylprednisolone pulse should be followed by oral prednisolone, cyclophosphamide, dipyridamole and warfarin. Plasma exchange and intravenous immunoglobulins can be instituted.

**Grade C, Level IV**

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

**Grade C, Level IV**

**GPP** No specific treatment is recommended in treatment of recurrent IgA nephropathy post renal transplantation. Treatment options are similar to the *de novo* disease.

## Membranous Nephropathy

**C** Patients with membranous nephropathy should undergo evaluation to identify secondary causes. Specifically, evaluation should be performed to exclude secondary causes such as autoimmune conditions, infections, drugs and malignancies.

**Grade C, Level IV**

**B** Patients with idiopathic membranous nephropathy and nephrotic syndrome or Stage III or IV disease on histology should be treated with immunosuppressive therapy as they are at risk for progression to end stage renal failure.

**Grade B, Level IIb**

**B** There is no evidence for benefit with immunosuppressive therapy for those with sub-nephrotic range proteinuria, normal renal function or Stage I or II disease on renal biopsy.

**Grade B, Level IIb**

**B** Patients with idiopathic membranous nephropathy and progressive renal dysfunction should be treated with immunosuppressive therapy.

**Grade B, Level III**

**A** Patients with nephrotic syndrome due to membranous nephropathy may be treated with steroids alone to induce remission of proteinuria.

**Grade A, Level Ib**

**A** There is no evidence for long-term benefit with steroids in the treatment of patients with membranous nephropathy.

**Grade A, Level Ia**

**A** Patients with membranous nephropathy at high risk for progression to end stage renal failure can be considered for treatment with alkylating agents, together with steroids, for 6 months.

**Grade A, Level Ia**

**B** As alkylating agents are associated with drug-related toxicities, patients receiving these agents should be closely monitored during and after therapy.

**Grade B, Level III**

**A** In patients with membranous nephropathy and renal dysfunction, daily oral cyclophosphamide for 12 months, together with steroids, should be considered to prevent renal failure.

**Grade A, Level Ib**

**A** Patients with membranous nephropathy at high risk for progression to end stage renal failure should be treated with 6 months of Cyclosporin A and steroids.

**Grade A, Level Ib**

**A** Patients with membranous nephropathy and progressive renal dysfunction should be treated with 12 months of Cyclosporin A.

**Grade A, Level Ib**

## **Rapidly Progressive Glomerulonephritis**

**A** Patients with rapidly progressive glomerulonephritis due to anti-glomerular basement membrane antibody should be treated with corticosteroids, cytotoxic therapy and plasma exchange.

**Grade A, Level Ib**

**C** Corticosteroid therapy in rapidly progressive glomerulonephritis due to anti-glomerular basement membrane antibody should be with pulse methylprednisolone followed by oral prednisolone.

**Grade C, Level IV**

**A** Daily plasma exchange with 4-L exchanges is recommended in rapidly progressive glomerulonephritis due to anti-glomerular basement membrane antibodies for 14 days or until the antibody disappears.

**Grade A, Level Ib**

**B** Methylprednisolone pulse therapy followed thereafter by oral prednisolone at 1 mg/kg/day is recommended for treatment of pauci-immune rapidly progressive glomerulonephritis.

**Grade B, Level IIa**

**B** Cyclophosphamide can be given orally or by monthly intravenous pulse for treatment of pauci-immune rapidly progressive glomerulonephritis.

**Grade B, Level IIa**

**B** Plasmapheresis should be considered for patients with pulmonary hemorrhage and in those with pauci-immune, rapidly progressive glomerulonephritis and severe renal disease who do not respond to conventional therapy.

**Grade B, Level III**

**B** Rapidly progressive glomerulonephritis due to Wegener's granulomatosis can be treated with either oral or intravenous cyclophosphamide.

**Grade B, Level IIa**

**B** High dose corticosteroids, either oral or pulse therapy, should be used to treat rapidly progressive glomerulonephritis due to Wegener's granulomatosis.

**Grade B, Level IIa**

**B** Plasmapheresis is not likely to be beneficial in patients with rapidly progressive glomerulonephritis due to Wegener's granulomatosis.

**Grade B, Level III**

## Mesangiocapillary Glomerulonephritis

**B** Treatment is recommended for adults and children with idiopathic mesangiocapillary glomerulonephritis and heavy proteinuria, tubulointerstitial disease on renal biopsy or impaired renal function.

**Grade B, Level III**

**A** Children with Type I Mesangiocapillary glomerulonephritis at high risk for progression to renal failure should be treated with high dose corticosteroids.

**Grade A, Level Ib**

**B** Children with Type II Mesangiocapillary glomerulonephritis at high risk for progression to renal failure can be treated with high dose corticosteroids.

**Grade B, Level III**

**B** There is no evidence of benefit with corticosteroids for therapy in adults with mesangiocapillary glomerulonephritis.

**Grade B, Level III**

**A** Cytotoxic therapy is not recommended for the treatment of idiopathic mesangiocapillary glomerulonephritis.

**Grade A, Level Ib**

**B** Dipyridamole and aspirin are recommended for treatment of idiopathic mesangiocapillary glomerulonephritis in adults at high risk for progression to renal failure.

**Grade B, Level III**

## Management of Childhood Nephrotic Syndrome

**A** Children experiencing their first episode of nephrotic syndrome should be treated with prednisolone at 60 mg/m<sup>2</sup>/day (maximum of 80 mg/day) for 4 weeks followed by 40 mg/m<sup>2</sup> of prednisolone every alternate day for 4 weeks and gradual taper over 4 weeks.

**Grade A, Level Ia**

**A** Prednisolone should be given as a single morning dose in treating children with nephrotic syndrome.

**Grade A, Level Ib**

**A** Children with a relapse of nephrotic syndrome should be treated with prednisolone at 60 mg/m<sup>2</sup>/day (maximum of 80 mg/day) (minimum 14 days) until urine is protein free for 3 consecutive days. This should be followed by alternate-day prednisolone of 40 mg/m<sup>2</sup> for 4 weeks, after which prednisolone should be gradually tapered over 4 weeks.

**Grade A, Level Ib**

**C** Children with frequently relapsing nephrotic syndrome can receive relapse therapy during relapses and be maintained on prednisolone 0.1-0.5 mg/kg/alternate days for 3 to 6 months.

**Grade C, Level IV**

**B** A 6-12 month course of Levamisole at 2.5 mg/kg/alternate days can be used for treatment of frequently relapsing nephrotic syndrome in children.

**Grade B, Level IIa**

**A** Cyclophosphamide at 2-2.5 mg/kg/day or chlorambucil at 0.15 mg/kg/day for 8 weeks can be used for the treatment of a relapse of nephrotic syndrome in children with frequent relapses.

**Grade A, Level Ia**

**GPP** For children with steroid dependent nephrotic syndrome, a repeat course of relapse therapy with prednisolone and alternate-day prednisolone 0.1-0.5 mg/kg/alternate days for 6 to 12 months can be administered.

**A** Levamisole at 2.5 mg/kg/alternate days for 6-12 months should be given for children with steroid dependent nephrotic syndrome as for children with the frequently relapsing condition.

**Grade A, Level Ib**

**B** Children with steroid dependent nephrotic syndrome can be treated with cyclophosphamide at 2-2.5 mg/kg/day or chlorambucil at 0.15 mg/kg/day for 8-12 weeks.

**Grade B, Level III**

**A** Cyclosporin A at 6 mg/kg/day should be administered to children with steroid dependent nephrotic syndrome.

**Grade A, Level Ib**

**C** Cyclosporin A therapy can be given for one year in the treatment of steroid dependent nephrotic syndrome.

**Grade C, Level IV**

**C** Renal biopsy is recommended in children with steroid resistant nephrotic syndrome to rule out other glomerular pathology.

**Grade C, Level IV**

**C** Treatment for hyperlipidaemia, symptomatic treatment of severe oedema with diuretics and intravenous albumin is recommended for children with steroid resistant nephrotic syndrome.

**Grade C, Level IV**

**C** Cyclophosphamide 2-2.5 mg/kg/day for 12 weeks can be used for treatment of steroid resistant minimal change nephrotic syndrome in children.

**Grade C, Level IV**

**B** Cyclosporin A 6 mg/kg/day can be used for treatment of childhood steroid resistant nephrotic syndrome.

**Grade B, Level III**

**GPP** Cyclosporin A therapy can be given for 2 years in the treatment of childhood steroid resistant nephrotic syndrome.

## 4 Overview of glomerulonephritis in Singapore

### 4.1 Introduction

The annual incidence of end stage renal failure (ESRF) in Singapore is estimated at 158 per million population.<sup>1</sup> Diabetic nephropathy is the leading cause of ESRF in Singapore while glomerulonephritis (GN) is the second leading cause. The course and prognosis of GN is often dependent on the type of glomerular disease, based on histology, as well as the response to treatment. GN is 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 following provides an overview of GN in Singapore in terms of its clinical presentation, histopathology and management.

### 4.2 Clinical syndromes

Haematuria and proteinuria are the hallmarks of glomerular disease; in addition, hypertension, impaired renal function and fluid retention are present to varying extents. The nature and severity of the underlying glomerular injury often dictate the nature and severity of these symptoms. Furthermore, some glomerular diseases tend to produce particular groups of symptoms that can be classified as a syndrome; thus the mode of presentation can often give clues to the underlying glomerular pathology. The major clinical syndromes of GN are listed in Table 4.1 below:

**Table 4.1 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 the various clinical syndromes, *haematuria and proteinuria*, in isolation or in combination are very common and may afflict as much as 2% of the general population. As only a small proportion of patients with these symptoms or signs has significant glomerular

disease, the vast majority of these patients would not be subjected to a renal biopsy. Patients with these abnormalities should thus undergo full evaluation as described in chapter 5 so as to identify the patients with significant renal disease.

Patients with *acute nephritic syndrome* present with oedema associated with gross haematuria (smoky urine) and hypertension. Often the aetiology is post-infectious GN; Streptococci, other bacteria, viruses and parasites can all cause this entity. As the diagnosis is often made following an infection, a renal biopsy may be deferred. Recovery is the rule and generally patients have a good prognosis with 95% renal survival at 5 years and 90% at 10 years.<sup>2</sup> Treatment is often symptomatic and includes salt and fluid restriction, diuretics, treatment of sepsis, hypertension and heart failure. Where the course is atypical, further investigation with a renal biopsy is indicated. Systemic lupus erythematosus (SLE) or rapidly progressive glomerulonephritis should be kept in mind in these situations.

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 the *nephrotic syndrome* present with the classical triad of oedema, proteinuria ( $> 3$  g/day) and hypoalbuminaemia (serum albumin  $< 30$  g/l). While primary GN 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 GN can also cause nephrotic syndrome as a result of kidney involvement from autoimmune diseases like SLE, cryoglobulinaemia and thyrotoxicosis. Finally, rarer causes such as infections including Hepatitis B, 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 SLE 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.

Among patients undergoing renal biopsies at the Singapore General Hospital between 1987 to 1997, the leading clinical presentations that prompted a renal biopsy were nephrotic syndrome (36%) and asymptomatic haematuria & proteinuria (35%), whilst hypertension was a presenting feature for biopsy in 14% of patients (Table 4.2).<sup>3</sup>

**Table 4.2 Primary Glomerulonephritis: Clinical Presentation (1987 - 1997)\***

<b>Clinical Presentation</b>	<b>No. of Cases</b>	<b>%</b>
Nephrotic Syndrome	238	36
Asymptomatic Haematuria & Proteinuria	236	35
Hypertension	93	14
Acute Nephritis	44	7
Gross Haematuria	26	4
Others	26	4
Chronic Renal Failure	3	<1
<b>Total</b>	<b>666</b>	<b>100</b>

\* Adapted with permission from Woo KT and Chiang GSC.<sup>3</sup>

### 4.3 Histopathological classification

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. The biopsy is useful to help determine the nature and severity of the underlying glomerular pathology, to prognosticate and to guide treatment. A simplified histopathological classification for primary GN is listed in Table 4.3.

**Table 4.3 Histopathological Classification of Glomerulonephritis**

1.	Minimal change disease
2.	Focal global sclerosis
3.	Diffuse mesangial proliferative GN
4.	Focal mesangial proliferative GN
5.	Membranous GN
6.	Mesangiocapillary GN
7.	Crescentic GN (Rapidly progressive GN)
8.	Focal and segmental glomerulosclerosis
9.	Diffuse sclerosing GN

The histological pattern of GN from cases at the Singapore General Hospital is shown in Table 4.4.<sup>3</sup> The commonest diagnoses were Mesangial proliferative GN (Diffuse and focal; 53%) and Focal global sclerosis or Minimal change disease (29%). Detailed guidelines on the management of these glomerular diseases are suggested in the following specific chapters. Among those with Mesangial proliferative GN, 68% were due to IgA nephritis.

**Table 4.4 Primary Glomerulonephritis : Histopathological Presentation (1987 - 1997)\***

<b>Histology</b>	<b>No. of Cases</b>	<b>%</b>
Diffuse mesangial proliferative GN	280	42
Focal global sclerosis	100	15
Minimal change	96	14
Focal mesangial proliferative GN	70	11
Focal and segmental glomerulosclerosis	62	9
Membranous GN	42	6
Crescentic GN	2	<1
Others	14	2
<b>Total</b>	<b>666</b>	<b>100</b>

\* Adapted with permission from Woo KT and Chiang GSC.<sup>3</sup>

Among patients with nephrotic syndrome at the Singapore General Hospital, the histopathological profile is shown in Table 4.5.<sup>3</sup> Minimal change disease (30%) was the commonest with Mesangial proliferative GN being the next commonest (25%).

**Table 4.5 Causes of Nephrotic Syndrome (1987 - 1997)\***

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

\* Adapted with permission from Woo KT and Chiang GSC.<sup>3</sup>

Thus, after analysing the various types of glomerular disease from biopsies of patients at the Singapore General Hospital, IgA nephritis, comprising 45% of GN, is likely the commonest GN in Singapore. Of note is that asymptomatic haematuria and proteinuria is the commonest mode of presentation of this condition. This would suggest that careful screening for glomerular disease and its early identification can lead to prompt and appropriate management. Strategies should be directed at managing the specific conditions so that their progression to end stage renal failure can be ameliorated.

#### **4.4 Principles of treatment of glomerulonephritis**

The management of GN is often targeted at treating several phases of the condition. General management includes treatment of hypertension, oedema and hyperlipidaemia. Specific treatment measures include those directed at the underlying pathology as well as those directed at retardation of progression of renal failure. Often the glomerular pathology can be considered as progressing in two phases:

##### **4.4.1 Immunological phase**

The first acute or early phase is referred to as the immunological phase which is related to the deposition of immune complexes in the glomerulus or in some instances non-immune complex mediated injury or injury due to an antibody directed at glomerular antigens as in Goodpasture's Syndrome.<sup>4</sup> In the immunological phase, noxious cytokines are released which in turn mediate the release of inflammatory chemo-attractants resulting in injury with glomerular scarring.<sup>4</sup> It is this immunological phase that may respond to therapy with immuno-modulating drugs like prednisolone, cyclophosphamide and cyclosporin A (CyA). Induction of remission with agents such as prednisolone or cyclophosphamide, alone or in combination or CyA or other immunosuppressants is the treatment goal in this inflammatory phase.<sup>5,6</sup>

##### **4.4.2 Hyperfiltration phase**

With progression of glomerulosclerosis, a chronic or late phase occurs due to injury resulting from glomerular hyperfiltration.<sup>7</sup> Glomerular hyperfiltration can be recognised by increasing proteinuria or emergence of a second phase of proteinuria which may be associated

with renal deterioration (elevated serum creatinine) and hypertension. It is this phase that may be amenable to therapy with angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor antagonist (ATRA) as well as dietary protein restriction.<sup>7-11</sup> This is what is termed secondary therapy, which aims at retardation of the progression to ESRF. The rationale for the use of these agents is that ACE inhibitor would reverse Angiotensin II mediated vasoconstriction of the efferent glomerular arteriole and ATRA would prevent the action of angiotensin II by blocking the Angiotensin II receptors.

High protein diet has been suggested as a cause of increased macro-molecular traffic at the afferent glomerular arteriole which in turn induces deposition of the macro-molecules in the mesangial bed and incites proliferation of mesangial cells and matrix. A restricted or low protein diet is suggested to decrease the afferent glomerular vasodilation associated with hyperfiltration.<sup>7-9,11,12</sup> These therapies decrease afferent glomerular blood flow to the glomeruli and cause efferent glomerular arteriolar vasodilation. This in turn results in a decrease in intra-glomerular hypertension that occurs as a consequence of glomerular hyperfiltration and leads to decrease in proteinuria. The associated endothelial cell and platelet damage associated with hyperfiltration is also decreased when the glomeruli are subjected to a lowered intra-glomerular hypertension with the reduction of 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 kidney failure can be ameliorated.

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## 5 Management of haematuria and proteinuria

### 5.1 Introduction

Glomerulonephritis (GN) is the second leading cause of end stage renal failure (ESRF) in Singapore. Early detection of glomerular disease by screening and its early treatment is likely to reduce the incidence of ESRF. Haematuria, generally microscopic, and proteinuria are hallmarks of glomerular disease and they can be detected by urinalysis. Screening with urinalysis can be undertaken at the primary health care level and also opportunistically in other health care settings. In addition to screening, urinalysis can also be used to serially monitor the activity and severity of glomerular disease in those with confirmed, established renal disease, and its response to therapy.

This chapter deals with the interpretation and further diagnostic steps required in the presence of haematuria and/or proteinuria on urinalysis at the primary health care level. Most of the available data are from non-randomised, uncontrolled studies with the majority being single centre prospective or retrospective series. To date, there have been no prospective, randomised, controlled studies in the area of urinalysis interpretation and renal outcome assessment.

### 5.2 Microscopic haematuria

**B** Patients with microscopic haematuria ( $\geq 5$  RBCs/hpf) should undergo evaluation to exclude renal/urinary tract disease.

Grade B, Level III

Asymptomatic microscopic haematuria is defined as the presence of  $\geq 5$  erythrocytes per high power field (RBCs/hpf) on urine microscopy of unspun urine in subjects without any urinary tract symptoms, but having a positive dipstick test for microscopic haematuria.<sup>1</sup> Patients with gross haematuria, urinary tract infections and menstruating women should be re-evaluated after the intercurrent episode has resolved. 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

where clues to the presence of glomerular disease can be elicited (Tables 5.1 and 5.2).<sup>1</sup>

**Table 5.1 History for Patients with Haematuria**

<b>History</b>	
◆	Urinary Symptoms: <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>
◆	Past Medical History: <ul style="list-style-type: none"> <li>● Lower or upper urinary tract infections (pyelonephritis)</li> <li>● Autoimmune diseases</li> <li>● Sexually transmitted diseases pre-disposing to urethritis and urethral stricture</li> <li>● Previous renal or extra-renal tuberculosis</li> <li>● Pelvic oncological radiotherapy</li> <li>● Renal trauma</li> </ul>
◆	Drug History: <ul style="list-style-type: none"> <li>● Warfarin</li> <li>● Non steroidal anti inflammatory drugs</li> <li>● Previous cytotoxic/immunosuppressive therapy</li> <li>● Industrial carcinogen exposure</li> <li>● Smoking, drugs that may cause a false positive dipstick reaction such as certain antiseptic solutions</li> </ul>
◆	Family History of: <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>
◆	Others: <ul style="list-style-type: none"> <li>● Recent upper respiratory tract infection (URTI) or tonsillitis suggesting post-infectious GN</li> <li>● Ongoing URTI and/or gastroenteritis, suggesting IgA nephropathy</li> <li>● Constitutional symptoms such as myalgia, arthralgia and cutaneous rash, suggesting Henoch-Schonlein purpura or Crescentic GN</li> <li>● Diabetes mellitus and diabetic nephropathy</li> <li>● Evidence of a bleeding diathesis</li> </ul>

**Table 5.2 Physical Examination and Laboratory Evaluation for Patients with Haematuria**

<b>Physical Examination</b>	
◆	Blood pressure
◆	Skin examination for purpura, digital vasculitis
◆	Throat/tonsil inspection
◆	Cardiac auscultation for murmurs
◆	Signs of pulmonary and peripheral fluid overboard
◆	Abdominal examination for enlarged, ballotable kidneys or other organomegaly
◆	Digital rectal examination of the prostate in males
<b>Initial Laboratory Investigations</b>	
◆	Full blood count
◆	Renal function test: 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 to clarify the aetiology of microhaematuria</li> </ul>
◆	Urine phase contrast microscopy

**B** Urine phase contrast microscopy under standard conditions is recommended to differentiate glomerular from non-glomerular sources of haematuria.

**Grade B, Level III**

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>2</sup> Those with predominantly isomorphic or mixed isomorphic and dysmorphic haematuria should be evaluated for urological disease (vide infra).<sup>2,3</sup> In subjects with predominantly dysmorphic urinary RBCs ( $\geq 90\%$ ), the underlying pathology is likely to be non-urological, i.e. reno-parenchymal, and long-term follow-up is advocated.<sup>2</sup>

**B** Patients with isolated asymptomatic microhaematuria should remain on follow-up at 6-12 month intervals to monitor renal function and blood pressure.

**Grade B, Level III**

In those with persistent isolated microhaematuria, follow-up is recommended since data suggests that there is a 10.6% chance of them subsequently developing concomitant proteinuria during the

course of follow-up.<sup>4</sup> Nephrological referral should be initiated in patients with microhaematuria if there are, in addition, concomitant red cell casts, renal insufficiency or proteinuria.<sup>1</sup> Histopathologically, the commonest diagnoses in patients with isolated asymptomatic microhaematuria in one series are IgA nephropathy and thin basement membrane disease.<sup>5</sup> There is, however, no data to support routine diagnostic renal biopsy solely on the basis of asymptomatic isolated microhaematuria and in the absence of other clinical findings such as hypertension and/or significant proteinuria.<sup>1</sup> Hence, after an initial assessment, patients may be discharged by the nephrologist for follow-up by the general practitioner. The general practitioner should then continue to monitor both the blood pressure and urinalysis results biennially for these patients.<sup>1</sup> Figure 5.1 provides a flow chart on the management of haematuria.

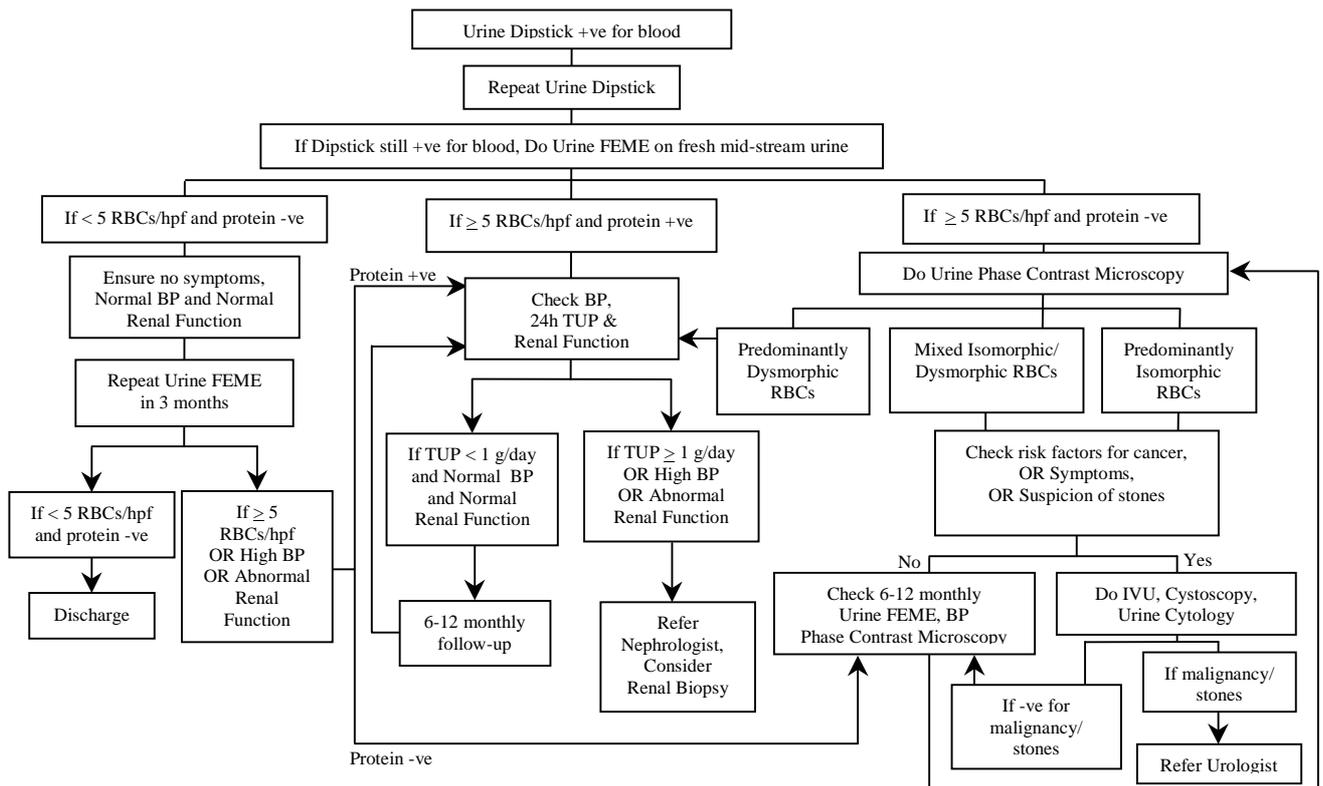
**B** Asymptomatic microhaematuria < 5 RBCs/hpf in patients < 40 years of age does not require full urological evaluation in the absence of other clinical features of malignancy.

**Grade B, Level III**

Ideally every case of isolated microhaematuria should be investigated urologically to exclude malignancy. However, from a meta-analysis, the cost-benefit is likely to be low as the incidence of malignancy is < 3%.<sup>6,7</sup> In one series, it was found that the incidence of urological malignancies ranged from 0.09 to 0.1% in subjects with isolated asymptomatic microhaematuria. Nevertheless, it is recommended that patients with asymptomatic isolated microhaematuria but who are < 40 years of age, do not need to undergo full urological evaluation in the absence of other indications.<sup>8,9</sup> Finally, any male patient with a first episode of microscopic haematuria in the context of proven urinary tract infection should still be referred for urological assessment.<sup>1</sup>

In the absence of contraindications, intravenous urography (IVU) is the recommended initial imaging of choice and may be complemented by ultrasonography. With a negative or equivocal sonographic result, flexible cystourethroscopy is still required to definitively evaluate the bladder and lower urinary tract for malignancy.<sup>1</sup> The reason for this is that ultrasonography fails to detect smaller urothelial tumours in the bladder and upper urinary tract.<sup>1</sup>

**Figure 5.1 Approach to Haematuria**



## 5.3 Proteinuria

### 5.3.1 Orthostatic proteinuria

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

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 proteinuria 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>11</sup> Following this re-evaluation, the patient can be classified as having either intermittent or persistent proteinuria as described below.

### 5.3.2 Intermittent proteinuria

**B** Patients with intermittent isolated proteinuria have a favourable renal prognosis but should still be followed up six monthly until its resolution.

Grade B, Level III

Patients with urine dipstick positive for proteinuria on *one of two* dipstick tests performed on early morning urine samples collected one week apart have intermittent proteinuria. These patients need to be seen and dipstick tested six months later and then tested annually thereafter until resolution of proteinuria. As part of their follow-up, the patients' blood pressure, urinalysis, serum urea, creatinine and electrolytes should all be checked concomitantly (Table 5.3).<sup>10</sup> Subjects with intermittent proteinuria have a good renal prognosis and data suggests that proteinuria usually resolves within 5 years of onset.<sup>10</sup>

**Table 5.3 History, Physical Examination and Laboratory Evaluation for Patients with Proteinuria**

<b>History</b>	
<ul style="list-style-type: none"> <li>◆ Urinary Symptoms:               <ul style="list-style-type: none"> <li>● Dysuria, frequency suggestive of urinary tract infection</li> <li>● Ureteric or renal colic</li> <li>● Symptoms suggestive of bladder outlet obstruction</li> </ul> </li> <li>◆ Past Medical History:               <ul style="list-style-type: none"> <li>● Adult polycystic kidney disease (APCKD)</li> <li>● Reflux nephropathy</li> </ul> </li> <li>◆ Drug History:               <ul style="list-style-type: none"> <li>● Gold, penicillamine and captopril in relation to secondary membranous nephropathy</li> <li>● Non Steroidal Anti-inflammatory Drugs and penicillins in relation to (allergic) interstitial nephritis</li> </ul> </li> </ul>	
<b>Physical Examination</b>	
<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>◆ Oedema</li> </ul>	
<b>Initial Laboratory Investigations</b>	
<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, electrolyte, creatinine and fasting glucose (in the presence of glycosuria)</li> <li>◆ 24 hour urine collection for quantification (24h TUP) <u>OR</u> Random or spot urinary protein and creatinine measurement to derive the urinary protein/creatinine ratio</li> <li>◆ Exclusion of monoclonal gammopathy in subjects &gt; 45 years of age</li> <li>◆ Referral to a Nephrologist is indicated in the following two clinical situations:               <ul style="list-style-type: none"> <li>● 24h TUP &gt; 500 mg/l or urinary protein/creatinine ratio &gt; 30 mg/mmol</li> <li>● 24h TUP &gt; 250 mg/l or urinary protein/creatinine ratio &gt; 20 mg/mmol and co-existent elevated serum creatinine or hypertension</li> </ul> </li> </ul>	
<b>Nephrological Evaluation</b>	
<ul style="list-style-type: none"> <li>◆ Ultrasound of the kidneys to evaluate structure and size</li> <li>◆ Urine phase contrast microscopy, as clinically indicated</li> <li>◆ 24h urinary creatinine clearance (CCT)</li> <li>◆ Renal biopsy (24h TUP <math>\geq</math> 1 g/day) in non-diabetics</li> </ul>	

### 5.3.3 Persistent proteinuria

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

Grade B, Level III

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 5.3 since they have a worse renal prognosis with a higher risk of subsequently developing hypertension and renal insufficiency within ten years of follow-up.<sup>10</sup> Mandatory follow-up of such patients should include blood pressure and renal function assessment at regular intervals. Figure 5.2 provides an algorithmic approach to management of patients with proteinuria.

**B Patients with persistent proteinuria  $\geq 1$  g/day have adverse renal histopathology and therefore worse ultimate renal prognosis and should undergo renal biopsy.**

**Grade B, Level III**

There is no data comparing renal outcomes in relation to timing of renal biopsy for those with 24 hour urinary protein (TUP)  $\geq 1$  g/day vs. TUP  $\geq 2$  g/day. Nevertheless, data from Lim et al suggest that 24h TUP  $\geq 1$  g/day correlates with adverse renal histology and therefore, would represent a useful threshold for biopsy.<sup>12</sup> Patients suspected to have diabetes mellitus and incipient diabetic nephropathy should be screened for albuminuria as well.<sup>10</sup>

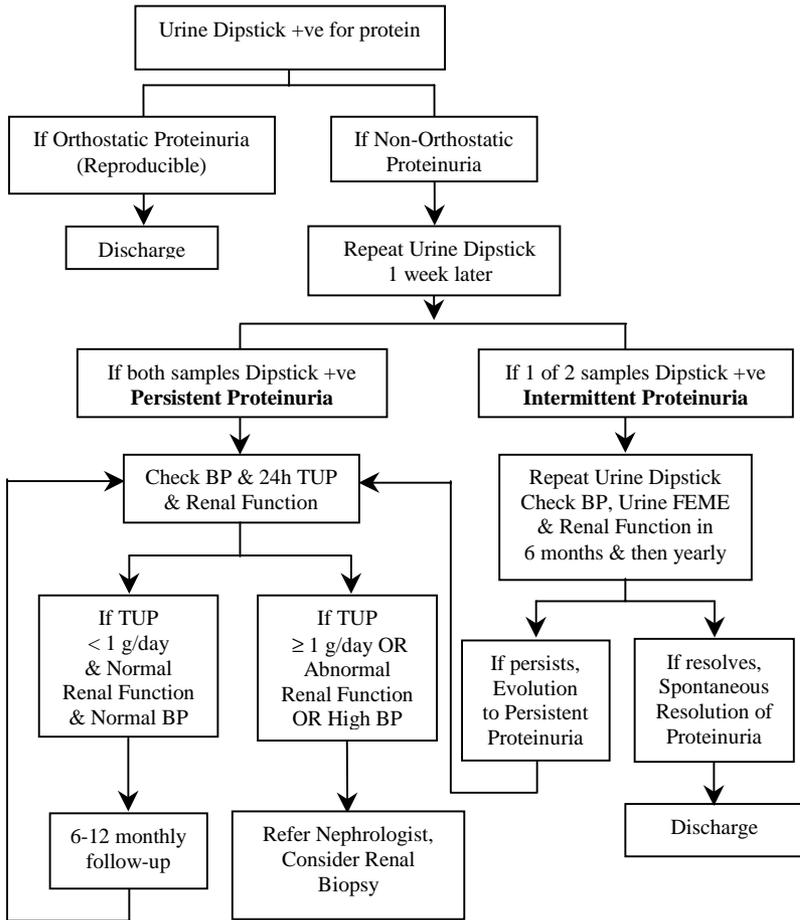
## **5.4 Microhaematuria and proteinuria**

**B Patients with microhaematuria and proteinuria, especially in the presence of red cell casts, hypertension and/or renal insufficiency should be referred for further nephrological assessment.**

**Grade B, Level III**

Patients with microhaematuria as well as proteinuria need to be referred for nephrological assessment, particularly if there are signs of renal parenchymal involvement such as renal insufficiency and urinary red cell casts.<sup>1</sup> Combined microhaematuria and proteinuria is the commonest mode of presentation of GN.<sup>13</sup> According to one series, secondary GN accounted for 9% of such cases and primary GN was found in 91% of such subjects.<sup>13</sup>

**Figure 5.2 Approach to Proteinuria**



Unfavourable prognostic indices include: hypertension, severe proteinuria > 2 g/day and histological changes such as crescents in the renal biopsy. Among the different primary glomerulonephritides, the commonest histopathological type associated with microhaematuria and proteinuria is IgA nephropathy.<sup>5,13-15</sup> Prognostically, the severity of proteinuria has a more important correlation than microscopic haematuria with the histopathological type and grade and thus ultimate renal prognosis. In addition, there is no correlation between the severity of haematuria and severity of the histopathological changes. In contrast, proteinuria > 1 g/day is significantly associated with the concomitant presence of granular casts ( $p < 0.001$ ) which in turn correlates with the presence of glomerular sclerosis ( $p = 0.005$ ). The evidence suggests that proteinuria of 1 g/day is a useful predictive index of glomerular sclerosis.<sup>12</sup> This also represents the threshold for diagnostic renal biopsy in the course of nephrological follow-up.

In addition to being a marker of renal disease, proteinuria per se is an important adverse risk factor for renal disease progression, since it has itself been linked to the aggravation of renal injury.<sup>16</sup> Therapeutically, it is an equally important target to lower as is blood pressure, in the retardation of renal failure progression.<sup>17</sup>

## 5.5 Gross Haematuria

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

Grade B, Level III

All patients with gross haematuria should 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>18,19</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>1,9</sup>

## 5.6 Summary

An algorithmic approach to the management of haematuria and proteinuria is given in Figures 5.1 and 5.2. With appropriate screening and investigation, early diagnosis and management of glomerulonephritis can be initiated.

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## 6 Management of glomerular disease - General measures

### 6.1 Introduction

Haematuria and proteinuria are hallmarks of glomerular disease. Though some types of glomerular disease such as minimal change disease are relatively benign with a good prognosis, others have a slow progressive course and may be associated with hypertension and progressive renal failure. Oedema may also be present in various degrees if there is nephrotic range proteinuria or renal impairment. Those with nephrotic syndrome may also suffer from complications such as hyperlipidaemia and the hypercoagulable state. Thus, in the general management of glomerular diseases, treatment measures should be directed at treating the associated features of the condition, especially hypertension. Diuretics with appropriate potassium supplementation should be administered to treat oedema in patients with the nephrotic state. Nephrotic patients, especially those with severe forms of membranous nephropathy, are at higher risk for thrombosis and may benefit from prophylactic anticoagulation. However, among the most important complications of glomerular disease is that related to the progression of renal dysfunction.

Many types of GN are associated with a progressive course culminating in ESRF.<sup>1</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 ESRF. Reduction in renal function from whatever aetiology results in adaptive changes that contribute to hyperfiltration of the remaining glomeruli. The resulting glomerular hypertension may lead to ultimate loss of the remaining nephrons and is likely to be mediated by a variety of non-immunologic factors such as intra-glomerular hypertension, glomerular hypertrophy, abnormal flux of macromolecules through the mesangial areas and factors associated with tubulointerstitial damage.<sup>2</sup>

Apart from eradication or control of underlying disease, consideration should be given to non-specific measures designed to ameliorate the pathophysiologic processes contributing to progressive renal damage. The following recommendations refer to non-specific renoprotective

interventions that have been studied and these include blood pressure control, antihypertensive medications, low protein diets (LPDs), and lipid-lowering agents.<sup>3</sup>

## 6.2 Blood pressure management

**B** Hypertension defined as blood pressure  $\geq 140/90$  mmHg in patients with renal disease should be treated in order to retard the rate of deterioration of renal function.

Grade B, Level IIb

Control of blood pressure (BP) remains the cornerstone of therapy to retard the progression of renal failure in virtually all forms of renal disease.<sup>4,6</sup> However, there have been no good controlled trials to date that have examined the impact of good control of BP on the progression of renal failure. In a prospective study in which patients were being followed up for other reasons, a correlation between BP control and slowing of deterioration of renal function was observed.<sup>4</sup> A significantly slower rate of renal deterioration was associated with diastolic BP of less than 90 mmHg in a retrospective study.<sup>5</sup> Another study showed the rate of rise of serum creatinine was significantly faster in hypertensive than in normotensive subjects.<sup>6</sup>

## 6.3 Target blood pressure

**B** A target blood pressure  $< 125/75$  mmHg (Mean arterial pressure  $< 92$  mmHg) is recommended for patients with serum creatinine  $< 600$   $\mu\text{mol/l}$  and total urinary protein excretion  $\geq 1$  g/day.

Grade B, Level III

**C** A target blood pressure  $< 130/80$  mmHg (Mean arterial pressure  $< 98$  mmHg) is recommended for patients with serum creatinine  $< 600$   $\mu\text{mol/l}$  and total urinary protein excretion  $< 1$  g/day.

Grade C, Level IV

The Modification of Diet in Renal Disease (MDRD) study, a randomised controlled trial, was designed to examine the impact of

different target BP on renal disease progression.<sup>7</sup> In the overall study, there was no difference in the rate of glomerular filtration rate (GFR) decline in the usual BP (Mean arterial pressure, MAP, 107 mmHg) versus low BP (MAP 92 mmHg) in patients randomised to a control diet or LPD.<sup>7</sup> Subgroup analysis showed renal benefit in patients with total urinary protein excretion (TUP) > 1 g/day and greater benefit in those with TUP > 3 g/day. However, tight BP control did not appear to alter the rate of renal deterioration in patients with no proteinuria. No significant difference was observed between the usual and low BP groups randomised to either a low protein or a very low protein diet plus essential amino acids in the absence of proteinuria. Thus, the MDRD study suggested that more aggressive BP control should be instituted in patients with higher degrees of proteinuria, a finding more likely to be seen in those with glomerular disease. Current guidelines by the World Health Organisation-International Society of Hypertension likewise recommend lower targets for BP control in patients with proteinuria  $\geq 1$  g/day.<sup>8</sup>

## 6.4 Choice of anti-hypertensive medication

**A** Angiotensin-converting enzyme inhibitor therapy is preferable to conventional therapy for treatment of hypertension in patients with glomerulonephritis as it confers greater renoprotection.

Grade A, Level Ib

Any agent, alone or in combination, that satisfactorily controls blood pressure can be used. Sodium restriction is also important for the control of BP. However, several studies suggest that an Angiotensin converting enzyme (ACE) inhibitor is the drug of choice. A large prospective study reported significantly fewer Benazepril-treated patients with renal dysfunction and target diastolic BP < 90 mmHg developing doubling of serum creatinine compared to placebo-treated after 3 years of follow-up.<sup>9</sup> The overall risk reduction was 53%. A greater risk reduction was observed in men, patients with glomerular disease and those with TUP > 1 g/day. The REIN study comparing Ramipril, an ACE inhibitor, to placebo, also demonstrated a better outcome for patients on ACE inhibitors.<sup>10</sup> Ramipril provided further renoprotection in patients with TUP > 3 g/day even when BP was optimally controlled.<sup>11</sup> Beta-blocker treated patients with initial serum creatinine of 200 to 400  $\mu\text{mol/l}$  had an increased relative risk of 3.3 for reaching renal death compared to the Enalapril-treated

patients.<sup>12</sup> The latter also showed a slower rate of decline in the reciprocal plot 1/Serum Creatinine and a fall in TUP that was not seen with beta-blocker therapy. ACE inhibitor therapy has also been demonstrated by other studies to be more renoprotective than beta-blocker therapy.<sup>13-16</sup>

**B** Angiotensin-converting enzyme inhibitor therapy is preferable to calcium channel blockers for treatment of hypertension in patients with glomerulonephritis as it confers greater renoprotection.

Grade B, Level III

With regards to the efficacy of ACE inhibitors over calcium channel blockers (CCBs), a small prospective study showed that Enalapril and Nifedipine both maintained renal function over 1 year.<sup>17</sup> In a longer comparative study, patients treated with either Captopril or Nifedipine had a significantly slower rate of decline in renal function compared to patients treated with one-year baseline conventional therapy.<sup>18</sup> A small study showed that patients treated with dihydropyridine CCBs had a faster decline in renal function than Enalapril-treated patients when the blood pressure reduction was only modest.<sup>19</sup> Though difficult to extrapolate to other forms of glomerular disease, in a randomised controlled trial of Ramipril versus Amlodipine on renal outcomes in hypertensive nephrosclerosis, the Ramipril group had a 36% slower mean decline in GFR over 3 years.<sup>20</sup> Furthermore, as many reports on dihydropyridine CCBs suggest that these antihypertensive drugs do not reduce proteinuria, ACE inhibitors are preferred for antihypertensive therapy in patients with glomerular disease as they confer renoprotection.<sup>21</sup>

**B** Angiotensin II receptor antagonists can be used as an alternative to Angiotensin converting enzyme inhibitors to treat hypertension in patients with glomerulonephritis.

Grade B, Level III

Angiotensin II receptor antagonists (ATRA) are also antihypertensive and have anti-proteinuric effects similar to that of ACE inhibitors.<sup>22</sup> They are renoprotective in experimental nephropathy.<sup>23</sup> Two controlled clinical trials in Type 2 diabetes have confirmed renoprotection by Losartan and Irbesartan respectively and are thus

likely to be useful in glomerular disease.<sup>24,25</sup> Therapy with ATRA is thus recommended as an alternative to ACE inhibitor and is especially useful in patients who are intolerant of ACE inhibitor from symptoms of hyperkalaemia, cough, angioedema or hypersensitivity.

**GPP** Angiotensin converting enzyme inhibitors or Angiotensin II receptor antagonists can be used to reduce proteinuria in patients with glomerulonephritis in the absence of hypertension.

As suggested by the above, ACE inhibitors and more recently ATRA have been suggested to reduce proteinuria in many glomerular diseases independent of blood pressure control.<sup>10-11,25,26</sup> However, clinical studies on the efficacy of these drugs to confer renoprotection in the absence of hypertension are lacking. In clinical practice, the therapeutic goal of ACE inhibitors or ATRA is a reduction in proteinuria by  $\geq 50\%$  from the pre-treatment value.

**GPP** For patients with serum creatinine levels  $> 265 \mu\text{mol/l}$ , Angiotensin converting enzyme inhibitors and Angiotensin II receptor antagonists should be used with particular caution, with regular monitoring of serum creatinine and potassium.

Renal impairment or chronic renal failure is not a contraindication for the use of ACE inhibitors or ATRA. A combination of ACE inhibitor and ATRA may be required to achieve this goal. Initiation of ACE inhibitor or ATRA therapy should be postponed in patients with hypovolemia or hyperkalemia until the conditions are corrected and is contraindicated in patients with renal artery stenosis. Caution should be exercised when initiating and maintaining these drugs in patients with abnormal renal function as hyperkalemia and acute deterioration of renal function (in patients with undetected renal artery stenosis) can ensue. Serum creatinine and potassium levels should be assessed within three to seven days after initiation of ACE inhibitors in patients with renal impairment.

## 6.5 Dietary protein restriction

**A** Patients with severe renal insufficiency (serum creatinine > 350  $\mu\text{mol/l}$ ) should be considered for treatment with low protein diets. However, low protein diets should be used judiciously so as to avoid malnutrition and its potential adverse effects.

Grade A, Level Ia

Dietary protein restriction has been suggested to reduce the metabolic load of nitrogen as well as to reduce compensatory hyperfiltration. In the first prospective randomised controlled study, LPD (0.4 to 0.6 g protein/kg/day) were found to be beneficial in retarding renal deterioration, with the greatest benefit for the group with the lowest renal function.<sup>27</sup> Subgroup analysis showed a benefit only for patients with glomerulonephritis. In another study, there was a trend to fewer end points i.e. doubling of serum creatinine or the need for dialysis, in patients with renal dysfunction on LPD (0.6 g protein/kg/day).<sup>28</sup> Significant renal benefit was shown only in LPD-treated patients with initial plasma creatinine of 222 to 442  $\mu\text{mol/l}$ . The MDRD study showed no significant difference between normal and LPD (1.3 vs. 0.58 g protein/kg/day) in influencing the rate of GFR decline over a mean follow-up of 2.2 years in a cohort of patients with initial GFR of 25 to 55 ml/min.<sup>29, 7</sup> There was no correlation between GFR decline and actual protein intake. In a smaller study, significantly fewer patients on LPD (0.4 g protein/kg/day) with entry serum creatinine greater than 350  $\mu\text{mol/l}$  developed ESRF after a follow-up period of 18 months.<sup>30</sup> Patients with the lowest initial renal function appeared to derive most benefit from LPD.<sup>27,31</sup> In two meta-analyses of low protein diets in moderate to severe renal failure, reducing protein intake reduced the occurrence of renal death by about 40% as compared with higher or unrestricted protein intake.<sup>32, 33</sup>

Despite numerous studies, the optimal level of protein intake has not been determined. As poor dietary compliance with the dietary restriction and nutritional safety of LPDs remain two major concerns, dietary protein restriction to 0.8 g protein/kg/day is recommended to retard progression of renal failure in patients with serum creatinine of more than 350  $\mu\text{mol/l}$ .

## 6.6 Lipid-lowering therapy

**A** Lipid-lowering therapy does not confer renoprotection in patients with glomerular disease.

Grade A, Level Ib

There is a higher prevalence of hyperlipidaemia among patients with renal disease than in the general population. The type and level of hyperlipidemia varies with the type of renal disease and the level of renal function.<sup>34</sup> On the one hand, control of lipids has been thought to be renoprotective as experimental studies have suggested that LDL cholesterol is deposited and oxidised in the glomeruli and may be implicated in the development of glomerulosclerosis by facilitating excessive mesangial-matrix production.<sup>34</sup> However, four interventional studies of non-diabetic nephropathy and hyperlipidaemia failed to show significant lowering of proteinuria or change in the rate of deterioration in renal function when effective lowering of serum cholesterol by Lovastatin was achieved in the long term.<sup>35-38</sup> There are concerns about toxicity of lipid-lowering drugs as Clofibrate has been associated with toxicity in patients with reduced renal function. The use of a combination of lipid-lowering drugs and Cyclosporine in renal transplants has resulted in muscle toxicity and acute renal failure.<sup>39-42</sup>

**C** Lipid-lowering therapy is recommended for cardiovascular benefit in patients with glomerular disease.

Grade C, Level IV

Nevertheless, cardiovascular disease is the leading cause of mortality among patients with renal disease. There is conclusive evidence that controlling blood lipids protects against atherosclerosis.<sup>43</sup> While there are few randomised clinical trials studying the effects of lipid lowering therapy on cardiovascular mortality in patients with renal disease, inferences may be drawn from its benefits in the general population. As such, appropriate measures should be instituted so as to modify other known risk factors for cardiovascular disease including hyperlipidaemia in patients with renal disease.<sup>34, 44</sup>

## 6.7 Summary

Recent large interventional studies have indicated hypertension, heavy proteinuria, and initial serum creatinine as predictors of unfavourable long-term outcome in patients with renal disease. Underlying renal disease such as nephrosclerosis is associated with the slowest rate of renal deterioration and polycystic kidney disease with the fastest. Glomerular diseases benefit the most from control of hypertension and LPDs. Blood pressure control is consistently most renoprotective especially in the presence of significant proteinuria. ACE inhibitor therapy appears to be superior to conventional therapy or calcium channel blockers in retarding the rate of renal deterioration and in preventing the need for dialysis. Alternatively, ATRA may also be used for similar indications. Patients with poor renal function may benefit more from LPDs. Serum lipid levels have not been found to have a positive impact on renoprotection in humans, but are nevertheless important for overall reduction of cardiovascular mortality in patients with glomerular disease.

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## 7 Minimal change disease

### 7.1 Introduction

Minimal change disease (MCD) is an idiopathic glomerular disease that occurs in up to 20% to 43 % of cases of adult nephrotic syndrome (NS).<sup>1,2</sup> It is characterised by an acute onset of oedema and facial swelling with or without ascites. Renal function is usually normal at presentation. Hypertension is uncommon and occurs in between 13-30% of cases; however, this is usually not persistent and resolves with treatment of the underlying disease. Albuminuria is the predominant form of urinary protein excreted (i.e. selective proteinuria); microhaematuria is rare and red cell casts are absent. The histological hallmark is the relative paucity of glomerular or tubular abnormalities. 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

The actual rate of spontaneous resolution of the disease has been estimated to be between 10-75% of cases; however, awaiting this spontaneous resolution is impractical as the disease can persist for months to years. It has an excellent long-term renal outcome, with less than 5% of cases going into end stage renal failure. Minimal change disease is characterised by multiple relapses and remissions of the NS; it also shows marked sensitivity to corticosteroid (CS) therapy. Despite adequate steroid therapy, relapse rates in adults can vary from 70 to 80%, similar to that in children. However, the incidence of frequently-relapsing disease or steroid-dependent disease is less likely in adults as compared to children. If untreated, the disease is associated with progressive malaise, anasarca, malnutrition, thromboembolism and a predisposition to infection.

### 7.3 Disease patterns

The disease is classified into steroid responsive vs. steroid resistant, based on its response to steroid therapy. However, these terms are less well defined in adults unlike in children.<sup>3</sup> Specifically the duration of steroid therapy after which the disease is accepted as being steroid resistant varies with different studies. Steroid resistance is

defined by Meyrier as persistence of NS after 4 months of prednisolone, whereas, it is defined by Ponticelli as persistence of NS after 6 weeks of therapy.<sup>4,5</sup> Most authors would accept a complete remission as the absence of proteinuria plus normal serum albumin levels, partial remission as proteinuria of 0.5 to < 3 g/day in a 24-hour urine collection. A frequent relapser is defined as one who has either  $\geq 2$  relapses in 6 months or  $\geq 3$  relapses in 12 months.

## 7.4 Treatment of minimal change disease

Several immunosuppressive therapies have been used in the treatment of nephrotic syndrome to achieve a cure. These include:

- Corticosteroids
- Alkylating agents
- Cyclosporin A

### 7.4.1 Corticosteroids

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

Grade A, Level Ib

Corticosteroids form the mainstay of therapy of NS due to MCD. Black, in a prospective controlled trial (using a mean starting dose of 26 mg/day of prednisolone for a treatment duration of 6 to 48 months), reported a complete remission rate of 80%.<sup>6</sup> Unfortunately the actual spontaneous remission rate in the control arm could not be determined as some patients also received prednisolone in the follow-up period. 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 77% to 97%.<sup>2,7-10</sup>

**A** Prednisolone dose should be tapered after remission in nephrotic syndrome is achieved and subsequently discontinued.

Grade A, Level Ib

Dosing regimens as well as duration of the steroid taper differ between the studies. Imbasciati treated 89 patients (67 children and 22 adults) with MCD in a prospective controlled trial.<sup>11</sup> He compared the

relative efficacy of either high-dose oral prednisone for 4 weeks followed by low-dose oral prednisone for 5 months against a second regimen using 3 intravenous methylprednisolone pulses, followed by low-dose oral prednisone for six months. There were no significant differences in complete remission rates (94% vs. 97%) nor in relapse rates (68% vs. 64%); nevertheless, the time to response was shorter in the methylprednisolone group, as well as in children. Nolasco 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>12</sup> He 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>7,8</sup> Korbet and Fujimoto achieved complete remission in 91% and 97% respectively, using high dose steroids.

The time to remission after starting treatment was longer for older patients. Fujimoto reported a 76% response rate at 8 weeks, compared to 51% to 60% in other series.<sup>5,6,10</sup> Patients were younger (27.7 years) in Fujimoto's series compared to that of Nolasco (42 years) and Korbet (41 years).

Alternate day steroid therapy has also been used to induce remission in NS due to MCD, in order to reduce the incidence of steroid complications. 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>2</sup> Nair used prednisolone at 2 mg/kg/day on alternate days for 6 to 12 weeks, tapering this off over 13 weeks.<sup>13</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. Although this regimen was effective, the prolonged duration of therapy implied that the total amount of corticosteroids used was not lower in comparison to daily corticosteroid therapy.

It is recommended that patients with NS due to MCD should be started on prednisolone at 1 mg/kg/day. High dose therapy should be given for at least 4 weeks and extended up to 8 weeks before considering a patient a non-responder. Steroid therapy should be tapered slowly over the subsequent 2 to 6 months. Alternate day prednisolone may be used during the steroid taper.

In patients who relapse after an initial remission, a second course of corticosteroids may be administered. After achieving a remission, steroids should be tapered slowly and low-dose, alternate day prednisolone should be continued for 6-12 months in relapsers.

## 7.4.2 Alkylating Agents - Cyclophosphamide

**B** Cytotoxic therapy with cyclophosphamide can be used in the treatment of frequently relapsing, steroid dependent or steroid resistant nephrotic syndrome due to minimal change disease.

Grade B, Level III

Therapy with an alkylating agent, specifically cyclophosphamide, in steroid-dependent or frequently relapsing patients can produce a sustained remission in up to 67%.<sup>10</sup> Al Khader treated 8 adult MCD patients with cyclophosphamide alone and compared the outcome to that in 8 patients not treated with immunosuppressive therapy. Seven of those treated with cyclophosphamide achieved remission, whereas 2 of the controls went into spontaneous remission. There was no relapse in the cyclophosphamide treated group at 6 years of follow-up. The use of alkylating agents compared to prednisolone has also been reviewed retrospectively.<sup>12</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.

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>.

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

Cyclophosphamide however is associated with an increased risk of gonadal toxicity with a cumulative dose of 200 mg/kg, and most cases of late malignancy occur in patients treated for more than a year. Thus patients should be advised of these potential complications prior to starting therapy. It is recommended that male patients be given an opportunity for sperm storage. Furthermore, in view of these risks, repeat courses of cyclophosphamide should be avoided in patients with this benign condition.

### 7.4.3 Cyclosporin A

**A** Cyclosporin A can be used in the treatment of frequently relapsing, steroid dependent or steroid resistant nephrotic syndrome due to minimal change disease.

Grade A, Level Ib

Ponticelli, in a randomised controlled trial, treated frequent relapsers or steroid-dependent patients with NS due to MCD and focal and segmental glomerulosclerosis (FSGS) with either cyclosporin A (CyA, at 5 mg/kg/day for 9 months) or cyclophosphamide (for 8 weeks).<sup>14</sup> Cyclosporin A therapy resulted in a better remission rate (88% vs. 68%,  $p>0.05$ ). The remission however was unsustainable after discontinuation of therapy and relapse was more common in the CyA group (75% vs. 37%). In another randomised controlled trial of CyA vs. supportive therapy (diuretics) in steroid-resistant MCD, Ponticelli demonstrated partial remission in 60% and complete remission in 32% as compared to none in the control group.<sup>4</sup> Nevertheless, the relapse rate was high (69%) following a 6-month course of CyA therapy.

However, the optimal dose and duration of CyA therapy has not been determined. Meyrier, in an uncontrolled study, treated 41 steroid-dependent and steroid-resistant nephrotics with either MCD or FSGS with CyA for a mean of 19.6 months. This regimen was associated with complete remission in 86%; the remission was sustained only in 10 patients after CyA withdrawal.<sup>4</sup> Longer therapy was not associated with better outcomes. Ittel treated frequent relapsers, steroid-dependent and steroid-resistant nephrotics (again a mixed group of MCD and FSGS) for a longer median time of 32 months, and achieved only 60% complete remission; none had a sustained remission on CyA withdrawal.<sup>15</sup> The doses used in these studies ranged from 4-6 mg/kg/day.

**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.

Grade B, Level III

Nephrotoxicity has been the major complication in the use of CyA. The serum creatinine can remain normal despite histological changes in the kidney.<sup>16</sup> Habib et al reviewed serial renal biopsies in 42 children with the nephrotic syndrome (35 of whom had MCD) who had been treated with CyA for 4 to 63 months. Tubulointerstitial lesions were present in 24 children; 9 of them had extensive lesions but all had a normal glomerular filtration rate. Nephrotoxicity is however dose related as suggested by Meyrier, who studied serial renal biopsies of adults with MCD on treatment for up to 78 months with CyA.<sup>4</sup> The factors most predictive of CyA nephrotoxicity were a dose of more than 5.5 mg/kg/day, the presence of renal insufficiency prior to treatment and the percentage of lesions with FSGS.

In local practice, starting CyA doses of 4-5.5 mg/kg/day are used. A minimum duration of therapy of 6 months is recommended. Serial monitoring of the renal function is important, and a renal biopsy should be considered if therapy is to extend beyond 12 months.

## 7.5 Summary

Minimal change disease is a common cause of NS in adults. It is generally steroid responsive. Frequent relapsers and steroid-dependent or steroid-resistant cases can be treated with cyclophosphamide, but risks of gonadal and other toxicities should be considered. Alternatively, CyA therapy can be considered to induce remission for these cases; however, CyA nephrotoxicity should be avoided by limiting the duration of therapy and monitoring the renal function.

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## 8 Focal and segmental glomerulosclerosis

### 8.1 Introduction

Focal and Segmental Glomerulosclerosis (FSGS) is a glomerular disease that frequently leads to the nephrotic syndrome. Two major forms have been identified: an idiopathic variety where no etiology can be ascertained and a secondary form whose causes including 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>1</sup> In Singapore, idiopathic or primary FSGS accounts for about 9% of all biopsies performed for nephrotic syndrome.<sup>2</sup> Males are affected twice as often as women. The following discussion focuses mainly on idiopathic or primary focal segmental glomerulosclerosis in the adult population.

### 8.2 Course and prognosis

The spectrum of presentation is varied and adults may present at the stage of asymptomatic proteinuria. The majority however, present with nephrotic syndrome (NS), and the degree of proteinuria is usually quite severe. Up to 40-60% of patients have associated microhaematuria. Hypertension is present in about 50% of adults and impaired glomerular filtration rate (GFR) in 20-40%. The prognosis depends on the degree of proteinuria, renal impairment and severity of tubulo-interstitial lesions on biopsy. Rydel et al reported 5 and 10-year renal survival of 100% for patients in remission and 66% and 41% respectively for nephrotic patients not in remission.<sup>3</sup>

### 8.3 Treatment of focal segmental glomerulosclerosis

Although initial studies have reported little benefit with treatment, more recent data suggests that response rates range from 30% to 50%.<sup>4,5</sup> Non-responders had a high chance of renal impairment ranging from 45-67%.<sup>6,7</sup> Conversely, renal survival of patients who achieve remission may be as high as 100% at 10 years.<sup>3,8</sup> Patients with non-nephrotic proteinuria should be treated with symptomatic therapy as suggested in the chapter on "General Measures".

Treatment options for those with nephrotic syndrome include:

- Corticosteroids
- Cytotoxic agents such as cyclophosphamide
- Cyclosporin A
- Other therapies

### 8.3.1 Corticosteroids

**B** High dose prednisolone should be given as first line therapy for treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis. Prednisolone dose should be tapered slowly after remission is achieved and total treatment duration should be for at least 6 months.

Grade B, Level III

Corticosteroids are considered the mainstay of treatment of nephrotic syndrome due to FSGS. Studies reviewed show that 33 to 94% of patients used initial doses of about 60 mg/day. Ponticelli et al gave either prednisolone 1 mg/kg/day for 8 weeks and tapered by 5-10 mg/wk 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>9</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 40% 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>3,7</sup> Response rates using prednisolone alone vary widely but majority of the studies reported rates between 40-60%. Mean time to remission was 3.7 months but the 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>8</sup>

It is thus recommended that patients with NS due to FSGS 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. High dose prednisolone should be given for 6-8 weeks and then tapered slowly. Relapse in nephrotic syndrome occurring during the steroid taper or poor tolerance of prolonged, high dose corticosteroids may be indications for cytotoxic therapy. Alternatively, steroid resistance has

been considered an indication for alternative therapy, especially Cyclosporin A.

### 8.3.2 Cytotoxic agents

**B** Cytotoxic therapy with cyclophosphamide should be considered for patients with steroid dependent nephrotic syndrome due to focal and segmental glomerulosclerosis, or those with steroid-related side effects.

Grade B, Level III

**B** Cytotoxic therapy may be considered as alternative therapy in patients with steroid resistant nephrotic syndrome due to focal and segmental glomerulosclerosis.

Grade B, Level III

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

To date, there has been no controlled trial comparing corticosteroids alone versus corticosteroids with cytotoxic agents as first line therapy for NS due to FSGS. In fact a significant proportion of patients may have been treated with a course of empiric high dose corticosteroids while awaiting renal biopsy, making such a study difficult to conduct. Thus cytotoxic therapy, primarily with cyclophosphamide, has been used as second line therapy in inducing remission of NS in FSGS. Banfi et al gave cytotoxics in 32 corticosteroid resistant NS and obtained 50% response.<sup>5</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>7</sup> However, Ponticelli's series showed remission (complete or partial) in 58% with steroids as the first agent compared to 41% with cytotoxics (cyclophosphamide and azathioprine either alone or in combination with each other and low dose prednisolone) as the first agent.<sup>9</sup> Nevertheless, cyclophosphamide may be less effective in patients who are steroid resistant and barring cost considerations, Cyclosporin A may be the preferred therapy in these patients. As cyclophosphamide use is associated with the potential for sterility, patients in whom such

therapy is anticipated should be informed of the risk and sperm storage offered to male patients.

### 8.3.3 Cyclosporin A

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

Grade A, Level Ib

Cyclosporin A (CyA) is an immunosuppressant that has been used to induce remission in NS due to FSGS. The drug has been tried at starting doses of 3 to 5 mg/kg/day either alone or in combination with low dose prednisolone (up to 15 mg/day) or high dose prednisolone (60 mg/day).<sup>10-12</sup> Prednisolone was stopped by 6-8 weeks. Among 49 steroid-resistant patients treated for 26 weeks in Cattran's series, 67% responded to CyA therapy (12% had complete remission, 57% had partial remission). Mean time to complete remission was 7 weeks (range 1-15 weeks).<sup>10</sup> Six of seven patients in Ittel's series responded (1 complete, 3 partial remission, 2 reduction in proteinuria) at 6 months.<sup>11</sup> In the latter series all but one relapsed after stopping CyA, suggesting that CyA dependency may be a problem with the use of this drug.

Thus, CyA at starting doses of 3-5 mg/kg/day is recommended for treatment of patients with NS due to FSGS. Concomitant therapy with corticosteroids at starting doses of at least 15 mg/day is also recommended. After remission is achieved, prednisolone doses can be tapered or even discontinued. Due to the paucity of data, it is difficult to recommend the duration of CyA therapy. However, relapses may occur with short-term therapy and the proposed minimum duration of therapy should be 6 months.

While there are no studies on use of CyA in steroid-dependent NS due to FSGS, CyA can be used in these cases as in steroid-resistant cases at similar doses.

### 8.3.4 Other therapies

**C** There is no firm evidence for benefit from other therapies in the treatment of nephrotic syndrome due to focal and segmental glomerulosclerosis.

Grade C, Level IV

Use of other therapies such as Mycophenolate Mofetil (MMF) or plasmapheresis have been reported as single case reports or small series. MMF was used in a patient with steroid resistant FSGS who already had renal impairment after the use of CyA.<sup>13</sup> Renal function subsequently stabilised even after withdrawal of MMF. A report by Radhakrishnan et al a showed reduction in proteinuria, unchanged serum creatinine over one year in 11 steroid and CyA-resistant patients, but there was a lack of complete remission.<sup>14</sup> Plasmapheresis has been disappointing,<sup>15</sup> although in combination with cyclophosphamide, the therapy may have a better response.<sup>16</sup>

## 8.4 Summary

Treatment for patients with nephrotic range proteinuria is recommended using steroids as the first line agent. If unsuccessful, cytotoxic therapy or use of CyA should be considered.

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## 9 IgA nephropathy

### 9.1 Introduction

IgA nephropathy is the most common glomerulonephritis in Singapore accounting for 45% of all renal biopsies.<sup>1</sup> It typically presents in children and young adults and is seldom seen in infancy or after the age of 50 years.<sup>2</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%).<sup>1</sup>

### 9.2 Course and prognosis

IgA nephropathy pursues a highly variable course. It is not a benign disease as 30-50% of patients develop ESRF after 25 years of follow-up.<sup>2</sup> There are clinical and histological factors that predict the likelihood of progression to ESRF and these prognostic factors can be employed in selecting patients for therapy.<sup>3-5</sup>

Clinical factors	Histological factors
<ul style="list-style-type: none"><li>• Magnitude and character of proteinuria</li><li>• Impaired renal function at discovery</li><li>• Hypertension</li></ul>	<ul style="list-style-type: none"><li>• Chronic tubulointerstitial infiltration/fibrosis</li><li>• Extensive crescents (&gt;30-50%)</li><li>• Advanced glomerulosclerosis (&gt;20%)</li><li>• Medial hypertrophy of arterioles</li></ul>

### 9.3 Specific treatment

There is a lack of complete understanding of the pathogenesis of IgA nephropathy and as such, most therapeutic options remain empirical. There have been several reviews of treatment of the disease over the years.<sup>3,6-9</sup> 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 mesangium.<sup>10,11</sup> Therapeutic efforts have been directed at either

reducing or preventing antigen entry and altering the abnormal immune response and its consequences. Therapeutic recommendations for the following clinical syndromes are discussed: isolated haematuria, haematuria and proteinuria (normal and abnormal renal function), nephrotic syndrome and acute renal failure.

### 9.3.1 Isolated haematuria

**C** No therapy is recommended for patients with IgA nephropathy and isolated haematuria without proteinuria. These patients should be monitored regularly (every 3-12 months) for the development of proteinuria.

Grade C, Level IV

There are no therapeutic trials in patients with isolated haematuria without proteinuria. However, clinicopathological studies suggest a benign course in patients with recurrent isolated episodes of gross haematuria without adverse histological features.<sup>4</sup> In fact, in local practice, biopsy of patients with isolated haematuria is not generally carried out as there is little impact on treatment. Thus, no specific therapy is recommended and the patient should be monitored for the development of proteinuria.

### 9.3.2 Haematuria and proteinuria

**C** No therapy is recommended for patients with IgA nephropathy and asymptomatic haematuria with proteinuria of 0.15 g/day to 1 g/day and no other adverse clinical or histological indicators. Proteinuria should be monitored at 3-12 month intervals.

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) and no 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>9</sup> Therapy should be thus reserved for patients with one or more adverse prognostic features, especially those with proteinuria  $\geq 1$  g/day.

Four categories of treatment have been used in the treatment of patients with IgA nephropathy and proteinuria  $\geq 1$  g/day. These include:

- A. Angiotensin converting enzyme inhibitors and Angiotensin II receptor antagonists (ATRA)
- B. Dipyridamole and Warfarin combination therapy
- C. Dietary supplementation with Fish Oil
- D. Other therapies

**A. *Angiotensin converting enzyme inhibitors and Angiotensin II receptor antagonists***

They have been shown to reduce proteinuria and 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. ACE inhibitors and ATRA exert their effects through a number of mechanisms including alteration of the hemodynamics 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 ACE inhibitors and ATRA also improve glomerular permselectivity.<sup>12,13</sup>

**A** Angiotensin converting enzyme inhibitor therapy is recommended for treatment of hypertension in patients with IgA nephropathy.

Grade A, Level Ib

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 ACE inhibitor is the preferred drug of choice.<sup>14-17</sup> Sodium restriction is also important.

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

Grade A, Level Ib

In addition to blood pressure control, several studies have been conducted using ACE inhibitors in IgA nephropathy for retardation of progression in renal failure. These studies have looked at various end-points including reduction in proteinuria and stabilisation of renal function (serum creatinine or creatinine clearance). Almost all the studies enrolled patients with a proteinuria of  $\geq 1$  g/day<sup>14-18</sup> with the exception of one randomised trial comparing an ACE inhibitor with an ATRA that enrolled patients with proteinuria of  $\geq 0.5$  g/day.<sup>12</sup> Some studies suggest that the deletion DD ACE genotype is linked with more rapid progression and it is in this group of patients that ACE inhibitor may be more effective.<sup>19</sup> As these latter findings have not been confirmed, it is recommended that all patients with significant proteinuria be started on ACE inhibitor therapy.

**B** Angiotensin II receptor antagonists can be used as alternatives to Angiotensin converting enzyme inhibitors in patients with IgA nephropathy for similar indications.

Grade B, Level IIa

**B** Angiotensin converting enzyme inhibitors and Angiotensin II receptor antagonists can be used in combination to reduce proteinuria in patients with IgA nephropathy and proteinuria  $\geq 1$  g/day.

Grade B, Level IIb

Recent trials using the newer ATRA have shown similar beneficial effects on proteinuria and progression of disease when compared with ACE inhibitor. A combination of ACE inhibitor and ATRA was found to have an additive anti-proteinuric effect in one study by Russo et al, while therapy with either an ACE inhibitor or ATRA was found to have similar anti-proteinuric effects in a trial by Perico et al and improve renal function in some patients in another trial by Woo et al.<sup>20,21,13</sup>

Thus treatment with an ACE inhibitor is recommended in hypertensive or normotensive patients with IgA nephropathy and significant proteinuria ( $\geq 1$  g/day). Renal impairment or chronic renal failure is not a contraindication for the use of ACE inhibitor although caution should be exercised when initiating and maintaining the ACE

inhibitor in patients with abnormal renal function as hyperkalemia and acute deterioration of renal function can ensue.

### ***B. Dipyridamole and Warfarin combination therapy***

Increased platelet aggregation and activation of the coagulation pathway, in part, the result of endothelial cell damage occurring from the intraglomerular hypertension, are features of IgA nephropathy. These observations form the rationale for the use of dipyridamole and warfarin in IgA nephropathy.

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

Grade A, Level Ib

The initial trials included six months of cyclophosphamide<sup>22,23</sup> but the most recent trial used only dipyridamole and warfarin in patients with renal impairment in order to avoid the haematological and gonadal toxicity of cyclophosphamide.<sup>24</sup> 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 (75-100 mg tds) 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 of 1 g/day or more. Abnormal renal function is not a contraindication to treatment. The INR has to be monitored at regular intervals during treatment.

### ***C. Dietary supplementation with Fish Oil***

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>25</sup>

**A** Fish oil supplementation is not beneficial in every patient with IgA nephropathy.

Grade A, Level Ia

There are five studies (three randomised controlled trials) using fish oil in IgA nephropathy and the results have been conflicting.<sup>26-31</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>32</sup>

**C** Fish oil supplementation can be used in patients with IgA nephropathy and proteinuria > 3 g/day.

Grade C, Level IV

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. Another study compared low-dose and high-dose fish oil and found no difference in preservation of renal function between the two groups.<sup>31</sup> The low-dose was 12 g of fish oil containing 1.88 g of eicosapentanoic acid and 1.47 g of docosahexanoic acid.

*D. Other therapeutic options*

Many other treatment regimens have been used in patients with IgA nephropathy and current interest is in the use of long-term alternate-day steroids with large trials in progress. Other treatment options 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.<sup>3</sup>

### 9.3.3 Nephrotic syndrome

Nephrotic syndrome is an uncommon presentation of IgA nephropathy. Although nephrotic range proteinuria is associated with poor prognosis, patients with selective proteinuria are likely to respond to therapy irrespective of histology.<sup>34</sup> Furthermore, patients with nephrotic syndrome and IgA nephropathy can be stratified for treatment based on severity of histological changes.

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.

Grade B, Level IIb

There is only one controlled study by Lai et al using steroids in patients with IgA nephropathy and the nephrotic syndrome.<sup>35</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.

Grade B, Level IIa

**C** Cyclosporin A at an initial dose of 5 mg/kg/day can be initiated 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.

Grade C, Level IV

There are only a few anecdotal reports on the management of relapses and some have responded to another course of steroids or cyclophosphamide at a dose of 1.5-2.0 mg/kg/day given for 8-12 weeks.<sup>36-37</sup> Support for the use of cyclophosphamide comes in 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>38</sup> A single short-term controlled trial using cyclosporin A (CyA) in patients with heavy proteinuria showed reduction in proteinuria but there was also a more rapid decline in renal function.<sup>39</sup> However, CyA has been used in other forms of glomerular disease with the nephrotic syndrome and found to be beneficial at inducing and maintaining remission.<sup>40-41</sup> However, continuous therapy of up to 12 months or more is often required. CyA may be considered in non-responders, frequent relapsers<sup>42</sup> and those who are steroid dependent, at an initial dose of 5 mg/kg body weight/day with tapering to 2-3 mg/kg/day at 5-6 months for a total treatment period of 6-12 months. Concomitant low dose prednisolone is also recommended with CyA therapy (30 mg tapering to 10 mg).

#### 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.

Grade C, Level IV

**GPP** However, response to therapy in these patients is less favourable and over-immunosuppression should be avoided in non-responders.

Patients with more severe histological changes are less likely to respond to therapy although the meta-analysis by Schena et al suggested that corticosteroids and/or cytotoxic drugs are beneficial in patients with heavy proteinuria whether or not associated with the nephrotic syndrome.<sup>38</sup> A similar treatment approach as for those with mild histological changes is suggested in this group of patient but care should be taken to avoid over aggressive therapy in the non-responders.

### 9.3.4 Acute renal failure

Acute renal failure is also an uncommon presentation in IgA nephropathy and occurs in about 9-10% of patients with 20-25% of these patients requiring 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.

### Crescentic glomerulonephritis

Crescentic glomerulonephritis presents with the clinical syndrome of rapidly progressive glomerulonephritis and because of the small number of patients there have been no therapeutic controlled studies.

**C** Standard treatment as for other forms of crescentic glomerulonephritis is recommended for patients with acute renal failure due to crescentic IgA nephropathy. Treatment with methylprednisolone pulse should be followed by oral prednisolone, cyclophosphamide, dipyridamole and warfarin. Plasma exchange and intravenous immunoglobulins can be instituted.

Grade C, Level IV

General consensus recommends standard treatment as for other forms of crescentic glomerulonephritis. Treatment is with prednisolone at an initial dose of 1 mg/kg/day (with subsequent taper over 3-4 months and a total treatment period of 6 months) and cyclophosphamide at 2 mg/kg/day (total treatment period of 3-4 months).<sup>3</sup> A methylprednisolone pulse of 500 mg to 1 g per day for three days can be given prior to initiation of oral prednisolone. Dipyridamole (75-100 mg tds) and warfarin (low dose to keep INR between 1.2 to 1.5) can be added. There is no standard regimen for plasma exchange and if required, it should be tailored to the patient's clinical progress. Intravenous immunoglobulin therapy can also be considered.

### Mild glomerular changes with acute tubular necrosis

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

Grade C, Level IV

Some patients present with gross haematuria, flank pain and reversible acute renal failure. Renal biopsy in these patients reveals mild glomerular changes with predominantly acute tubular necrosis. The renal failure may be recurrent in certain patients and is thought to be the result of glomerular bleeding leading to tubular damage due to local production of toxic haemoglobin degradation products and/or toxic oxygen radicals. Dialysis may be required in some patients. All patients eventually recover and no definitive treatment is recommended.

### 9.3.5 Recurrent disease in renal transplants

About 50% of renal allograft biopsies will reveal recurrent IgA deposits 2-5 years post-transplant. Haematuria and low-grade proteinuria may signal recurrence of the disease.

**GPP** No specific treatment is recommended in treatment of recurrent IgA nephropathy post renal transplantation. Treatment options are similar to the *de novo* disease.

Fortunately, the recurrent disease is usually mild and does not impact significantly on graft survival in the majority of patients. No specific therapy is recommended for recurrent disease. An ACE inhibitor should be prescribed if hypertension is present. Recurrent crescentic glomerulonephritis should be treated as the *de novo* disease with steroids, cyclophosphamide and plasma exchange.

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## 10 Membranous nephropathy

### 10.1 Introduction

Membranous nephropathy (MN) is a common cause of nephrotic syndrome (NS) in adults. Though its actual incidence in different studies varies, MN has been reported to account for 33% to 36% of cases of adult NS in western series while accounting for 12% of cases in a recent report from Singapore.<sup>1,2</sup> Though the most common presentation is the NS, other clinical presentations of MN include sub-nephrotic range proteinuria (i.e. proteinuria < 3.0 g/day), hypertension and renal insufficiency in various combinations.<sup>3,4</sup>

Histologically, MN is characterised by the presence of subepithelial immune complexes with thickening of the glomerular basement membrane and results in thickened capillary loops on light microscopy. These changes are associated with an increase in glomerular capillary permeability and proteinuria. Four stages of MN (I to IV) that reflect the evolution and severity of the disease have been described; tubulointerstitial lesions and vascular lesions may also be present in the more progressive forms of the disease.<sup>5</sup>

### 10.2 Course and prognosis

The course of idiopathic MN is generally considered to be benign. In the majority of patients with NS due to MN, the course is indolent with spontaneous complete remissions of proteinuria occurring in 5 to 20% of patients, and partial remission of proteinuria to less than 2 g/day occurring in 25% to 40% of patients.<sup>3,4,6</sup> In one series, up to 65% of patients were either in remission or in partial remission after 5 years of follow-up.<sup>3</sup> In unselected series of patients not treated with corticosteroids or other immunosuppressants, progression to ESRF occurred in 16% to 35% of patients over 10 years of follow up.<sup>3,4,6,7</sup>

Several clinical and histopathologic criteria have been suggested to correlate with adverse outcomes. These include clinical features such as male gender, HLA type, magnitude of proteinuria and its selectivity index, hypertension and renal dysfunction.<sup>8</sup> Histological features include glomerular staging and the presence of tubulointerstitial changes.<sup>6,8</sup> In a Cox proportional hazards model, Marx identified histological stage III-IV grading on renal biopsy and nephrotic

syndrome as predictors of ESRF with hazard ratios of 5.3, (CI 1.9 to 15.0) and 7.9, (CI 1.1 to 61.5) respectively.<sup>6</sup>

Given the variable course of the disease, there is considerable controversy over which patients should be initiated on treatment. On the one hand, it has been suggested that those destined to a benign course would not benefit from immunosuppressive therapy but would instead be unnecessarily exposed to the toxicities of such therapy. This school would suggest that only those at risk for ESRF should be subjected to therapy and/or trials. On the other hand, proponents of therapy for the majority of patients with MN argue that treatment of MN in patients with progressive renal insufficiency may be less effective and associated with more side effects. The following discussion evaluates therapeutic options in the management of MN and provides evidence-based guidelines for its management.

### 10.3 Evaluation of membranous nephropathy

**C** Patients with membranous nephropathy should undergo evaluation to identify secondary causes. Specifically, evaluation should be performed to exclude secondary causes such as autoimmune conditions, infections, drugs and malignancies.

Grade C, Level IV

While idiopathic in the majority, 15% to 30% of MN may be secondary to autoimmune conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis and Sjogren's syndrome), infections (e.g. hepatitis B and C), drugs (e.g. organic gold, mercury, penicillamine or non-steroidal anti-inflammatory agents), and malignancies (e.g. carcinoma of the lung, gastrointestinal tract, breast or lymphoma).<sup>8</sup>

### 10.4 Indications for treatment

**B** Patients with idiopathic membranous nephropathy and nephrotic syndrome or Stage III or IV disease on histology should be treated with immunosuppressive therapy as they are at risk for progression to end stage renal failure.

Grade B, Level IIB

**B** There is no evidence for benefit with immunosuppressive therapy for those with sub-nephrotic range proteinuria, normal renal function or Stage I or II disease on renal biopsy.

Grade B, Level IIB

Patients without underlying secondary causes of MN are defined as having idiopathic membranous nephropathy. These patients should be stratified into high, intermediate and low risk categories based on the presence of nephrotic syndrome (proteinuria > 3.0 g/day), histological staging of MN on renal biopsy or the presence of renal dysfunction.<sup>6,4</sup> In a retrospective review of patients with MN, 15 patients, identified as being at high risk for ESRF, with both the nephrotic syndrome *and* Stage III/IV lesions, had a 53% incidence of ESRF over 5 years.<sup>6</sup> In contrast, among the 38 patients with sub-nephrotic range proteinuria *and* histological stage I or II MN, defined as low-risk, none progressed to ESRF over a median follow-up of 5 years.<sup>6</sup> The 67 patients with *either* nephrotic syndrome *or* Stage III/IV lesions on renal biopsy were defined as having intermediate risk and had a 10% incidence of ESRF at 5 years.

Thus while high and intermediate risk patients should be treated with immunosuppressive therapy, there is no indication for such treatment for low risk patients as they have a relatively good prognosis. These low risk patients should nevertheless be treated for proteinuria as described under general measures and monitored regularly for disease progression.

**B** Patients with idiopathic membranous nephropathy and progressive renal dysfunction should be treated with immunosuppressive therapy.

Grade B, Level III

Patients with renal impairment at presentation or on follow-up are also at high risk for progression to ESRF. In a study on the natural history of MN, Donadio reported that renal function at study entry was significantly worse among 17 patients who progressed to ESRF, in comparison to those who retained normal renal function (1.8 mg/dl vs. 1.2 mg/dl,  $p < 0.001$ ).<sup>4</sup> Of note was that progression in this group occurred in 2.5 years or less. These patients should also be treated with immunosuppressive therapy as recommended below.

## 10.5 Treatment of membranous nephropathy

Specific treatment of MN with immunosuppressive therapy is reserved for patients at high or intermediate risk for progression to ESRF including those with renal dysfunction. Treatment can be classified into three categories, namely:

- Corticosteroids
- Alkylating agents such as cyclophosphamide and chlorambucil
- Cyclosporin A

### 10.5.1 Corticosteroids

**A** Patients with nephrotic syndrome due to membranous nephropathy may be treated with steroids alone to induce remission of proteinuria.

Grade A, Level Ib

**A** There is no evidence for long-term benefit with steroids in the treatment of patients with membranous nephropathy.

Grade A, Level Ia

Corticosteroids (CS) are the mainstay of treatment for many types of GN. There have been three prospective, randomised, placebo-controlled trials of corticosteroids in patients with MN published between 1979 and 1990.<sup>9-11</sup> In these studies, dose ranges of oral prednisone varied from 100-150 mg/day to 45 mg/m<sup>2</sup> on alternate days while duration of therapy varied from 8-12 weeks to 6 months. Only two of the three trials documented remission in proteinuria at the end of therapy.<sup>9,11</sup> Cameron, in a randomised controlled double blind trial of CS versus placebo in patients with NS due to MN, demonstrated significant improvements in proteinuria and serum albumin in treated patients at the end of 8 weeks of therapy.<sup>11</sup>

However, and notwithstanding the short-term benefits of CS, there is little evidence for long-term benefit with CS in the treatment of MN. In fact, two of the randomised controlled trials failed to demonstrate differences in proteinuria at the end of the study period ( $\geq 3$  years).<sup>10,11</sup> A meta-analysis of trials of CS in MN also demonstrated no

significant benefit of therapy on remission of proteinuria or for preservation of renal function in the long term.<sup>7</sup>

Despite the conflicting results, many experts consider treatment with CS to be useful in inducing remission of the nephrotic state.<sup>12</sup> Inducing remission leads to short-term benefits (reduced tendency to thrombosis and lipid abnormalities) and a subset of patients, albeit small, may actually have long-term remission.<sup>12</sup> Alternate day CS should be used at starting doses of 2 mg/kg/day (or its equivalent in daily dosing) for 8 weeks. Doses should be tapered once remission is induced and total treatment course should be limited to 6 months. Failure to achieve remission at 8 weeks may be considered steroid failure and alternative treatment regimens as suggested below should be considered.

As the therapy may be of limited benefit, only patients in the intermediate risk category should undergo a trial of steroids alone for treatment of MN. Thus patients at high risk for progression of renal failure such as those with nephrotic syndrome *and* histological grade III/IV changes on renal biopsy or those with renal impairment should be considered for alternative therapies as listed below.

### 10.5.2 Alkylating agents

**A** Patients with membranous nephropathy at high risk for progression to end stage renal failure can be considered for treatment with alkylating agents, together with steroids, for 6 months.

Grade A, Level Ia

**B** As alkylating agents are associated with drug-related toxicities, patients receiving these agents should be closely monitored during and after therapy.

Grade B, Level III

Several prospective, randomised controlled trials (RCT) have examined the efficacy of alkylating agents in inducing remission of proteinuria and/or preventing renal deterioration in patients with MN.<sup>13-17</sup> As shown in Table 10.1, both oral chlorambucil (dose of 0.15-0.2 mg/kg/day) and cyclophosphamide (intravenous dose of 0.5-

0.75 g/m<sup>2</sup>; oral dose of 1.5-2.5 mg/kg/day) have been shown to induce remission in proteinuria in different studies. In the study with the longest follow-up by Ponticelli et al, the authors demonstrated significant advantage at 10 years to the chlorambucil-treated group (88% vs. 47% complete or partial remission, p=0.0000; 92% vs. 60% renal survival, p=0.0038 in treated vs. placebo groups respectively).<sup>15</sup> The combination of CS with alkylating agent was more efficacious than treatment with CS alone at 1 year.<sup>16</sup>

A meta-analysis of the 3 RCT of alkylating agents versus no treatment confirmed that the relative chance of complete remission was improved with alkylating agents (Odds Ratio 4.8, CI 1.44-15.96).<sup>7</sup> However, evaluation of renal survival revealed no benefit with therapy when compared to no treatment and differences in outcome between groups diminished with time.<sup>13-16</sup>

Complications and tolerability of treatment also need to be considered in evaluating benefits of therapy. Treatment with alkylating agents is associated with multiple toxicities including late malignancy, cystitis and sterility. In Ponticelli's studies, 9,5% in the treated group had to stop treatment because of side effects.<sup>15</sup> In addition, many patients in the treatment group required additional courses of cyclical alkylating/CS therapy to sustain the treatment benefit, suggesting that duration of alkylating therapy could be prolonged. In a study comparing the two alkylating agents, Ponticelli et al documented that cyclical therapy with oral cyclophosphamide and pulse CS was as efficacious as the cyclical chlorambucil/pulse CS combination, but the former combination was associated with fewer side effects.<sup>17</sup>

Thus, either agent can be used together with corticosteroids, for a total duration of 6 months, to induce long-term remission in proteinuria in patients with MN at high risk for progression to ESRF. Lower starting doses of intravenous (iv) Methylprednisolone (0.5 gm/dose) and alkylating therapy (0.15 mg/kg/day of chlorambucil or 2 mg/kg/day of cyclophosphamide) are used in local practice. Leucocyte counts should be checked 2 weeks after starting alkylating therapy and doses adjusted for counts < 4000/mm<sup>3</sup>. Given the inherent toxicities of alkylating agents, only patients at high risk for progression to ESRF should be selected for therapy with these drugs. Moreover regular monitoring for these side effects during and after therapy is mandatory.

**Table 10.1 Summary of Clinical Trials of Alkylating Therapy in Membranous Nephropathy**

<b>Author (Trial Type)</b>	<b>Therapy</b>	<b># patients (Duration of follow-up)</b>	<b>Renal survival/ Function</b>	<b>Remission of proteinuria</b>
Donadio <sup>13</sup> (RCT)	Cyclo for 1 year vs. No therapy	22 with NS (1 year)	No difference	No difference
Murphy <sup>14</sup> (RCT)	Cyclo for 6 months + dipyridamole/warfarin for 2 years vs. Symptomatic therapy	40 (2 years)	No difference	Less proteinuria with treatment
Ponticelli <sup>15</sup> (RCT)	*Alternating monthly courses for 6 months: MP in Months 1, 3, 5 + Ch in Months 2, 4, 6 vs. Symptomatic therapy	81 with NS (10 years)	Better with treatment	More remission with treatment
Hogan <sup>7</sup> (Meta Analysis of RCT)	Alkylating therapy vs. No therapy	143	No difference	Higher remission rate with treatment
Ponticelli <sup>16</sup> (RCT)	* Ponticelli Regimen vs. MP for 6 months	92 with NS (4 years)	No difference	Better with MP + Ch at 1 year; No difference at 4 years
Ponticelli <sup>17</sup> (RCT)	* Ponticelli Regimen vs. MP + PO Cyclo	87 with NS (1 year)	Better with both treatments	Better with both treatments
Falk <sup>18</sup> (RCT)	Alternating monthly courses for 6 months: MP/Pred + IV Cyclo vs. Pred	36 with renal dysfunction (29 months)	No difference	No difference
Reichert <sup>19</sup> (RCT)	* Ponticelli Regimen vs. MP + IV Cyclo for 6 months	18 with renal dysfunction (15 months)	Worse in IV cyclo group	No difference
Branten <sup>20</sup> (RCT)	* Ponticelli Regimen vs. Pred + PO Cyclo for 1 year	32 with renal dysfunction (26 months)	Better in PO Cyclo group	Higher in PO Cyclo group

Abbreviations:Ch=Chlorambucil,Cyclo=Cyclophosphamide,MP=Methylprednisolone, Pred=Prednisolone

\* Refers to Ponticelli Regimen of alternating monthly courses of MP and Ch.

**A** In patients with membranous nephropathy and renal dysfunction, daily oral cyclophosphamide for 12 months, together with steroids, should be considered to prevent renal failure.

Grade A, Level Ib

Alkylating agents have also been used in several small RCTs in the subset of patients with MN and progressive decline in renal function. (Table 10.1)<sup>18-20</sup> While Falk demonstrated no benefit with an iv cyclophosphamide/CS regimen in such patients, Reichert demonstrated improvement in renal function with an oral chlorambucil/CS regimen.<sup>18,19</sup> In a recent study using oral cyclophosphamide and CS vs. oral chlorambucil and CS in a comparable dose, cyclophosphamide was associated with a better outcome.<sup>20</sup> Further, treatment related complications were also reported as lower in cyclophosphamide-treated patients than in chlorambucil-treated patients (40% vs. 63%,  $p < 0.05$ ).<sup>20</sup>

Thus daily oral cyclophosphamide at 1.5-2 mg/kg/day, together with CS is recommended for 1 year in patients with MN and progressive renal dysfunction. Nevertheless, drug related toxicities are high as discussed above and patients require long term monitoring.

### 10.5.3 Cyclosporin A

**A** Patients with membranous nephropathy at high risk for progression to end stage renal failure should be treated with 6 months of Cyclosporin A and steroids.

Grade A, Level Ib

Cyclosporin A (CyA) has also been used for the treatment of many glomerular diseases. Early uncontrolled trials of CyA in MN demonstrated decrease in proteinuria and remission in NS.<sup>21,22</sup> These early studies, using 12 weeks to 30 months of CyA at doses between 4-6 mg/kg/day, demonstrated complete or partial remission in 71-74% of patients. In a recent randomised, placebo controlled trial in 51 patients unresponsive to a 6-month course of CS, CyA (doses adjusted to achieve trough levels of 150 to 225 ng/mL) with CS (prednisolone 0.15 mg/kg/day) therapy for 6 months was associated with a higher incidence of remission at 78 weeks versus placebo (43% vs. 19%).<sup>23</sup>

There was however no significant difference in the rate of decline of renal function at 2 years between treated and placebo groups.

Cyclosporin A at starting doses of 4-6 mg/kg/day, together with CS, is thus recommended for 6 months as first line therapy in patients at high risk for progression to ESRF. Doses of CyA should be adjusted to achieve trough CyA levels of 150-225 ng/mL. However, as for other renal conditions, renal function should be monitored carefully during the course of therapy so as to avert CyA nephrotoxicity.

**A Patients with membranous nephropathy and progressive renal dysfunction should be treated with 12 months of Cyclosporin A.**

**Grade A, Level Ib**

Use of CyA in patients with MN and progressive renal dysfunction has also been described. In a randomised, placebo controlled trial of CyA in 17 patients with NS and progressive renal dysfunction due to MN, CyA-treated patients experienced a significant improvement in the slope of reciprocal serum creatinine ( $p < 0.02$ ).<sup>24</sup> Cyclosporin A in this study was started at 3.5 mg/kg/day at twice daily dosage to maintain trough levels of 110-170 ng/ml and therapy was continued for 12 months. 6 of the 8 (75%) CyA-treated patients had halving of proteinuria while none in the placebo group experienced this improvement.

Thus, in patients with MN and deteriorating renal function, CyA can be used, but recommended duration is for 12 months. A six-month course of CyA therapy may be equally effective; there is also no data on whether concomitant administration of steroids is useful in this setting and trials are clearly needed to delineate these issues. However, CyA nephrotoxicity may be a complication of prolonged CyA therapy. The risk of nephrotoxicity versus the toxicities of alkylating agents should be evaluated for each patient, prior to initiating therapy in patients with declining renal function.

## **10.6 Other therapies**

There are few studies that have addressed the use of other immunosuppressants in the treatment of MN. To date, no benefit has been demonstrated with the use of Azathioprine in MN while

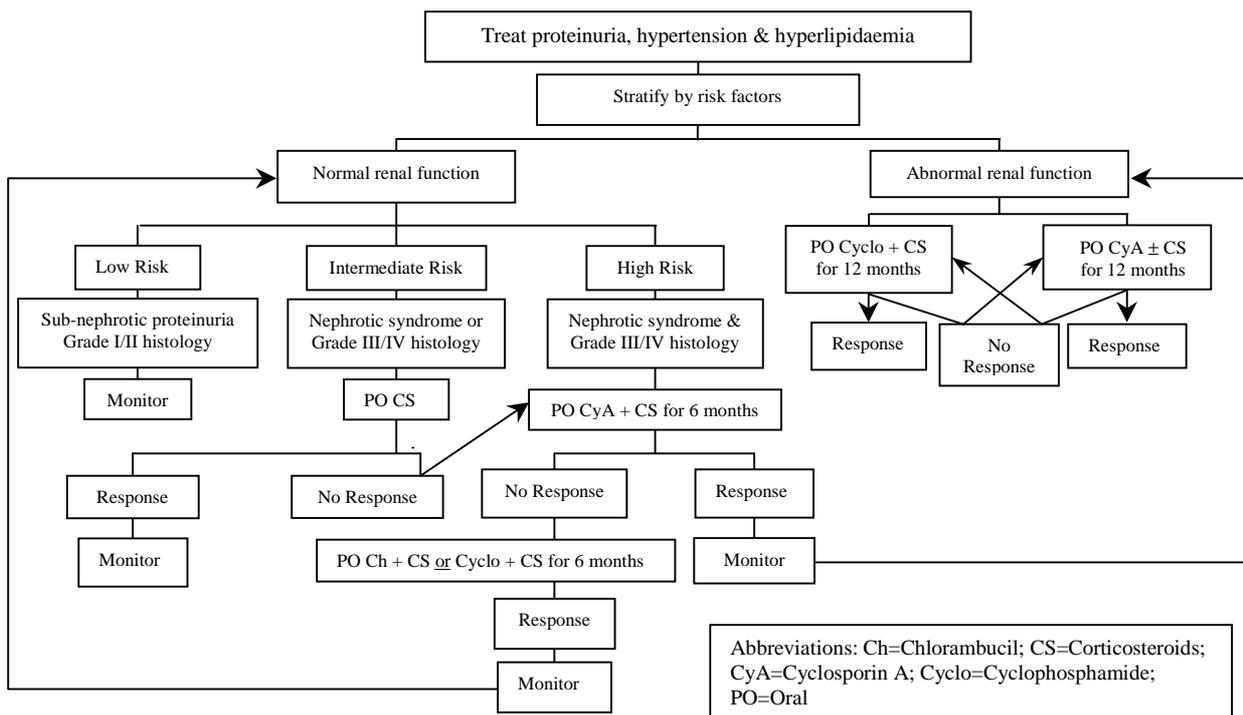
anecdotal report on the use of Mycophenolate Mofetil in resistant MN is encouraging.<sup>25,26</sup>

## 10.7 Summary

Patients with idiopathic MN should be stratified into high, intermediate and low risk groups based on presence of NS, renal dysfunction and histological grading on renal biopsy. Patients in the high-risk group with NS and high-grade histological changes should be started on a course of CyA together with CS for 6 months. Patients failing this therapy may be considered for a 6-month course of oral chlorambucil or cyclophosphamide together with CS. Those with renal dysfunction can be treated with a course of oral cyclophosphamide with CS or CyA with or without CS for 1 year, based on the risk-toxicity profile of each drug.

Patients in the intermediate risk category with symptomatic NS, unresponsive to general measures, can be considered for a course of CS therapy for 6 months, followed by treatment with CyA and CS for steroid resistant groups or those with relapsing disease. All patients including patients at low risk for progression to ESRF should receive treatment to reduce proteinuria as well as to control hypertension and hyperlipidemia. An algorithmic approach to treatment as outlined in Figure 10.1 is likely to result in remission of proteinuria as well as preservation of renal function.

**Figure 10.1 Management of Membranous Nephropathy**



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## 11 Rapidly progressive glomerulonephritis

### 11.1 Introduction

Rapidly Progressive Glomerulonephritis (RPGN) is a condition characterised by extensive crescent formation and a rapid loss of renal function. The glomerular inflammation may result in progression to ESRF over a few weeks to months, the rapidity being dependent on the proportion of crescents found on renal biopsy. There are 3 categories of RPGN, with the classification based on pathoetiology:

- Anti-glomerular basement membrane (GBM) antibody-mediated
- Pauci-immune RPGN
- Immune Complex-mediated

### 11.2 Anti-Glomerular Basement Membrane antibody-mediated

**A** Patients with rapidly progressive glomerulonephritis due to anti-glomerular basement membrane antibody should be treated with corticosteroids, cytotoxic therapy and plasma exchange.

Grade A, Level Ib

Anti-GBM antibody-mediated RPGN is one of the three major forms of crescentic glomerulonephritis. It is characterised by the presence of severe renal injury which, if untreated, progresses rapidly to ESRF. When associated with pulmonary haemorrhage, the condition is labelled as Goodpasture's syndrome. Early diagnosis of RPGN due to anti-GBM antibodies should be established as this determines response to therapy and prognosis.

Table 11.1 provides a summary of treatment for anti-GBM antibody disease.<sup>1-4</sup> If instituted early, plasma exchange, steroids and cyclophosphamide improve renal function, especially in those with milder forms of anti-GBM antibody disease. Plasma exchange removes circulating anti-GBM antibodies and other mediators of inflammation while corticosteroids and cyclophosphamide reduce

antibody formation. As long as patients are not anuric, some with advanced renal failure may also respond to this therapeutic regimen.

**C** Corticosteroid therapy in rapidly progressive glomerulonephritis due to anti-glomerular basement membrane antibody should be with pulse methylprednisolone followed by oral prednisolone.

Grade C, Level IV

**A** Daily plasma exchange with 4-L exchanges is recommended in rapidly progressive glomerulonephritis due to anti-glomerular basement membrane antibodies for 14 days or until the antibody disappears.

Grade A, Level Ib

Intravenous methylprednisolone should be administered at doses from 0.5-1 g/day for 3 days followed by daily oral prednisolone (1 mg/kg/day) which can be tapered once remission is achieved. 4-L plasma exchange should be given daily for 14 days or until anti-GBM antibody disappears. Human albumin can be used as replacement fluid although fresh frozen plasma can be given at the end of the procedure if there is risk of haemorrhage. No plasma exchange should be initiated in patients with anuria and crescents involving more than 85% of the glomeruli, unless there is pulmonary hemorrhage.<sup>5</sup> Cyclophosphamide should also be given at starting dose of 2 mg/kg/day, with subsequent doses titrated to white counts. Immunosuppressive therapy should usually be given for 6-12 months as this is the time usually required for cessation of anti-GBM antibody formation. Adequacy of immunosuppressive therapy can be monitored by following anti-GBM antibody titers.

**Table 11.1 Studies on the Treatment of Anti-glomerular Basement Membrane Induced Rapidly Progressive Glomerulonephritis\***

<b>Level of Evidence</b>	<b>Author</b>	<b>Study design</b>	<b>N</b>	<b>Treatment</b>	<b>Result</b>
Ib	Johnson <sup>1</sup>	Randomised control trial	17	Steroids, Cyclo vs. Plasma exchange, Steroids, Cyclo	Better renal survival with Plasma exchange
Ila	Simpson <sup>2</sup>	Non-randomised control trial	20	Steroids, Cyclo, Aza vs. Steroids, Cyclo, Aza and Plasmapheresis	Better renal survival with Plasmapheresis
III	Rees <sup>3</sup>	Uncontrolled case series	59	Steroids, Cyclo, Plasmapheresis	44% had improved renal function
III	Wilson <sup>4</sup>	Uncontrolled case series	81	Steroids + Cytotoxic agents	ESRF in 85%

Abbreviations: Aza = Azathioprine; Cyclo = Cyclophosphamide; N=Number of patients in study  
 \*Adapted from Jindal KK.<sup>22</sup>

### 11.3 Pauci-immune RPGN

**B** Methylprednisolone pulse therapy followed thereafter by oral prednisolone at 1 mg/kg/day is recommended for treatment of pauci-immune rapidly progressive glomerulonephritis.

Grade B, Level IIa

**B** Cyclophosphamide can be given orally or by monthly intravenous pulse for treatment of pauci-immune rapidly progressive glomerulonephritis.

Grade B, Level IIa

Pauci-immune RPGN is characterised by the presence of necrotising glomerulonephritis with few or no immune deposits by immunofluorescence or electron microscopy. Most patients have antineutrophil cytoplasmic antibodies (ANCA) and systemic symptoms of vasculitis. Table 11.2 provides a summary of studies with levels of evidence for treatment of pauci-immune crescentic RPGN.<sup>6,7</sup> Intravenous pulse methylprednisolone should be given at doses of 0.5-1 g/day for 3 days followed by daily oral prednisolone (1 mg/kg/day) which can be tapered once remission is achieved. Cyclophosphamide should also be given either orally at doses of 1-2 mg/kg/day or by monthly pulse intravenous therapy (0.5-1.0 g/m<sup>2</sup>/month). The dose of cyclophosphamide should be adjusted to maintain a nadir leukocyte count of between 3,000 to 5,000/mm<sup>3</sup> at 2 weeks post-treatment.

**B** Plasmapheresis should be considered for patients with pulmonary hemorrhage and in those with pauci-immune, rapidly progressive glomerulonephritis and severe renal disease who do not respond to conventional therapy.

Grade B, Level III

Table 11.3 provides a summary of studies on plasmapheresis in idiopathic RPGN along with levels of evidence.<sup>8-12</sup> The results of these randomised trials argue against a role for plasmapheresis in

**Table 11.2 Studies on the Treatment of Pauci-immune Crescentic Rapidly Progressive Glomerulonephritis\***

<b>Level of Evidence</b>	<b>Author</b>	<b>Study design</b>	<b>N</b>	<b>Treatment</b>	<b>Result</b>
IIa	Nachman <sup>6</sup>	Non-randomised control study	97	Pulse Steroids + PO Steroids vs. Pulse Steroids + Cyclo	Better renal and patient survival with cyclophosphamide
III	Lobo <sup>7</sup>	Uncontrolled case series	21	Pulse Steroids + PO Steroids + Cyclo	76% had improvement in renal function

Abbreviations: Cyclo = Cyclophosphamide, PO = Oral; N=Number of patients in study

\*Adapted from Jindal KK<sup>22</sup>

**Table 11.3 Studies on Plasma Exchange in Idiopathic Rapidly Progressive Glomerulonephritis\***

<b>Level of Evidence</b>	<b>Author</b>	<b>Study design</b>	<b>N</b>	<b>Treatment</b>	<b>Result</b>
Ib	Glockner <sup>8</sup>	RCT	26	PE + Cytotoxic vs. Cytotoxic alone	No benefit of PE
Ib	Cole <sup>9</sup>	RCT	32	PE + Steroids + Aza vs. Steroids + Aza	No benefit of PE
Ib	Pusey <sup>10</sup>	RCT	48	PE + Aza + Steroids + Cyclo vs. Aza + Steroids + Cyclo	No benefit for entire group. For dialysis-dependent patients discontinuation of dialysis more on PE 91% vs. 37%
Ib	Rifle <sup>11</sup>	RCT	14	Steroids + Cyclo + PE + Heparin vs. Steroids + Cyclo + Heparin	For dialysis-dependent patients discontinuation of dialysis 75% on PE vs. 0% for those without PE
Ib	Mauri <sup>12</sup>	RCT	22	Steroids + Cyclo vs. Steroids + Cyclo + PE	No benefit of PE

Abbreviations: Aza = Azathioprine, Cyclo = Cyclophosphamide, PE = Plasma exchange, RCT = Randomised control trial; N=

Number of patients in study

\*Adapted from Jindal KK<sup>22</sup>

milder forms of pauci-immune RPGN. Plasmapheresis may be potentially beneficial when used as an adjunct to conventional immunosuppression for patients with severe disease.

### Wegener's granulomatosis

Wegener's granulomatosis is a systemic vasculitis and is an important cause of pauci-immune RPGN. The classic form of Wegener's granulomatosis primarily involves the upper and lower respiratory tracts and the kidneys. Granuloma formation is seen in the respiratory tract and the kidneys exhibit a focal necrotising pauci-immune glomerulonephritis.

A cyclophosphamide-corticosteroid combination should be used in the treatment of Wegener's granulomatosis. Different studies have shown renal and patient survival of over 75% on follow-up at 3-8 years.<sup>6,13-15</sup> Early therapy is essential as tissue necrosis cannot be reversed once it occurs. In the acute phase of the disease, severe renal failure requiring dialysis does not preclude a good initial response to therapy. Antineutrophil cytoplasmic antibodies, particularly c-ANCA are usually present in this condition but renal biopsy is advisable to confirm the diagnosis. Between 55 and 90% of patients will recover enough function to come off dialysis.<sup>6,14,16,17</sup>

### Cyclophosphamide therapy in Wegener's granulomatosis

**B** Rapidly progressive glomerulonephritis due to Wegener's granulomatosis can be treated with either oral or intravenous cyclophosphamide.

Grade B, Level IIa

Cyclophosphamide can be given orally at a dose of between 1-2 mg/kg/day; the lower dose of 1 mg/kg/day may be effective in patients with mild disease. The role of monthly intravenous pulses of cyclophosphamide (0.5 to 1.0 g/m<sup>2</sup> body surface area) is incompletely defined. Studies comparing intravenous with oral cyclophosphamide have produced conflicting results.<sup>6,14,18</sup> A recent prospective multi-centre randomised trial comparing oral and intravenous

cyclophosphamide showed similar rates of remission with both forms of therapy.<sup>19</sup> However, the patient outcomes in this study were so much worse than in other studies that it is difficult to draw conclusions from it. The mortality was 44% with oral and 33% with intravenous therapy. Thus the role of pulse cyclophosphamide remains unclear and should not be used in patients with severe or life-threatening disease.<sup>20,21</sup> Cytotoxic therapy should generally be continued for 6 to 12 months after complete remission is induced.<sup>13,14</sup>

#### Corticosteroid therapy in Wegener's granulomatosis

**B** High dose corticosteroids, either oral or pulse therapy, should be used to treat rapidly progressive glomerulonephritis due to Wegener's granulomatosis.

Grade B, Level IIa

Oral prednisolone (0.5 to 1 mg/kg/day) should be given concurrently until the disease is brought under control by cyclophosphamide after which it can be tapered down slowly. Low dose steroids should be given as long as cytotoxic therapy is maintained. In those with more fulminant renal or respiratory disease, pulse methylprednisolone is the preferred therapy.<sup>6,13</sup>

#### Plasmapheresis in Wegener's granulomatosis

**B** Plasmapheresis is not likely to be beneficial in patients with rapidly progressive glomerulonephritis due to Wegener's granulomatosis.

Grade B, Level III

Several controlled studies on plasmapheresis have been conducted in patients who were treated with cyclophosphamide and corticosteroid, and plasmapheresis has not generally produced any added benefit for the renal disease in Wegener's granulomatosis.<sup>10,16,17</sup>

## 11.4 Immune complex RPGN

Immune complex RPGN can be due to one of a number of systemic diseases. These include:

- Post-infectious GN
- IgA nephropathy
- Henoch-Schonlein nephritis
- Lupus nephritis
- Mixed cryoglobulinemia
- Membranous nephropathy
- Mesangiocapillary GN

In immune complex RPGN, the nature of the immune deposits is not diagnostic of any specific disorder but the serologic and histological findings usually point to the underlying disorder. For example, mesangial IgA deposits on renal biopsy are indicative of IgA nephropathy, antinuclear antibodies and subendothelial deposits on biopsy of lupus nephritis and anti-streptococcal antibodies and subepithelial humps on biopsy of post-infectious glomerulonephritis. As these patients often have associated systemic disease, they should be treated according to the specific underlying condition.

## 11.5 Summary

Immunohistopathology and serology are helpful to differentiate the three major types of RPGN. Treatment of RPGN generally requires intensive treatment with corticosteroids and cytotoxic therapy. Plasmapheresis may also be beneficial in certain subtypes.

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## 12 Mesangiocapillary glomerulonephritis

### 12.1 Introduction

Mesangiocapillary glomerulonephritis (MCGN) is a relatively rare form of glomerulonephritis. It is known under other names such as membranoproliferative GN and hypocomplementaemic GN. It is divided into idiopathic and secondary types and further classified into Types I, II and III according to the histological features. Secondary causes associated with this condition include collagen vascular diseases such as systemic lupus erythematosus, hepatitis B, hepatitis C and human immunodeficiency virus-related renal disease. Hypocomplementaemia is common in all types of MCGN and has been attributed to complement activation. Hypocomplementaemia is especially marked in Type II MCGN, in which there is increased peripheral catabolism of the C3 complement component by a circulating immunoglobulin called C3 nephritic factor.

MCGN affects both children and young adults and can manifest with the nephrotic syndrome, proteinuria, haematuria and the acute nephritic syndrome. The secondary causes described above must be excluded once the histological diagnosis is made.

### 12.2 Course and prognosis

The course of MCGN is dependent on the underlying cause. The disease has an indolent course with ESRF occurring in 50-60% of untreated patients within 10 to 15 years.<sup>1,2</sup> The prognosis is worsened by the presence of heavy proteinuria (> 3 g/day in adults), hypertension and the presence of tubulointerstitial infiltrates or crescents on renal biopsy.<sup>3,4</sup>

### 12.3 Treatment of mesangiocapillary GN

Evidence for effective treatment of MCGN is difficult to find as the disease is not common. Treatment objectives have also differed in different studies, though most commonly changes in renal function and proteinuria have been used. Moreover, as MCGN may be due to

secondary causes such as hepatitis C in a significant proportion of cases, many previous studies have been confounded by the inclusion of secondary MCGN due to hepatitis C in the study. The treatment options listed below are restricted to primary idiopathic cases.

**B Treatment is recommended for adults and children with idiopathic mesangiocapillary glomerulonephritis and heavy proteinuria, tubulointerstitial disease on renal biopsy or impaired renal function.**

**Grade B, Level III**

Studies on the natural history of MCGN have shown that adverse prognosis is associated with the presence of adverse risk factors as listed above, suggesting that this group should receive treatment.<sup>2-4</sup> The age group of the patient is an additional factor to consider in deciding on therapy. Adults with milder forms of the disease (eg. proteinuria < 3 g/day and normal renal function) should be followed up regularly for the development of adverse risk factors and treated when these arise. It is currently unclear whether children with proteinuria < 1 g/day/1.73 m<sup>2</sup>, with the absence of hypertension or renal impairment, should be treated.

Two forms of therapy have been used in patients with MCGN. These are immunosuppressants (corticosteroids and cytotoxic therapy) and anti-thrombotic agents (dipyridamole, aspirin and warfarin).

### **12.3.1 Corticosteroids**

**A Children with Type I Mesangiocapillary glomerulonephritis at high risk for progression to renal failure should be treated with high dose corticosteroids.**

**Grade A, Level Ib**

**B Children with Type II Mesangiocapillary glomerulonephritis at high risk for progression to renal failure can be treated with high dose corticosteroids.**

**Grade B, Level III**

Only therapy with corticosteroids has been found to be effective in stabilising renal function in children with MCGN. In a randomised controlled trial including 80 children with MCGN Type I treated for a mean duration of 130 months, Tarshish et al documented 61% renal survival in children treated with alternate day prednisone at 40 mg/m<sup>2</sup>/dose compared to 12% in the placebo group.<sup>5</sup> In an uncontrolled study of six children with Type II MCGN, McEnery et al documented improved histological changes in children treated with steroids, 37% remission rate and 89% 10-year renal survival.<sup>6</sup> Other studies have likewise documented benefits in children with MCGN.<sup>7,8</sup> The optimal duration of therapy is not determined; nevertheless, 6 to 12 months of high dose therapy (equivalent to Prednisolone 40 mg/m<sup>2</sup>/dose) is recommended. Hypertension, nephrotic syndrome or heavy proteinuria at onset, warrant initial treatment with at least 3 doses of intravenous methylprednisolone 10-20 mg/kg/day (maximum 1 g), followed by prednisolone 40-60 mg/m<sup>2</sup> on alternate days for 12 months. Children with significant renal impairment and crescentic GN merit the addition of pulse intravenous cyclophosphamide 500 mg/m<sup>2</sup>.

**B There is no evidence of benefit with corticosteroids for therapy in adults with mesangiocapillary glomerulonephritis.**

**Grade B, Level III**

There have been, to date, no controlled studies evaluating the efficacy of corticosteroids in MCGN in adults. However, retrospective studies suggest that corticosteroids have no benefit in therapy of MCGN in adults.<sup>9,10</sup>

### 12.3.2 Cytotoxic therapy

**A** Cytotoxic therapy is not recommended for the treatment of idiopathic mesangiocapillary glomerulonephritis.

Grade A, Level Ib

There is limited data on the use of cytotoxic therapy in the treatment of MCGN in either children or adults. In an uncontrolled retrospective study of steroids with cytotoxic agents (cyclophosphamide, azathioprine or chlorambucil), the combination was suggested to be superior to treatment with steroids alone in improving proteinuria.<sup>11</sup> Ten year renal survival was 82% in this series, higher than that obtained from other studies on the natural history of the untreated disease. However, a randomised controlled trial of cyclophosphamide, dipyridamole and warfarin versus no therapy in 59 patients demonstrated no benefit in treated patients.<sup>12</sup>

### 12.3.3 Anti-thrombotic agents

**B** Dipyridamole and aspirin are recommended for treatment of idiopathic mesangiocapillary glomerulonephritis in adults at high risk for progression to renal failure.

Grade B, Level III

Anti-thrombotic agents have been used in several trials of therapy in MCGN. The rationale for the use of antiplatelet agents is that platelet consumption is increased in MCGN suggesting a possible etiologic role for platelets in the glomerular injury. In a randomised controlled trial of aspirin (500 mg/day) and dipyridamole (75 mg/day) versus no therapy, Zauner et al demonstrated a clinically significant reduction of proteinuria with therapy.<sup>13</sup> In another study, aspirin (975 mg/day) and dipyridamole (225 mg/day) for 1 year reduced the rate of decline of glomerular filtration rate (14% in treated group versus 47% in control group at 3-5 years).<sup>14</sup> The rate of decline in renal function in the control group was rapid in this study, casting doubts on its validity. In addition, there was no difference in benefit at 10 years, suggesting that prolonged therapy is required for sustained benefit.<sup>9</sup> Thus, prolonged

therapy with aspirin (500 to 975 mg/day) and dipyridamole (75 to 225 mg/day) is recommended in the treatment of MCGN in adults at high risk of progression to ESRF.

Another randomised controlled trial of warfarin together with dipyridamole versus placebo on 18 patients demonstrated reduction in proteinuria but no difference in renal function. However, treatment was complicated by bleeding.<sup>15</sup> Thus warfarin is not suggested for treatment in this condition.

## 12.4 Summary

Mesangiocapillary GN is a rare type of GN with an indolent course. A variety of histological and clinical features have an impact on outcome and determine benefits from therapy. In patients at high risk for progression to ESRF, corticosteroid therapy and antiplatelet therapy with aspirin and dipyridamole for children and adults respectively is recommended. However, clear evidence of efficacy in all types of MCGN is scanty and questions remain on exact dosing and duration of therapy. Issues on when to stop or taper therapy, or the efficacy of combined prednisolone and antiplatelet therapy have also not been subjected to rigorous study. Thus, the clinical situation as well as side effects of drugs must be carefully considered before therapy is instituted.

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## 13 Management of childhood nephrotic syndrome

### 13.1 Introduction

Nephrotic syndrome (NS) is characterised by the presence of gross proteinuria, hypoalbuminaemia and generalised oedema. With the decline in acute post-infectious glomerulonephritis in children in Singapore over the past 15 years due to improving socio-economic conditions, nephrotic syndrome is now the most common childhood glomerulonephritis. The incidence of childhood primary NS is 2-7 cases per 100,000 children under the age of 18 years annually. Minimal change nephrotic syndrome (MCNS) is the most common cause of childhood NS accounting for more than 90% of childhood primary NS. Although the pathogenesis of MCNS remains unknown, its prognosis is excellent with low incidence of progression to chronic renal failure. However, its complications, which include infections such as cellulitis and peritonitis, and hypercoagulable states with thrombosis, are well recognised. As such, selective immunosuppressive regimens are required to induce and maintain disease remission, prevention of disease complications and the detrimental side effects of therapy.

Definitions used in the management of childhood NS are shown in Table 13.1.

### 13.2 Treatment

There are several treatment options for the treatment of NS in children. These include:

- Prednisolone
- Levamisole
- Alkylating agents: Cyclophosphamide, Chlorambucil
- Cyclosporin A

As a remitting-relapsing course of NS is typical in children, the choice of therapy is based in part on the clinical course and in part on the toxicity of administered therapy.

**Table 13.1 Useful Definitions in Childhood Nephrotic Syndrome**

	<b>Definition</b>
Nephrotic syndrome	Presence of generalised oedema, heavy proteinuria: (urine protein/creatinine > 0.2 g/mmol or urine total protein > 3.5 g/day/1.73m <sup>2</sup> or urine total protein > 40 mg/m <sup>2</sup> /hour) and Hypoalbuminaemia (< 25 g/l). Hypercholesterolaemia (> 5.2 mmol/l), invariably present, is not conventionally included as part of the diagnosis.
Remission	Loss of oedema and urine total protein < 4 mg/m <sup>2</sup> /hour or early morning (first void) urine dipstick negative/trace for 3 consecutive days.
Steroid responsive	Remission achieved with steroid therapy alone.
Relapse	Sustained proteinuria of urine protein/creatinine ratio > 0.2 g/mmol or early morning (first void) urine dipstick > 2+ for 3 consecutive days (partial biochemical relapse) and/or generalised oedema, hypoalbuminaemia (< 25 g/l) (full clinical relapse), having previously been in remission.
Infrequent relapses	Relapses after the first episode, but < 2 episodes within first 6 months or < 4 episodes within any subsequent one-year period.
Frequent relapses	Relapses after the first episode, with ≥ 2 episodes within first 6 months or ≥ 4 within any subsequent one-year period.
Steroid dependence	Frequent relapsers with 2 consecutive relapses while on steroid therapy or within 2 weeks of cessation of steroid therapy.
Steroid resistance	Failure to achieve remission despite 6 weeks of daily high dose (60 mg/m <sup>2</sup> /day) prednisolone therapy.

The recommendations below are made based on the clinical presentation, and presence and frequency of relapses.

### 13.2.1 First episode of nephrotic syndrome

**A** Children experiencing their first episode of NS should be treated with prednisolone at 60 mg/m<sup>2</sup>/day (maximum of 80 mg/day) for 4 weeks followed by 40 mg/m<sup>2</sup> of prednisolone every alternate day for 4 weeks and gradual taper over 4 weeks.

Grade A, Level Ia

**A** Prednisolone should be given as a single morning dose in treating children with NS.

Grade A, Level Ib

More than 90% of children are steroid responsive and have been shown to clear their proteinuria by about 2 weeks of therapy.<sup>1</sup> Alternate-day prednisolone has been shown to be superior to prednisolone given 3 days out of 7 in the second 4 to 6 weeks of therapy.<sup>2</sup> Shorter courses of initial treatment have been associated with a higher frequency of relapses (twice the number) and twice as early as the standard protocol.<sup>3</sup> Longer periods of initial therapy to a total of 12 weeks have also been associated with longer remission periods and fewer frequent relapses compared to the 8-week regimen.<sup>4</sup> Although the steroid side effects have not been significantly different,<sup>5</sup> recent meta-analysis of randomised controlled trials advocated a 3 months course.<sup>6</sup> As such, it is recommended that the first episode be treated with the 8-week regimen of prednisolone followed by gradual tapering over 4 weeks. Prednisolone should be administered in a single morning dose to reduce adrenal suppression and improve compliance. A single daily dose is as effective as divided doses in inducing and maintaining remission.<sup>7</sup>

### 13.2.2 Relapse

**A** Children with a relapse of NS should be treated with prednisolone at 60 mg/m<sup>2</sup>/day (maximum of 80 mg/day) (minimum 14 days) until urine is protein free for 3 consecutive days. This should be followed by alternate-day prednisolone of 40 mg/m<sup>2</sup> for 4 weeks, after which prednisolone should be gradually tapered over 4 weeks.

Grade A, Level Ib

Treatment should be considered when there is a full clinical relapse or at least 1 week of partial biochemical relapse. The above regimen, defined as “relapse therapy”, was associated with fewer relapses in the first 6 months of treatment. A longer course of initial high dose prednisolone at 60 mg/m<sup>2</sup>/day for 4 weeks, as recommended by the International Study of Kidney Diseases in Children (ISKDC), was associated with a more prolonged remission (3.27 vs. 1.48 months) but at the cost of more steroid usage.<sup>8</sup> In addition, most children who relapsed after receiving either the short or long relapse therapy of prednisolone, would relapse by 8 months, indicating no extra benefit of the long relapse therapy.

### 13.2.3 Frequent relapsing nephrotic syndrome

**C** Children with frequently relapsing NS can receive relapse therapy during relapses and be maintained on prednisolone 0.1-0.5 mg/kg on alternate days for 3 to 6 months.

Grade C, Level IV

The above was recommended by the British Association for Paediatric Nephrology and Research Unit, Royal College of Physicians.<sup>9</sup> One non-randomised study indicated that long-term low dose daily prednisolone significantly reduced the frequency of relapses with its beneficial effects persisting after discontinuation of therapy.<sup>10</sup> There were no side effects except for mild growth retardation. On the other hand, alternate-day prednisolone is associated with a lower risk of steroid toxicity. Children on long-term steroids should be followed-

up with a minimum of 3-monthly intervals for blood pressure and growth assessment, and reviewed yearly for cataracts.<sup>11</sup> Steroid sparing agents are indicated in the presence of unacceptable steroid toxicity.

**B** A 6-12 month course of Levamisole at 2.5 mg/kg/alternate days can be used for treatment of frequently relapsing NS in children.

Grade B, Level IIa

There are only a few randomised or controlled studies on levamisole in frequent relapsing and steroid dependent NS. Levamisole has been shown to be effective in inducing remission or maintaining a relapse free period in these studies.<sup>12-16</sup> The duration of therapy remains unclear but the duration of 6-12 months is justifiable for these children.<sup>9,16</sup> However most children relapse early upon discontinuation of therapy.<sup>15</sup> An important complication of levamisole includes agranulocytosis and as such, monthly monitoring of total white count is required.

**A** Cyclophosphamide at 2-2.5 mg/kg/day or chlorambucil at 0.15 mg/kg/day for 8 weeks can be used for the treatment of a relapse of NS in children with frequent relapses.

Grade A, Level Ia

This therapy is indicated only for those children with unacceptable steroid side effects or diabetes mellitus. Cyclophosphamide in combination with prednisolone has been shown to lead to a more prolonged remission in children who were frequent relapsers compared to prednisolone alone.<sup>17-19</sup> An 8 weeks course of cyclophosphamide has been shown to be effective in maintaining a prolonged remission.<sup>17,20</sup> Chlorambucil has the same benefit in maintaining remission in children with frequent relapsing nephrotic syndrome.<sup>21,22</sup> There was no difference between the efficacy of cyclophosphamide and chlorambucil.<sup>23</sup> However, chlorambucil has higher rates of severe side effects.<sup>24</sup>

### 13.2.4 Steroid dependent nephrotic syndrome

**GPP** For children with steroid dependent NS, a repeat course of relapse therapy with prednisolone and alternate-day prednisolone 0.1-0.5 mg/kg/alternate days for 6 to 12 months can be administered.

The minimum dose of prednisolone should be given to maintain remission in order to minimise side effects. Prolonged steroid usage is associated with a high risk of steroid side effects such as growth retardation, cataracts and obesity. Alternate-day prednisolone is associated with lower risk of steroid toxicity. Steroid sparing agents are indicated if the dose of prednisolone used to maintain remission exceeds 0.5 mg/kg/alternate days, or the presence of unacceptable steroid toxicity.

**A** Levamisole at 2.5 mg/kg/alternate days for 6-12 months should be given for children with steroid dependent NS as for children with the frequently relapsing condition.

Grade A, Level Ib

**B** Children with steroid dependent NS can be treated with cyclophosphamide at 2-2.5 mg/kg/day or chlorambucil at 0.15 mg/kg/day for 8-12 weeks.

Grade B, Level III

Children with steroid dependency and unacceptable steroid side effects can receive an 8-12 week course of alkylating agents. The 8-week course has been found to be ineffective in steroid dependent children.<sup>23</sup> A subsequent prospective study showed a superior cumulative rate of sustained remission in the 12-week course (67% versus 22%) compared to the 8-week course.<sup>25</sup> The cumulative dose of cyclophosphamide of 168 mg/kg is well below the known threshold for gonadal toxicity in prepubertal boys. Nevertheless, a later randomised controlled Japanese study showed that a 12-week course did not confer any advantage compared with an 8-week course, with both courses showing a similar relapse rate.<sup>26</sup>

**A** Cyclosporin A at 6 mg/kg/day should be administered to children with steroid dependent NS.

Grade A, Level Ib

**C** Cyclosporin A therapy can be given for one year in the treatment of steroid dependent NS.

Grade C, Level IV

Cyclosporin A (CyA) treatment reduced relapses, induced remission in frequently relapsing and steroid dependent children; most children were able to discontinue prednisolone while on CyA.<sup>27-29</sup> It is equally successful in inducing remission compared with alkylating agents.<sup>30</sup> Unfortunately, it does not maintain a prolonged remission state with most children relapsing upon tapering or discontinuation of therapy.<sup>31</sup> The duration of CyA therapy is uncertain. There is minimal long-term nephrotoxicity in one study.<sup>32</sup> The British Association for Paediatric Nephrology recommends therapy for 1 year.<sup>9</sup> However, close monitoring of renal function and a repeat renal biopsy at the end of therapy may be indicated to assess the nephrotoxic effects of this therapy.

### 13.2.5 Steroid resistant nephrotic syndrome

**C** Renal biopsy is recommended in children with steroid resistant NS to rule out other glomerular pathology.

Grade C, Level IV

Renal biopsy is indicated to rule out pathology other than minimal change disease for treatment outcome and long-term renal prognosis.<sup>9</sup>

**C Treatment for hyperlipidaemia, symptomatic treatment of severe oedema with diuretics and intravenous albumin is recommended for children with steroid resistant NS.**

**Grade C, Level IV**

Children who have steroid resistant NS are at risk of steroid toxicity as well as complications of infection, hypercoagulable state and malnutrition. The mortality rate is about 1-4%.<sup>33</sup> Dietary control and use of HMG-CoA reductase inhibitors may be indicated for those with severe hyperlipidaemia.<sup>34,35</sup> Diuretic therapy combined with albumin infusion may be indicated in severe nephrotic oedema in cases of respiratory distress due to diaphragmatic splinting or perineal skin infection.<sup>36</sup>

**C Cyclophosphamide 2-2.5 mg/kg/day for 12 weeks can be used for treatment of steroid resistant minimal NS in children.**

**Grade C, Level IV**

As over 46% of steroid resistant NS in children have minimal change on renal biopsy, the following discussion focuses on MCNS. There is no widely acceptable treatment in steroid resistant minimal change NS. Likewise, there is to date no good clinical data on cyclophosphamide therapy in these children. Favourable results from studies in the frequent relapsing and steroid dependent group suggest that 12-weeks of cyclophosphamide therapy may be beneficial in the steroid resistant group in inducing remission and reduction in steroid dosages. Again, the cumulative dose is well below the gonadal toxicity threshold.

**B Cyclosporin A 6 mg/kg/day can be used for treatment of childhood steroid resistant NS.**

**Grade B, Level III**

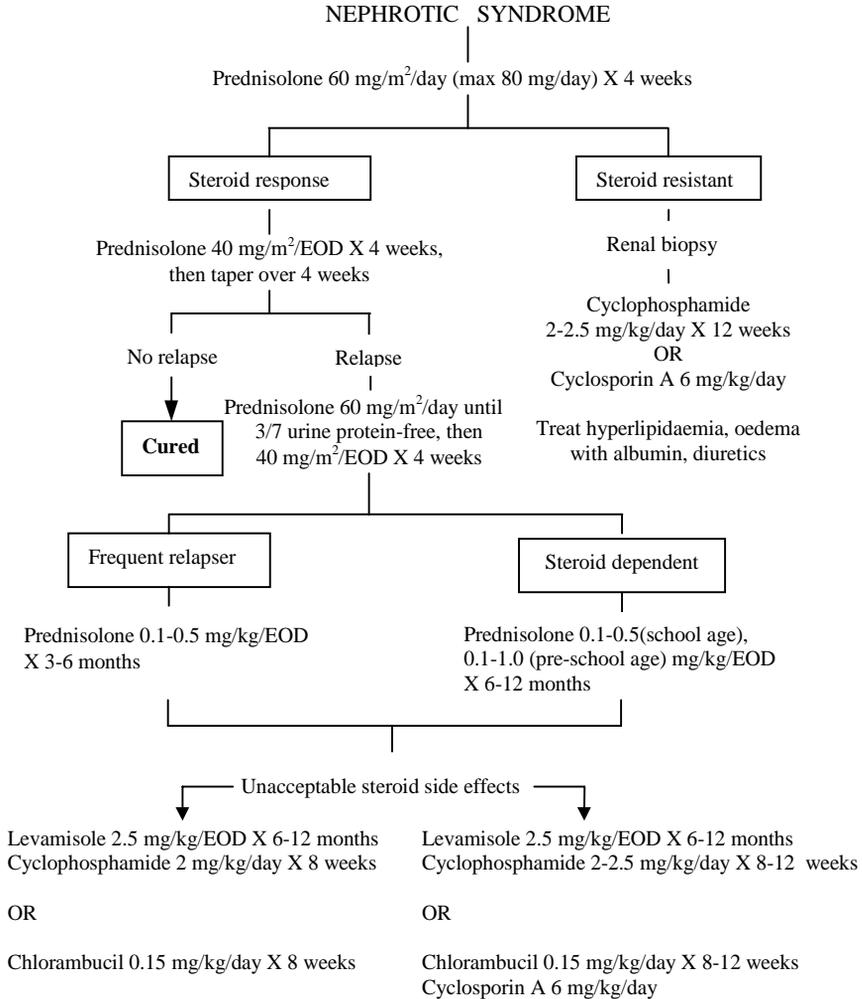
**GPP Cyclosporin A therapy can be given for 2 years in the treatment of childhood steroid resistant NS.**

Several uncontrolled studies showed some beneficial effects of CyA in children with steroid resistant NS with remission rates (partial or complete) of between 28-50%.<sup>37-40</sup> One randomised trial in 45 children and adults showed a 59% remission rate with no significant renal or extra-renal toxicity.<sup>41</sup> Another study reported a 78% remission rate.<sup>42</sup> The recommended duration of CyA treatment is 2 years but a repeat renal biopsy is advocated for those children who are in long-term complete remission with a view to stopping therapy especially in those who show chronic CyA nephrotoxicity on biopsy.

### **13.3 Summary**

The goals for successful management of childhood NS are to induce remission, to prevent relapses and disease complications, and lastly to avoid the side effects of therapy. The algorithm for the management of childhood nephrotic syndrome is provided in Figure 13.1. The overall prognosis in these children is excellent. More than 80% of children would respond to initial steroid treatment, but more than 75% would relapse. Of these children who relapse, 50% would have frequent relapses or become steroid dependent.<sup>43,44</sup> Mortality from disease and treatment complications and progression to end stage renal disease is less than 5%.<sup>44</sup> Careful selection of immunosuppressive therapy and monitoring of their potential side effects are mandatory in the overall management of these children.

**Figure 13.1 Algorithm for the Management of Childhood Nephrotic Syndrome**



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## 14 Recommendations for Evaluation

The success of the implementation of these Guidelines can be evaluated by monitoring various parameters associated with the condition. Two important parameters to monitor are the prevalence of the condition and the impact of intervention on outcome.

### 14.1 Prevalence and pattern of glomerulonephritis

Early detection of glomerular disease is a key step in the prevention of renal failure due to glomerulonephritis. To assess the impact of these Guidelines on the early detection of glomerulonephritis, the true incidence of glomerulonephritis should be quantified and monitored over time. Ideally, this would require the identification of all patients with haematuria and proteinuria managed at primary, secondary and tertiary health care settings. Although, the vast majority of these patients are likely to be identified at the primary health care setting, the data would be difficult to capture and may be difficult to evaluate. A more realistic evaluation parameter would be to identify numbers of patients with more severe forms of glomerulonephritis. The high risk category of patients would include patients with proteinuria  $\geq 1$  g/day and those undergoing renal biopsy.

Renal biopsies are performed mainly to evaluate the cause of glomerular disease, to guide treatment and prognosticate; usually, they are performed in the presence of more severe glomerular disease. Thus the number of renal biopsies performed annually in the nation as well as the type and severity of glomerular disease should be evaluated to detect changing disease patterns. Changing patterns of glomerular disease can be obtained from renal biopsies and may predicate the need to change management guidelines.

The committee would thus recommend inclusion into the evaluation the following parameters:

1. Numbers of new referrals to nephrologists for proteinuria  $\geq 1$  g/day
2. Renal function, presence of hypertension and level of proteinuria at the time of referral for these patients
3. Numbers of renal biopsies performed annually by nephrologists
4. Pattern of glomerulonephritis in Singapore as obtained from renal biopsies

## 14.2 Outcome measures

In addition to prevalence and pattern of disease, outcome of interventions should be evaluated to determine the impact of implementation of evidence-based guidelines. These include:

1. Blood pressure, renal function and proteinuria following optimal management of high-risk patients with glomerulonephritis
2. Incidence of new End Stage Renal Failure due to glomerulonephritis in Singapore.

Ideal management of glomerulonephritis will result in reduction in level of proteinuria, stabilisation or improvement of renal function and excellent control of blood pressure. Thus, percent of patients with >50% reduction in proteinuria, the rate of deterioration of renal function and percent of patients with blood pressure below 130/80 mmHg should be monitored as parameters of efficacy of these Guidelines.

Finally, early and appropriate management of glomerular disease may result in a reduction in renal failure due to glomerulonephritis in Singapore and a shift in the pattern of renal failure.

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## Glomerulonephritis



Ministry  
of Health

NMRC  
National Medical  
Research Council

National Committee  
On Renal Care

### Management of glomerular disease – General measures

**B** Hypertension defined as blood pressure  $\geq 140/90$  mmHg in patients with renal disease should be treated in order to retard the rate of deterioration of renal function.

Grade B, Level IIb

**B** A target blood pressure  $< 125/75$  mmHg (Mean arterial pressure  $< 92$  mmHg) is recommended for patients with serum creatinine  $< 600$   $\mu\text{mol/l}$  and total urinary protein excretion  $\geq 1$  g/day.

Grade B, Level III

**C** A target blood pressure  $< 130/80$  mmHg (Mean arterial pressure  $< 98$  mmHg) is recommended for patients with serum creatinine  $< 600$   $\mu\text{mol/l}$  and total urinary protein excretion  $< 1$  g/day.

Grade C, Level IV

**A** Angiotensin converting enzyme inhibitor therapy is preferable to conventional therapy for treatment of hypertension in patients with glomerulonephritis as it confers greater renoprotection.

Grade A, Level Ib

**B** Angiotensin converting enzyme inhibitor therapy is preferable to calcium channel blockers for treatment of hypertension in patients with glomerulonephritis as it confers greater renoprotection.

Grade B, Level III

**B** Angiotensin II receptor antagonists can be used as an alternative to Angiotensin converting enzyme inhibitors to treat hypertension in patients with glomerulonephritis.

**Grade B, Level III**

**GPP** Angiotensin converting enzyme inhibitors or Angiotensin II receptor antagonists can be used to reduce proteinuria in patients with glomerulonephritis in the absence of hypertension.

**GPP** For patients with serum creatinine levels  $> 265 \mu\text{mol/l}$ , Angiotensin converting enzyme inhibitors and Angiotensin II receptor antagonists should be used with particular caution, with regular monitoring of serum creatinine and potassium.

**A** Patients with severe renal insufficiency (serum creatinine  $> 350 \mu\text{mol/l}$ ) should be considered for treatment with low protein diets. However, low protein diets should be used judiciously so as to avoid malnutrition and its potential adverse effects.

**Grade A, Level Ia**

**A** Lipid-lowering therapy does not confer renoprotection in patients with glomerular disease.

**Grade A, Level Ib**

**C** Lipid-lowering therapy is recommended for cardiovascular benefit in patients with glomerular disease.

**Grade C, Level IV**

## Approach to Haematuria

**B** Patients with microscopic haematuria ( $\geq 5$  RBCs/hpf) should be evaluated to exclude renal/urinary tract disease.

**Class B, Level III**

**B** Urine phase contrast microscopy under standard conditions is recommended to differentiate glomerular from non-glomerular sources of haematuria.

**Class B, Level III**

**B** Patients with isolated asymptomatic microhaematuria should remain on follow-up at 6-12 month intervals to monitor renal function and blood pressure.

**Class B, Level III**

**B** Asymptomatic microhaematuria  $< 5$  RBCs/hpf in patients  $< 40$  years of age does not require full urological evaluation in the absence of other clinical features of malignancy.

**Class B, Level III**

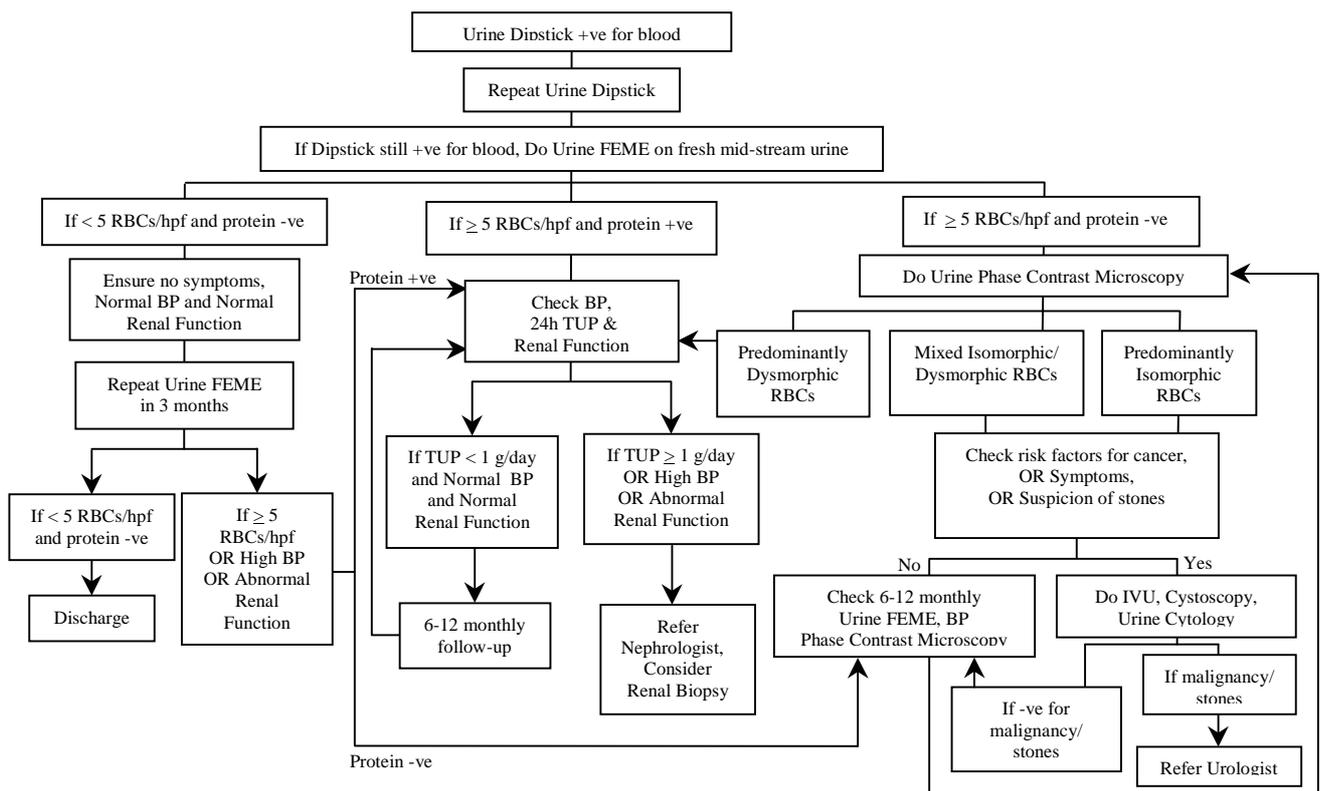
**B** All patients with gross haematuria should be evaluated for urological pathology with a combination of ultrasound, intravenous urography and flexible cystourethroscopy.

**Class B, Level III**

### Level of Evidence and Grade of Recommendations

Level	Type of Evidence
<b>Ia</b>	Evidence obtained from meta-analysis of randomised controlled trials.
<b>Ib</b>	Evidence obtained from at least one randomised controlled trial.
<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.
Grade	Recommendation
<b>A</b> (evidence levels Ia, Ib)	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 IIa, IIb, III)	Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation.
<b>C</b> (evidence level IV)	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.

## Approach to Haematuria



## Approach to Proteinuria

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

**Class B, Level III**

**B** Patients with intermittent isolated proteinuria have a favourable renal prognosis but should still be followed up six monthly until its resolution.

**Class B, Level III**

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

**Class B, Level III**

**B** Patients with persistent proteinuria  $\geq 1\text{g/day}$  have adverse renal histopathology and therefore worse ultimate renal prognosis and should undergo renal biopsy.

**Class B, Level III**

**B** Patients with microhaematuria and proteinuria, especially in the presence of red cell casts, hypertension and/or renal insufficiency should be referred for further nephrological assessment.

**Class B, Level III**

# Approach to Proteinuria

