

Current Therapeutic Strategies in Glomerulonephritis

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Abstract

Over the past 20 years the therapy of glomerulonephritis (GN) has evolved. Today apart from steroids and cyclophosphamide, newer agents like cyclosporine A and tacrolimus (FK 506) have been reported to achieve remission (partial or complete) in patients with nephrotic syndrome due to various GN which have failed to respond to steroids and cyclophosphamide. For those patients who do not respond to any of the primary therapeutic agents, there are now other therapies available like angiotensin II converting enzyme inhibitors, angiotensin II receptor antagonists, dipyridamole, low dose warfarin including protein restriction and therapy aimed at hypercholesterolaemia in an attempt to retard progression to end stage renal failure. This paper presents a therapeutic approach for the various forms of primary GN.

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Introduction

Twenty years ago, the therapy of glomerulonephritis (GN) was relatively simple as it was believed that treatment with prednisolone should be confined to patients with minimal change nephrotic syndrome and lupus nephritis.¹ For those patients who failed to respond, they were treated with oral cyclophosphamide. For all other forms of GN, treatment was empirical, consisting of diuretics and treatment of hypertension and sepsis when necessary. Minimal change nephrotic syndrome was treated with prednisolone as it was associated with selective proteinuria whereas all other forms of GN were generally considered to be associated with non-selective proteinuria and poor response to steroid therapy.²

Since then it has been documented that selective proteinuria was not confined only to patients with minimal change nephrotic syndrome and that patients with mesangial proliferative GN can also have selective proteinuria² and hence response to prednisolone and cyclophosphamide.³

In 1979, a collaborative study of idiopathic nephrotic syndrome reported high dose alternate day steroid responsiveness in adult membranous GN in spite of non-selective proteinuria⁴ and ever since, many nephrologists have prescribed steroids to patients with membranous GN, in spite of a subsequent report stating poor response to steroids in membranous GN.⁵

Today the rationale for steroid or cyclophosphamide therapy is no longer based on protein selectivity alone as

charge selectivity and documentation of other agents like angiotensin converting enzyme (ACE) inhibitors affecting shunt pathways and restoring glomerular permselectivity have widened the choice of therapeutic agents which decrease proteinuria in glomerular disease.

Into the 1990s and extending into the next millennium we are already seeing an array of various therapeutic agents like cyclosporine A, tacrolimus (FK 506) and even mycophenolate mofetil (MMF) being employed to treat different glomerulopathies.⁶

This paper attempts to provide a rational approach to therapy of the various glomerulopathies starting with conventional therapeutic choices and extending to newer options depending on the therapeutic response of the patients and for those who fail to respond to conventional therapy it offers alternate therapy to retard the progression to renal failure. This work is based largely on the experience of our Department and relates to the various forms of primary glomerulopathies excluding secondary glomerulopathies like lupus nephritis and diabetic nephropathy.

Pathogenesis of Renal Damage in Glomerulonephritis and the Rationale for Therapy

I. Immunological Phase

Glomerulonephritis can be considered a two-phase disease. The first acute or early phase is referred to as the immunological phase which is related to the deposition

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of immune complexes in the glomerulus or in some instances non-immune complex mediated injury or injury due to an antibody directed at the glomerular basement membrane (GBM) like linear anti-GBM antibody as in Goodpasture's syndrome.' In the immunological phase, noxious cytokines are released which in turn mediate the release of inflammatory chemo-attractants resulting in injury with glomerular scarring.⁷ It is this immunological phase which may respond to therapy with immuno-modulating drugs like prednisolone, cyclophosphamide and cyclosporin A (CyA).

In an attempt to treat any form of primary or idiopathic glomerulonephritis the ideal principle is to induce a remission with a primary agent, usually prednisolone or cyclophosphamide, sometimes a combination of both.* Now, a third agent, cyclosporin A (CyA) is also being offered as a second or third line therapeutic agent when the patient failed to respond to prednisolone followed by a course of cyclophosphamide.⁹

II. Hyperfiltration Phase

Later, with progression of glomerulosclerosis, a chronic or late phase occurs due to injury resulting from glomerular hyperfiltration.¹⁰ 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^{11,12} or angiotensin II receptor antagonist (ATRA) as well as dietary protein restriction.^{10,13} This is what is termed secondary therapy which aims at retardation of the progression to end stage renal failure (ESRF). Such therapy is based on the rationale 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 its receptors at the efferent glomerular arteriole; whilst a restricted or low protein diet would decrease the afferent glomerular vasodilation associated with hyperfiltration because a high protein diet acts to increase the macro-molecular traffic at the afferent glomerular arteriole since the macro-molecules act as blood-attractant causing deposition of the macro-molecules in the mesangial bed inducing proliferation of mesangial cells and matrix.^{10-12,14}

The end result of the above therapy therefore decreases afferent glomerular blood flow to the glomeruli and causes efferent glomerular arteriolar vasodilation, hence resulting in a decrease in intraglomerular hypertension due to glomerular hyperfiltration causing a decrease in proteinuria since hyperfiltration pressure is now decreased. The associated endothelial cell and platelet damage associated with hyperfiltration is also de-

creased when the glomeruli are subject to a lowered intraglomerular blood pressure with the reduction of glomerular hyperfiltration.¹⁵ Dipyridamole and low dose warfarin may ameliorate endothelial and platelet injury resulting from intraglomerular hypertension. Warfarin prescribed in an anticoagulant dose may cause intraglomerular haemorrhage with renal deterioration.

Clinical and Pathological Classification of Glomerulonephritis

I. Clinical Syndromes

In clinical practice the major clinical syndromes are:

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

II. Pathological Classification

Histological classification defines GN in the following categories:

1. Minimal change disease
2. Focal global sclerosis
3. Diffuse mesangial proliferative GN, focal proliferative GN
4. Membranous GN
5. Mesangio-capillary GN
6. Crescentic GN (RPGN)
7. Focal sclerosing glomerulosclerosis (FSGS)
8. Diffuse sclerosing GN

I. Acute Nephritic Syndrome

Aetiology

Patients with acute nephritic syndrome present with oedema associated with gross haematuria (smoky urine) and hypertension. The aetiology could be post-streptococcal. However post-infectious GN (PIGN) is a better term since bacteria, virus and parasite can cause PIGN. Histology reveals diffuse endocapillary GN with exudation of polymorphs.

Course and Prognosis

Generally patients have a good prognosis with 95% renal survival at 5 years and 90% at 10 years.¹⁷ Singhal et al¹⁸ reported that 25% of patients developed renal failure at 10 years. Systemic lupus erythematosus (SLE) should be excluded from any patients with nephritic nephrotic syndrome.

Treatment is symptomatic and one has to restrict salt and fluid intake, treat sepsis, hypertension and heart failure.

II. Nephrotic Syndrome

Aetiology

Screening Causes for Nephrotic Syndrome

When screening for nephrotic syndrome, the following have to be excluded:

1. Drugs e.g. Gold, Penicillamine, Captopril and non-steroidal anti-inflammatory drugs (NSAIDs).
2. Infections e.g. hepatitis B, C, malaria and HIV.
3. Autoimmune diseases e.g. SLE, cryoglobulinaemia and thyrotoxicosis.
4. Neoplasm of the lungs and gastrointestinal tract as well as lymphoma.

To test for amyloidosis, perform protein electrophoresis and myeloma screening. To exclude diabetes mellitus, do fasting blood sugar and HbA1C.

General Management

Reduce gross oedema to a point where patient is comfortable and use high dose frusemide (80 mg to 750 mg daily), with spironolactone, hydrochlorothiazide and bumetanide if necessary. Limit malnutrition as it can be life-threatening. For those with a low serum albumin, introduce high protein diet. Also use ACE inhibitor to reduce GFR and limit protein loss in urine. Prevent thrombosis as it occurs in 30% to 50% (renal, deep vein thrombosis, cerebral, cardiac) of patients.¹⁹ Dipyridamole and low dose warfarin may be useful. Treat hyperlipidaemia and infection.

Prednisolone, Cyclophosphamide, Cyclosporine A (PCC) Regimen

a) Primary therapy to induce remission

Give prednisolone at 1 mg/kg body weight (BW) per day and reduce to 10 mg by 3 months; maintain for another 3 months (total of 6 months). If this fails, try cyclophosphamide at 2 mg/kg BW for 3 to 6 months (depending on GN) plus prednisolone 30 mg/day for 2 months, 20 mg/day for 1 month, then 10 mg/day. If the above fails, try cyclosporine A at 5 mg/kg for 3 months, 4 mg on the 4th month, 3 mg on the 5th month and 2 mg on the 6th month and maintain; plus prednisolone 30 mg/day for 2 months, 20 mg for 1 month, then 10 mg. Chlorambucil (0.15 to 0.2 mg/kg BW/day for 3 months) or tacrolimus (FK 506) (0.1 to 0.2 mg/kg BW/day for 3 months) can be considered in those who have failed other therapies. Mycophenolate mofetil (MMF) has been used empirically in some patients with resistant nephrotic syndrome or renal impairment with some success in a dose 0.75 to 1.0 gm twice daily for 3 months.⁶

b) Secondary therapy to retard progression to ESRF

1. Treatment for hypertension.
2. ACE inhibitor to reduce intraglomerular

hypertension.

3. Angiotensin receptor antagonist (ATRA) to reduce intraglomerular hypertension (Losartan).
4. Dipyridamole and low dose warfarin to reduce endothelial and platelet injury resulting from intraglomerular hypertension.
5. Restricted protein diet (0.8 gm/kg SW) to decrease afferent glomerular arteriolar vasodilation.
6. Treatment of hyperlipidaemia as cholesterol is toxic to mesangial cells.

Minimal Change Disease

Course and Prognosis

This is a disorder of the T-cells with abnormal lymphokine production.²⁰ In Singapore,²¹ adult minimal change disease accounts for 30% and focal global sclerosis (FGS) 20% of all nephrotics; both forms of GN are steroid responsive. In Singapore, adult minimal change disease is the most common histology for those with nephrotic syndrome. Thirty per cent of patients are primary responders and non-relapsers, 70% would relapse with 60% repeatedly. The frequency of relapse is less after 10 years. A relapse may occur after treatment has been stopped or during reduction of steroids (steroid dependent responders). A small number of patients after repeated relapses and remissions would acquire steroid resistance leading to focal and segmental glomerulosclerosis (FSGS) which has a bad prognosis. Five-year renal survival was 98% and 10-year survival was 95%.⁸

Treatment of Minimal Change Disease and Focal Global Sclerosis

Prednisolone should be prescribed at 1 mg/kg BW a day or 60 mg for an adult weighing 60 kg, with gradual reduction to reach 10 mg at 3 months (first 4 weeks 60 to 45 mg/day, next 2 weeks 30 mg, then 2 weeks 20 mg, 2 weeks 15 mg, and 2 weeks at 10 mg/day). If patient relapses after treatment is stopped or during reduction of steroids, then therapy will be re-started but with slower reduction. Maintain prednisolone at 10 mg/day. In a patient with steroid dependence or a frequent relapser (2 or more relapses in 6 months), start cyclophosphamide at 2 mg/kg BW for 3 months. In a patient with steroid and cyclophosphamide resistance, start cyclosporine A (CyA) 5 mg/kg BW for 3 months, reduce to 2 mg over next 3 months, maintain at 2 mg for another 3 months and thereafter attempt to withdraw CyA.

Mesangial Proliferative Glomerulonephritis

Course and Prognosis

This form of GN accounts for 25% of idiopathic nephrotic syndrome in Singapore [32% of them are immunofluorescence (IMF) negative].²¹ IgA Nx accounts for 8% of nephrotics. A negative IMF and selective proteinuria denote a good chance of steroid responsiveness. The

long-term evolution of this form of GN is steroid resistance with FSGS lesions (non-selective proteinuria) leading to chronic renal failure (CRF). Waldher's²² series showed that 50% patients were steroid resistant while 70% had associated FSGS.

Treatment of Mesangial Proliferative GN

Treat with prednisolone; if it fails, try cyclophosphamide, then CyA in that order. The rationale of using this stepwise progression of drugs is that the majority of patients, based on our experience, would respond to prednisolone. Those who fail to respond may respond to the more toxic cyclophosphamide.²¹ CyA which is the most expensive is kept as a reserve for those who fail cyclophosphamide or where it is less desirable like in younger patients because of the risk of infertility and sterility.

Membranous GN

Course and Prognosis

This is the commonest GN occurring in the West (35%).²³ In Singapore,²¹ it accounts for 12% of all nephrotics. The disease runs a slowly progressive course with remissions and exacerbations of nephrotic syndrome. Thirty-five per cent have spontaneous remission with another 25% having spontaneous partial remission (proteinuria <2 gm/day). There is a better prognosis in those with partial remission compared to those with no response at all. If a patient develops progressive renal failure within months, consider hypersensitivity interstitial nephritis, superimposed crescents, renal vein thrombosis or profound hypovolaemia from proteinuria.

Treatment of Membranous GN

The use of high dose prednisolone [120 mg every other day (eod) or 60 mg daily] reducing to 10 mg/day within 3 to 4 months is advocated.⁵ If the above regimen fails, a combination of low dose prednisolone (30 mg/day) and cyclophosphamide (2 mg/kg BW/day) is the best choice. If it also fails, try chlorambucil (0.15 to 0.2 mg/kg BW/day) for 3 months.²⁴ There is a potential role for CyA and tacrolimus (FK 506) (0.1 to 0.2 mg/kg BW/day for 3 months).²⁵ Reducing proteinuria to less than 2 gm/day improves survival. Renal survival was 75% at 5 years and 50% at 10 years.²⁶

Focal Segmental Glomerulosclerosis (FSGS)

Course and Prognosis

There is a rising incidence of this GN in most countries.²⁷ In Singapore,²¹ it accounts for about 9% of all nephrotics. This is due to an abnormal T-cell function with a lymphokine inducing a proteinuric factor which causes severe proteinuria. The prognosis depends on the

degree of proteinuria, renal impairment and severity of tubulo-interstitial lesions on biopsy. Rydel et al²⁸ reported at 10 years, 100% renal survival for responders, 39% for non-responders and 47% for untreated nephrotics. Cameron²⁹ reported that renal survival rates were 70% at 5 years and 50% at 10 years.

Treatment of Focal Segmental Glomerulosclerosis (FSGS)

Initial studies reported little benefit with treatment.³⁰ Nowadays with treatment, response ranges from 30% to 50% (including partial response).³¹ Start with high dose prednisolone (1 mg/kg BW/day) for 2 months, reduce to 10 mg/day by the end of the 4th month and maintain until 6 months together with cyclophosphamide (2 mg/kg BW) for 6 months. This combination gives the best response. If there is no response, try cyclosporine A and maintain with CyA for sustained response. Frequent monitoring of renal function and CyA levels when using CyA in patients with renal impairment is required. Potential role for tacrolimus (FK506) is being explored.²⁵ Transplant recurrence ranges from 20% to 50%. Treat as soon as proteinuria recurs after transplant using plasmapheresis and high dose CyA (8 mg/kg BW).

Mesangio-Capillary GN (MCGN)

Course and Prognosis

In this GN, spontaneous remissions are uncommon. Fifty per cent present with nephrotic syndrome, 20% acute nephritic syndrome and 30% asymptomatic haematuria and proteinuria. Fifty per cent would develop renal failure, prognosis is worse if patients are nephrotic and there are crescents on biopsy. In any patient with acute nephritic-nephrotic syndrome, always exclude SLE. Idiopathic MCGN is uncommon in Singapore. Renal survival rates for Type I MCGN were 80% at 5 years and 60% at 10 years. For Type II MCGN, the rates were 60% at 5 years and 40% at 10 years.¹⁷

Treatment of Mesangio-Capillary GN

Treatment is controversial as there are no prospective trials. McEnery et al³² showed beneficial effects of continuous alternate day low dose prednisolone (30 mg). Kincaid-Smith³³ reported a 3-year renal survival of 82% using a combination of cyclophosphamide, dipyridamole and warfarin (Melbourne Cocktail). In Singapore, we advise a trial of high dose prednisolone for 3 months (1 mg/kg BW/day, reduce to 10 mg/day by the end of 3 months and maintain for 3 months). If there is no response, switch to low dose prednisolone (30 mg/day for 2 months, then 20 mg/day for 1 month, then 10 mg) with cyclophosphamide 2 mg/kg BW for 6 months together with dipyridamole and low dose warfarin. For those with aggressive disease with crescents present on biopsy, use plasmapheresis, methyl-prednisolone pulse and cyclophosphamide. Exclude SLE in all patients.

III. Crescentic GN (Rapidly Progressive GN)

Aetiology

Suspect if a patient has proteinuria, microscopic haematuria with red blood cell casts and rapidly rising serum creatinine. This is a nephrologic emergency and treatment should commence within 24 hours of diagnosis. Fifty per cent of patients have preceding flu-like illness. Hypertension is mild to moderate. Classify by absence or presence of glomerular immune-complexes:

- i) Linear anti-GBM antibody-Goodpasture's syndrome.
- ii) Granular immune complexes-systemic lupus erythematosus, Henoch-Schonlein nephritis, subacute bacterial endocarditis, post-infections GN.
- iii) Pauci-immune complexes-Wegener's granulomatosis, polyarteritis nodosa, idiopathic crescentic GN.

Course and Prognosis

Renal biopsies showing circumferential crescents >80% with oliguria and serum creatinine >500 micro mol per litre (M/L) indicate poor recovery. Renal survival rates for those with 50% to 80% crescents were 30% at 5 years and 10% at 10 years. For those with more than 80% crescents renal survival rates were 8% at 5 years and 5% at 10 years.³⁴

Treatment of Crescentic GN

Therapy consists of plasmapheresis, methyl-prednisolone pulsing followed by prednisolone and cyclophosphamide for those with serum creatinine less than 500 micro M/L. Dipyridamole and low dose warfarin are usually added.

Wegener's Granulomatosis

Course and Prognosis

In this condition there is granulomatous vasculitis of small arterioles and venules. Patients present with rapidly progressive GN with crescents. Eighty per cent to 90% of patients are positive for cytoplasmic-anti neutrophilic cytoplasmic antibody (c-ANCA) which is highly specific and sensitive in the diagnosis. If untreated, there is 80% to 90% mortality.

Treatment of Wegener's Granulomatosis

Those treated with cyclophosphamide have 80% to 90% remission.²¹ There is a tendency for a high incidence of cancer of the bladder 10 years later resulting from cyclophosphamide therapy.²¹ Prednisolone is used as an adjunctive especially for severe renal, pulmonary, skin or cerebral vasculitis.

IV. IgA Nephritis

Course and Prognosis

This is the commonest GN occurring in Singapore

accounting for 52% of all biopsies.³⁵ Patients present as asymptomatic haematuria and proteinuria (65%), gross haematuria (15%), nephrotic syndrome (8%), acute nephritis (2%), chronic renal failure (4%) and hypertension (6%). Histologically, 72% of patients have diffuse mesangial proliferative GN, 9% focal proliferative GN, minimal change 2%, focal global sclerosis 4%, FSGS 7% and diffuse sclerosing GN 7%. The bad prognostic features are proteinuria more than 1 gm, hypertension, renal impairment, glomerulosclerosis more than 20%, crescents and medial-hyperplasia of blood vessels. This is not a benign disease as 30% of patients develop chronic renal failure at 10 years.³⁶

Clinical Syndromes

Asymptomatic Haematuria and Proteinuria

This is the most common sign for a wide variety of GN. In Singapore, IgA nephritis is the commonest cause of asymptomatic haematuria and proteinuria (Asymp H+P). Asymptomatic haematuria and proteinuria is often found on routine screening. SLE is to be excluded in all patients. Membranous GN may sometimes present with asymptomatic haematuria and proteinuria. If patient had a history of gross haematuria with dysuria and frequency, the diagnosis is cystitis. In those with gross haematuria with upper respiratory tract infection, it is synpharyngitic haematuria indicating a diagnosis of IgA nephritis. SLE has to be excluded too. In the elderly, suspect malignancy of the kidney or bladder. If patients have dysmorphic RBC, it is GN and if isomorphic RBC, do IVP to exclude stone or cancer. For those with significant proteinuria more than 0.5 gm, it is GN; reflux nephropathy may sometimes present with proteinuria.

Treatment of Specific Clinical Syndromes

(i) In those with asymptomatic haematuria and proteinuria, treatment^{16,37-39} consists of:

1. Dipyridamole and low dose warfarin (antiplatelet and anti-thrombotic therapy); 75 to 100 mg dipyridamole tds, 1 to 3 mg warfarin (INR 1.2 to 1.5). The rationale for therapy with dipyridamole and low dose warfarin is based on our earlier work showing increased platelet aggregation and a thrombogenic tendency in patients with IgA NX.^{16,37-39} Further indication for dipyridamole and low dose warfarin is to reduce platelet and endothelial cell damage resulting from intraglomerular hypertension. The therapeutic efficacy of these agents have been demonstrated in our earlier controlled trials.^{16,37-39}
2. Treatment of hypertension.
3. ACE inhibitor to decrease intraglomerular hypertension.
4. Angiotensin receptor antagonist (ATRA) to decrease intraglomerular hypertension (Losartan).

5. Restricted protein diet (0.8 gm/kg SW) to reduce afferent glomerular arteriolar vasodilation:
6. Treatment of hyperlipidaemia as high cholesterol is toxic to mesangial cells.

(ii) Therapy for IgA nephrotic syndrome

Those patients with nephrotic syndrome with selective proteinuria tend to respond to therapy irrespective of histology.⁴⁰ Treat with prednisolone at 1 mg/kg BW a day and reduce to 10 mg by 3 months, maintain for another 3 months. If this fails, use cyclophosphamide at 2 mg/kg BW a day for 3 months with 30 mg prednisolone a day for 2 months, then 20 mg/day for 1 month, then 10 mg. If the above fails, use cyclosporine A at 5 mg/kg BW for 3 months, then 4 mg on the 4th month, 3 mg on the 5th month and 2 mg on the 6th month plus prednisolone initially 30 mg/day with gradual tapering to 10 mg/day.

(iii) Therapy for IgA nephritis with tubule-interstitial nephritis

Patients with tubulo-interstitial nephritis exceeding the degree of glomerular involvement, are to be treated with low dose prednisolone at 30 mg/day for 2 months, 20 mg/day for 1 month, and 10 mg/day for next 3 months. The above therapy will reduce post-capillary fibrosis which causes ischaemic damage.⁴¹

(iv) Therapy for IgA nephritis with acute renal failure and crescents

Usually 30% to 50% of glomeruli in these patients would show crescents. Treat with methyl-prednisolone Pulse 0.5 gm I.V. daily e.o.d. for 6 doses. Thereafter start prednisolone 1 mg/kg BW a day and reduce over 3 to 4 months, maintain for 3 months at 10 mg/day. Also start cyclophosphamide 2 mg/kg BW a day for 3 to 4 months. Plasmapheresis should be instituted if there is no response to above after 2 weeks or if crescents exceed 50% on renal biopsy. Dipyridamole and warfarin should be given in addition.

Future Therapeutic Perspectives for Glomerulonephritis

Current therapeutic strategies either based on immunomodulation to secure long lasting primary remission or other strategies based on a rationale to ameliorate hyperfiltration injury are at best empirical. Future therapeutic strategies would lie in prevention of immune complex deposition in the glomerulus either by using agents targeted at dissolution of immune complexes or by agents which could inhibit receptors which bind immune complexes to the glomerulus. A more practical approach should probably be based on molecular biological intervention either to neutralise cytokines using their antagonists (eg anti-PDGF or Tumour Necrosis Factor (TNF) alpha antagonist or blocking cytokine receptors or even inhibiting their

intracellular signalling pathway. This would help to arrest progression of the disease. However in most forms of GN, by the time they are diagnosed, many patients would be in the chronic phase where immunomodulating therapy and anti-cytokine therapy may not be very efficacious. Therefore for a long time to come we would still have to rely on measures to retard progression to ESRF.

REFERENCES

1. Cameron J S. The clinical significance of glomerular permeability studies. *Proc R Soc Med* 1966; 59:512-5.
2. Woo K T, Wu A Y T, Lau Y K, Lee E J C, Edmondson R P S, Pwee H S, et al. Protein selectivity in IgA nephropathy. *Nephron* 1986; 42:236-9.
3. Woo K T, Lau Y K, Yap H K, Lee G S L, Chiang G S C, Lim C H. Protein selectivity: A prognostic in IgA nephritis. *Nephron* 1989; 52:300-6.
4. Collaborative study of the adult idiopathic nephrotic syndrome: a controlled study of short-term treatment in adults with membranous nephropathy. *N Engl J Med* 1979; 301:1301-6.
5. Cattran D C, Delmore T, Roscoe J. A randomised controlled trial of prednisolone in patients with idiopathic membranous nephropathy. *N Engl J Med* 1989; 320:210-5.
6. Briggs W A, Choi M J, Scheel P J Jr. Successful mycophenolate mofetil treatment of glomerular disease. *Am J Kidney Dis* 1998; 31:213-7.
7. Danoff T M, Neilson E G. The role of chemo-attractants in renal disease. In: Neilson E G, Couser W G, editors. *Immunologic Renal Diseases*. Philadelphia, New York: Lippincott-Raven, 1997:499-517.
8. Cameron J S. Treatment of primary glomerulonephritis using immunosuppressive agents. *Am J Nephrol* 1989; 9(Suppl1):33-40.
9. Broyer M, Meyrier A, Niaudet P, Habib R. Minimal changes and focal segmental glomerular sclerosis. In: Cameron J S, Davison A M, Grunfeld Y P, Ken D, Ritz E, editors. *Oxford Textbook of Clinical Nephrology*. Oxford: Oxford Univ Press, 1992:298-339.
10. Brenner B M, Meyer T W, Hostetter T H. Dietary protein and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in sclerosis in aging, renal ablation and intrinsic renal disease. *N Engl J Med* 1982; 307:652-9.
11. Maschio G, Cagnoli L, Claroni F, Fusaroli M, Rugiu C, Sanna G, et al. ACE inhibition reduces proteinuria in normotensive patients with IgA nephropathy: A multicentre, randomized, placebo-controlled study. *Nephrol Dial Transplant* 1994; 9:265-9.
12. Tanaka R, Kon V, Yoshioka T, Ichikawa I, Fogo A. Angiotensin converting enzyme inhibitor modulates glomerular function and structure by distinct mechanisms. *Kidney Int* 1994; 45:537-43.
13. Anderson S, Rennke H G, Brenner B M. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest* 1986; 77:1993-2000.
14. Yoshida Y, Kawamura T, Ikoma M, Fogo A, Ichikawa Y. Effects of antihypertensive drugs on glomerular morphology. *Kidney Int* 1989; 36:26-35.
15. Diamond J R, Karnovsky M J. Focal and segmental glomerulosclerosis: Analogies to atherosclerosis. *Kidney Int* 1988; 33:917-24.
16. Woo K T, Lee G S L, Lau Y K, Chiang G S C, Lim C H. Effects of triple therapy in IgA nephritis: A follow up study 5 years later. *Clin Nephrol* 1991; 36:60-6.
17. Glassock R J, Adler S A, Ward H J, Cohen A H. Primary glomerular diseases. In: Brenner B M, Rector F C, editors. *The Kidney*. Philadelphia: W B Saunders Co, 1991:1182-279.
18. Singhal P C, Malik G H, Narayan G, Khan A S, Bhusnurmath S, Datta B N, et al. Prognosis of post-streptococcal glomerulonephritis: Chandigarh Study.

- Ann Acad Med Singapore 1982; 11:36-41.
19. Becker G J. Nephrotic syndrome in adults – Principles of management. In: Yap H K, Tan C C, Woo K T, editors. Proceedings of the 11th Asian Colloquium in Nephrology. Singapore: Armour Publishing, 1996:235-40.
 20. Shalhoub R J. Pathogenesis of lipid nephrosis: A disorder of T cell function. *Lancet* 1974; 2:556-60.
 21. Woo K T. Nephrotic syndrome. In: Clinical Nephrology. Singapore: World Scientific Publishing and Singapore University Press, 1998:57-81.
 22. Waldher R, Gubler M C, Levy M, Broyer M, Habib R. The significance of pure diffuse mesangial proliferation in idiopathic nephrotic syndrome. *Clin Nephrol* 1978; 10:171-9.
 23. D'Amico G. Focal segmental glomerulosclerosis (FSGS) revisited. In: Yap H K, Tan C C, Woo K T, editors. Proceedings of the 11 th Asian Colloquium in Nephrology. Singapore: Armour Publishing, 1996:227-34.
 24. Ponticelli C, Zucchelli I, Passerini P, Cesana B, Locatelli F, Pasquali S, et al. A 10 year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. *Kidney Int* 1995; 48:1600-4.
 25. McCauley J, Shapiro R, Ellis D, Igdal H, T Zakis A, Starzl T E. Pilot trial of FK 506 in the management of steroid resistant nephrotic syndrome. *Nephrol Dial Transplant* 1993; 8:1286-90.
 26. Cameron J S. The long term outcome of glomerular diseases. In : Schrier R N, Gottschalk C V, editors. Diseases of the Kidney. London: Little Brown & Co, 1992:1895-958.
 27. Haas M, Spargo B H, Coventry S. Increasing incidence of focal-segmental glomerulosclerosis among adult nephropathies: A 20-year renal biopsy study. *Am J Kidney Dis* 1995; 26:740-50.
 28. Rydel J J, Korbet S M, Borok RZ, Schwartz MM. Focal segmental glomerular sclerosis in adults : Presentation, course, and response to treatment. *Am J Kidney Dis* 1995; 25:534-42.
 29. Cameron J S. The problem of focal segmental glomerulosclerosis. In: Kincaid-Smith P, d'Apice A J F, Atkins R, editors. Progress in Glomerulonephritis. New York: John Wiley and Sons, 1979:209-28.
 30. Beaufrils H, Alphonse J C, Guedon J, Legain M. Focal global sclerosis: Natural history and treatment. A report of 70 cases. *Nephron* 1978; 21:75-85.
 31. Banfi G, Moriggi M, Sabadini E, Fellin G, D'Amico G, Ponticelli C. The impact of prolonged immunosuppression on the outcome of idiopathic focal-segmental glomerulosclerosis with nephrotic syndrome in adults. A collaborative retrospective study. *Clin Nephrol* 1991; 36:53-9.
 32. McEnery P T, McAdams A J, West C D. Membranoproliferative glomerulonephritis: improved survival with alternate day prednisolone therapy. *Clin Nephrol* 1980; 13:117-24.
 33. Kincaid-Smith P. The natural history and treatment of mesangiocapillary glomerulonephritis. Morphology, natural history and treatment. Part I. New York: John Wiley and Sons, 1973:591-609.
 34. Davis C A, McEnery P T, Maby S, McAdams A J, West C D. Observations on the evolution of rapidly progressive glomerulonephritis. *Clin Nephrol* 1978; 9:91-102.
 35. Woo K T, Edmondson R P S, Wu A Y T, Chiang G S C, Pwee H S, Lim C H. The natural history of IgA nephritis in Singapore. *Clin Nephrol* 1986; 25:15-21.
 36. D'Amico G. Epidemiology, clinical and prognostic indices in IgA nephropathy. *Nephrology* 1997; 3:13-7.
 37. Woo K T. Treatment of IgA nephropathy in Singapore. *Nephrology* 1997; 3:S731-3.
 38. Woo K T, Edmondson R P S, Yap H K, Wu A Y T, Chiang G S C, Lee E J C, et al. Effects of triple therapy on the progression of mesangial proliferative glomerulonephritis. *Clin Nephrol* 1987; 27:56-64.
 39. Lee G S L, Woo K T, Lim C H. Controlled trial of dipyridamole and low dose warfarin in patients with IgA nephritis with renal impairment. *Clin Nephrol* 1989; 31:276.
 40. Woo K T, Lau Y K, Wong KS, Chin Y M, Chiang G SC, Lim C H. Isoelectric focussing and protein selectivity index as predictors of response to therapy in IgA nephrotic syndrome. *Nephron* 1994; 67:408-13.
 41. Bohle A, Mackensen-Haen S, von Gise H. Significance of tubulointerstitial changes in the renal cortex for the excretory function and concentration ability of the kidney: A morphometric contribution. *Am J Nephrol* 1987; 7:421-33.