Treatment of glomerulonephritis

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Summary

The management of a patient with glomerulonephritis depends on an understanding of the clinical features, pathology and possible aetiology. The treatment is then divisible into treatment of the syndrome and treatment of the cause.

Classification of Glomerular Disease

It is not possible to cover the treatment of glomerulonephritis without first outlining the classification of glomerular diease (Table 1). The unusual feature of glomerular disease is that clinicians commonly use all 3 forms of classification concurrently.

Table 1. Classification of Glomerular Disease

1.	Clinical	Syndromes
2.	Pathological:	Microscopic appearance
3.	Aetiological:	Primary and secondary

Classification by Clinical Syndrome. (Table 2)

The most impressive clinical syndromes are those of nephrosis and acute nephritis, though more patients overall present with the features of chronic glomerulonephritis i.e. a varying mixture of persistent microscopic haematuria, moderate proteinuria, hypertension and impaired renal function.

Table 2. Clinical Syndrome of Glomerular Disease

- Nephrotic Syndrome
- Acute Nephritic Syndrome
- Haematuria (macroscopic)
- Chronic glomerulonephritis
  - haematuria
  - proteinuria
  - hypertension
  - renal failure

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Classification by Aetiology

As research progresses we are becoming increasingly aware of the causes of glomerular disease, however there are still a large number of patients in whom the cause of renal disease is as yet unknown, hence it is currently termed "idiopathic".

Classification by Pathology

The advent of renal biopsy has allowed a classification based on the microscopic appearance of the glomerulus. This has resulted in the terms "glomerulopathies" where an inflammatory basis does not seem the most important feature (e.g. diabetes, amyloid, thrombotic microangiopathy) and "glomerulonephritis" where inflammation is believed to be present. We shall concentrate on the latter. For practical purposes it is simple to divide "glomerulonephritis" into those in which an excess of nuclei are seen in glomeruli-proliferative, and those in which this not a marked feature: non-proliferative. This division is particularly useful because in general diseases with marked proliferation are normally associated with haematuria, as in nephritis, while non-proliferative disease associates with proteinuria, as in nephrosis.

The Nephrotic Syndrome

Management of the nephrotic syndrome involves the treatment of the features of the syndrome and, when possible, of the cause.

Treatment of the Syndrome

Proteinuria and oedema

The mechanisms underlying the genesis and perpetuation of nephrotic oedema are not entirely understood, however, a considerable body of evidence has recently emerged which supports the notion that a primary impairment of salt and water excretion by the nephrotic kidney plays a major role in the pathogenesis of the nephrotic syndrome[1,2]. Modern management depends largely on the use of loop diuretics often in very high doses e.g. frusemide 160-500mg daily. Although the renal clearance of loop diuretics is normal and the total amount of drug reaching the urine is similar to that of normal subjects[3] there is decrease in the unbound drug accessible to its site of action in the loop of Henle secondary to increased urinary protein. The dose of loop diuretic should be titrated upward to combat both this pharmacodynamic resistance and the pharmakokinetic resistance if concomitant renal

insuffciency exists. Some benefit may be added by bed rest, aldosterone antagonism (spironoloctone) and thiazide diuretics. In refractory cases, intravenous salt poor albumin may be required to temporarily overcome a crisis of fluid overload with oliguria.

There is an argument in some chronic refractory cases to reduce proteinuria by deliberately reducing glomerular filtration rate with angiotensin converting enzyme inhibitors[4] or nonsteroidal anti-inflammatory drugs (NSAID's). The danger of precipitating acute renal failure is obvious, hence this is extremely unwise if dialysis is not readily available.

Thrombosis

Recently we have become increasingly aware of the high risk of thrombosis in nephrotic syndrome, paticularly in adults with membranous nephritis or amyloidosis. Accordingly all patients with nephrosis should be anticoagulated unless a constraindication exits. There is little published information on the use of fibrinolytic therapy in acute renal vein thrombosis. Also the relative efficacy of heparin versus fibrinolytic agents in renal vein thrombosis is undefined. Stopping warfarin in the continuing presence of a nephrotic syndrome may lead to late rethrombosis[5] and a reasonable policy is to countinue warfarin until the nephrotic syndrome remits or at least until the serum albumin in above 20 g/L.

Infection

Primary pneumococcal peritonitis and other infections are responsible for the rare deaths in childhood nephrosis, and in adults splitting of the skin with associated cellulitis can occur. Prophylactic penicillin, pneumococcal vaccination and intravenous immunoglobulin should be considered and a vigliant approach with early antibiotic therapy must be maintained.

Hypercholesteremia

Hypercholesteremia is a feature of most cases of severe nephrosis. Though poorly documented, an associated risk vascular disease is assumed[6] and, at least theoretically, hyerlipidemia may contribute to progression of renal failure[7]. As recently reviewed by D'Amico and Gentle[8] relatively few studies have examined the response of individuals with nephrotic syndrome-induced hyperlipidaemia to either pharmocologic or dietary therapy. The advent of effective treatment of hypocholesteremia with HMA CoA reductase inhibitors (e.g. simvastatin) has resulted in consideration of this feature in the overall treatment of chronic nephrosis. In general, fibrates and bile acid binders, are poorly tolerated in neprotic patients. Whether treatment will affect morbidity and mortality either during the nephrotic phase or during subsequent renal failure in those who progress is quite unknown.

Endocrine abnormalities

Clinically, both osteomalacia and hyperparathyroidism have been described in nephrotic children more often than adults although they are rarely of major clinical significance and renal biopsies are often normal. Vitamin D therapy is not recommended in all patients with the nephrotic syndrome. However it is indicated in patients with unremitting or relapsing nephrotic syndrome who have evidence of persistent decreases in ionising calcium and/or of altered bone histology. An important finding in the study of Tessitore et al[9] was that nephrotics with reduced renal function readily develop bone disease and early treatment with vitamin D may have a place.

Treatment of the Cause

Nephrotic syndrome can be caused by both glomerulonephritis and glomerulopathies (Table 3).

Table 3. Nephrotic Syndrome

Common Causes

1. *Glomerulonephritis*
   - Minimal change
   - Focal glomerulosclerosis (FGS)
   - Membranous
   - Membranoproliferative
2. *Glomerulopathy*
   - Diabetes
   - Amyloid

Minimal Change Nephritis

Characterised by very little in the way of light microscopic abnormality, minimal change nephritis is the commonest cause of simple nephrotic syndrome in childhood. The aeitiology is usually unknown, thought those causes that have been detected suggest that the glomerular permeability is due to the effect of lymphocyte derived agents or lymphokines[10,11]. The disease is characterised by the sudden onset of severe nephrotic syndrome, constituting over 80% of this picture in children, and 20% in adults. Associated renal failure is rare, and if present is due to prerenal effects as intravascular depletion or complicating sepsis.

Fortunately this is the most treatable of all glomerular diseases. Prednisolone (60 g/day or 1-1.5 mg/kg/day) will result in rapid reduction of the proteinuria usually at 10 days of treatment. In true minimal change disease virtually 100% of patients will have experienced resolution within 6-8 weeks (Figure 1). Prednisolone is then tapered over a further 6 weeks.

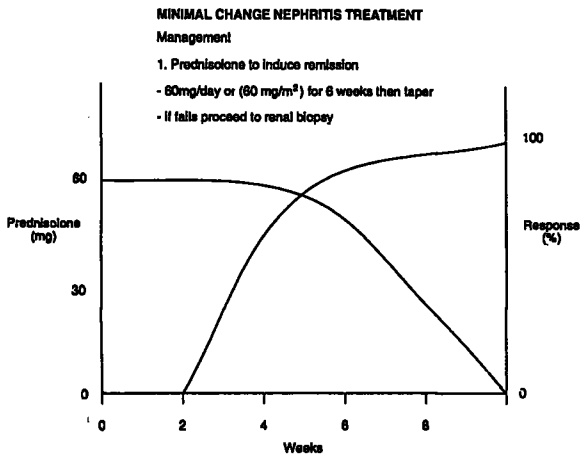

Figure 1

Unfortunately relapse occurs within 12 months in about 60% of cases. Relapse can be dealt with by repeated courses of Prednisolone. In frequent relapsers a threshold maintenance dose may be found, or a course of Cyclophosphamide considered. Cyclophosphamide (2.5 mg/kg/day) given for 6 weeks (a course insufficient to cause significant sterility, carcinogenesis or other long-term side effects) will reduce the relapse rate from 60% to about 20%.

Other immune active agents such as cyclosporine and levamisole have been ancedotally useful in minimal change disease. however expence and inconvenience generally contraindicate their use. In patients who have an indequate response to prednisolone the possibility that another cause is present should lead to renal biopsy.

Minimal change disease appears to merge clinically and therapeutically with a much more sinister disease-focal glomerulosclerosis (FGS).

Focal Glomerulosclerosis

Characterised histologically by wedges of sclerosis (scarring) and hyalinosis (pink glassy deposits) in glomeruli, the pathological entity FGS has wide variety of causes (Table 4). The primary or idiopathic form, however, is a common cause of nephritis both in adults and children. In adults primary FGS can also present with associated hypertension, renal failure and mild haematuria. In the nephrotic form FGS is a particularly noxious disease, with 50% of nephrotic patients progressing to renal failure over 6-8 years. Persistent nephrosis, hypertension and impaired function are all ominous prognostic features. Unfortunately this disease, recurs in about 20% of renal transplants. Like minimal change disease, a lymphocyte product is thought to be responsible for the glomerlular injury.

Table 4. Causes of Focal and Segmental Sclerosis

Primary

Secondary

* Secondary to reduction in renal mass; probably complicates all chronic renal diseases but particularly described in reflux and analgesic nephropathy.
* Secondary to focal and segmental proliferative GN
* Secondary to other focal and segmental glomerular damage
    - Heroin addicts
    - Atheroembolic disease
    - Familial glomerulonephritis (Alport's syndrome)

While the disease was once thought untreatable, it is now clear that similar treatment to minimal change disease can be effective, however the dose of prednisolone usually required is higher and the course longer. For example Pei et al describe a 44% response in children using prednisolone 120 mg/kg/day, for 6 months associated with cyclophosphamide for 2 months in 50% of cases[12].

Cyclosporine can be used as a alternative, however, relapse is common on withdrawal, and chronic cyclosporine nephrotoxicity is a danger. patients receiving renal transplants should be considered as candidates for plasma exchange therapy[13].

Membranous Glomerulonephritis

Characterised by granular immunoglobulin deposition on the outside of the glomerular basement membrance, this disease causes basement membrane thickening, and is attributable to local formation (in the idiopathic form) or deposition (in SLE) of immune complexes. A wide variety of causes are possible, the most important in practice being SLE (especially in adult females), drugs (in adults) and chronic infection (in populations where these are prevalent). In the elderly, underlying cancer can be the cause. After a diligent search for treatable causes, in the majority of Australian patients the disease is labelled "idiopathic".

In consideration of possible treatment, it must be realised that spontaneous remission of nephrosis will occur in about 30% of patients. A poor prognosis indicated by heavy (and persistent) proteinuria, already impaired function and severe tubulointerstitial scarring on renal biopsy. Treatment should therefore be reserved for patients with these features or those who deteriorate during observation.

The beneficial effect of various cocktails of prednisolone and alkylating agents cyclophosphamide or chlo-

rumbucil have now been widely published, and will be covered later in this series by Dr. Christopher Pugh. Currently in our institution we use a cocktail of cyclophosphamide and warfarin for 6 months. If this fails we observe for 3-6 months then institute the so called Ponticelli regimen[14] (Table 5).

Table 5. Ponticelli Regimen

6 month course
1 g intravenous methylprednisolone for 3 days
followed by 0.4 mg/kg/d for 27 days of oral steroids
alternated with chlorumbucil 0.2 mg/kg/d every other month

Acute Nephritic Syndrome

Most patients with the acute nephritic syndrome have a form of proliferative glomerulonephritis, though thrombotic microangiopathies can also result in this clinical picture. The proliferative diseases cover a spectrum, since the same cause (e.g. IgA disease or SLE) can result in anything from mild mesangial proliferation, through focal and segmental lesion to full blown diffuse proliferation involving all tufts of all glomeruli. Generally, however, there is some alignment of cause and pathology.

Treatment of the Syndrome

The major features potentially resulting in morbidity and mortality are salt and water retention, hypertension and renal failure.

Salt and water retention

Loop diurectic administration will usually result in an increase in urine flow, particularly in patients with good prognosis. Salt and water restriction is advisable until such a diuresis is established. Rarely dialysis will be necessary in the greatly overloaded patient, when left heart failure can be life threatening.

Hypertension

Saline retention and other poorly understood mechanisms can result in severe hypertension with possible left heart failure, convulsions or cerebral haemorrhage. Antihypertensive therapy is important, particularly in children in whom the normal blood pressure level is so much lower than adults.

Renal Failure

A variety of mechanisms can result in associated renal failure, the most common being crescentic nephritis (see rapidly progressive nephritis — below), and associated tubular necrosis. If sufficiently severe, dietary protein and potassium restriction or dialysis may be required.

Treatment of the Causes

A feature of proliferative GN is the wide variety of causes which can be ascertained by serological testing (Table 6). While often the results are not available until the crisis is past, many are still very helpful in the classification of disease and in later therapy. In particular the role of antibodies to neutrophil cytoplasm (ANCA) in the detection of underiying vasculitis illness has been an advance of immense importance. The staining of the glomeruli for immunoglobulin gives important immediate diagnostic information e.g. linear immune deposits in Goodpastures syndrome, mesangial IgA in IgA disease and Henoch Schonelein nephritis, lumpy immune deposists in post infectious GN, and granular deposits of all IgG, IgM and IgA with complement components such as Clq in SLE.

Table 6. Proliferative Glomerulonephritis Serological and Immunological Diagnosis

• SLE	- ANA, anti DNA Abs
	- Full House immunodeposits
• Vasculitis	- Antineutrophil cytoplasmic Abs (ANCA)
	- Pauci-immune
• Goodpastures	- Anti GBM Ab
	- Linear immune deposit

Diffuse Proliferative Glomerulonephritis

Here there is proliferation involving all tufts of all glomeruli. The cells involved vary between causes. The common causes are detailed in Table 7. In post infectious (poststreptococcal) GN the proliferation of endothelial cells and polymorphonuclear leucocyte infiltration of the capillary lumen is sufficiently characteristic to be virtually diagnostic. In many of the diseases more usually causing focal and segmental proliferation, this focal accentuation is commonly stil quite obvious.

Table 7. Diffuse Proliferative Glomerulonephritis

Aetiology

1. Secondary
   - *Intrinsic* - SLE
     - Vasculitis
     - Goodpastures

   (often cause RPGN)
   - *Extrinsic* - Postinfectious

   (Commonest histological renal disease in developing countries)

2. Primary
   - IgA Disease
   - Membranoproliferative
   - Idiopathic

In tropical countries such as Sri Lanka by far the most common cause is poststreptococcal nephritis. The predisposing in adults seems to be lower limb ulcers were as children often have secondarily infected scabies. . Over 85% of patients in Sri Lanka do well and improve with penicillin within 3-6 months[15].

Focal and Segmental Proliferative GN

When segmental proliferation is seen, the usual cause is an underlying systemic disease, or mesangial IgA deposition (see mesangial proliferative GN).

Recently it has been possible to divide most cases by the immune staining pattern supplemented by seriological tests as discussed above. Of these only mesangial IgA disease has no generally accepted treatment.

Mesangial Proliferative GN

The commonest glomerular disease in Australia and probably the world[16] is characterised by diffuse mesangial proliferation with granular mesangial deposits of IgA. Though the clinical picture can be of acute nephritis, rapidly progressive nephritis, chronic haematuria or chronic glomerulonephritis with hypertension and renal failure, the characteristic feature is of attacks of marcoscopic haematuria at the time of incidental, particularly upper respiratory tract, infection (synpharyngytic haematuria). No specific therapy is of given value, though immunosuppressive agents have been used with some reports of benefit[17].

Rapidly Progressive Nephritis

In this life threatening syndrome, the main features are macroscopic haematuria and rapid deterioration of renal function with oliguria. Usually a severe proliferative GN with extensive (>70%) crescents is found. Almost invariably there is cause for this which requires specific therapy, particularly prednisolone and immunosuppression[18]. There is good evidence for benefit from either pulse steroid therapy or plasma exchange — the former being cheaper, safer and more convenient and the latter possibly indicated in Goodpastures Syndrome and severe oliguric vasculitis (see accompanying paper by Dr. C. Pugh).

Chronic Glomerulonephritis

There is accumulating literature on the mechanisms of interfering with the chronic progressive renal failure that can occur in all forms of chronic renal disease. Of overwhelming importance is the control of hypertension, while the place of low protein diet, angiotensin converting enzyme inhibitors, treatment of hyperlipidemia and plasma phosphate control is still being investigated.

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