Unresolved issues and current concepts in management of primary glomerulonephritis

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The successful treatment of primary glomerulonephritis (GN) presenting with nephrotic syndrome in adults depends heavily on an accurate diagnosis. A successful diagnosis depends on a correct approach, combining light microscopy, immunofluorescence, and other special staining of renal biopsy material examined by a trained nephropathologist. A good clinical history and serological tests easily rule out possible secondary causes (for example, infection, autoimmune, metabolic or toxic) in most cases. Unfortunately, these procedures are not put into practice in most cases in developing countries, resulting in missed diagnosis and unnecessary steroid and immunosuppressant therapy with its inherent morbidity. Following the emergence of IgA and IgM nephropathies as very common forms of glomerular disorders in some countries, immunofluorescence has become absolutely necessary for their diagnosis. Moreover, a recent meta-analysis has defined different treatment protocols for minimal change nephropathy, focal segmental glomerulosclerosis, membranous nephropathy, and IgA nephropathy for a better outcome. This article emphasizes and elaborates on these issues for proper management of primary GN.

Despite substantial increases in our understanding of pathogenetic processes during the last four decades, therapeutic approaches to glomerular diseases are characterized by inadequacy in diagnosis, identification of etiology, and limitations in therapy. Diagnosis of primary glomerulonephritis (GN) can only be made after excluding secondary causes. Therefore, for proper diagnosis, investigations based on history, serology and histology are equally important as a deficiency could arise at any level. A light microscopic histological diagnosis on the basis of which most physicians treat patients is not enough. For example, membranous nephropathy is just a histologic appearance, which could be due to factors such as heavy metal exposure, hepatitis B or C and parasite infection, SLE and even neoplastic conditions. Similarly, a biopsy report of mesangioproliferative glomerulonephritis could be due to IgA or IgM nephropathy that requires immunofluorescence (IF) staining for diagnosis or it could be due to resolving poststreptococcal glomerulonephritis (PSGN) or lupus nephritis, among other possible causes. Every effort should be made to diagnose glomerulonephritis as accurately as possible for better management. Unfortunately, there is a tremendous lack of nephrologists and nephropathologists in developing countries. Deficiencies also exist in microbiological, immunological, immunofluorescence and immunohistochemical techniques. The author has personally come across patients with nephrotic syndrome being treated with prednisolone for weeks...
CURRENT CONCEPTS IN MANAGEMENT OF PRIMARY GLOMERULONEPHRITIS

Minimal Change Disease (MCD)

Minimal change disease generally presents with inidious leg edema. Acute onset is less common but may occur following infarction. In 30% to 60% of cases first attack of the disease and further relapses follow upper respiratory tract infection, which often is an apparent viral infection.\(^5\) Frequent complications such as cellulitis, peritonitis, pneumonia, deep vein thrombosis\(^6\) and infrequently acute renal failure in middle aged patients may occur.\(^7\) However, protein calorie malnutrition is a common complication in patients from poorer society. Spontaneous remission in children has been reported after many months. However, treatment is necessary if there is heavy proteinuria or nephrotic syndrome. In elderly patients, colon or lung cancer should be ruled out. The characteristic histology is a normal appearing glomeruli on light microscopy with or without expansion of mesangium. Immunofluorescence is negative for immunoglobulins, but mild hypercellularity and the presence of IgM in our experience is associated with late or poor response.

**Initial treatment of MCD.** For adults, prednisolone 1 mg/kg/day in a single morning dose is administered until remission or for 6 weeks followed by 1.6 mg/kg on alternate days for four weeks; thereafter the dose is tapered. Every month the dose should be reduced by 0.2-0.4 mg/kg and administered on alternate days. In case of no remission, prednisolone should be tapered for 4 to 6 months before labeling the patient steroid resistant. ACE inhibitors are a useful adjunct to therapy as they reduce proteinuria by altering glomerular hemodynamics.

**Relapse.** Wrong dose, duration of therapy and poor compliance are the main reasons for relapse. Infection may trigger relapse in which case treatment of the infection will result in remission. Steroids should therefore be avoided until infection is brought under control. Relapse is treated by prednisolone 1 mg/kg of body weight until the urine is protein free for three consecutive days followed by 0.75 mg/kg every alternate days for four weeks. Patients who respond to an initial course of corticosteroid, generally show steroid sensitiveness throughout course of their disease.\(^3\) Prolonged initial treatment for eight weeks results in less frequent relapses.\(^8\) In frequent relapsers, either in steroid dependent or steroid resistant patients, the addition of cyclophosphamide (2 mg/kg/day) or chlorambucil (0.15 mg/kg/day on alternate days) enables reduction of the steroid dose to 0.75 mg/kg and induces remission. Sodium restriction and diuretics are often necessary. However, infusion of albumin is advisable only when the serum albumin level is below 2 g/dL. Cyclosporine may induce remission in steroid resistant patients at a dose of 5 mg/kg/day for 6-12 months. A recent study observed 60% remission against 16% remission in a control group.\(^9\) Furthermore it has been found that treatment for 1 to 2 years and a slow tapering of dose over 6 months reduces the relapse rate following stoppage of cyclosporin.\(^10\) Our own experience (unpublished) with cyclosporine was similar in steroid dependent cases of MCD. We found complete recovery in 50% patients and, in another 45% there was reduction in proteinuria with a resultant increase of serum protein level and disappearance of edema.

Glomerulonephritis in Saudi Arabia

In biopsy studies from six Saudi Centres\(^4\) (four from Riyadh and one each from eastern and western provinces) the pattern and prevalence of primary glomerulonephritis was 21.3% for focal segmental glomerulonephritis (FSGS), 20.7% for minimal-change glomerular nephritis (MCGN), 16.3% for mesangial PGN was the commonest type in the southern region. whereas mesangial PGN was the commonest type of primary glomerulonephritis seen in Saudi and HSP in 2.3%. Clearly, FSGS is the commonest (57%) case of primary glo- membranous glomerulonephritis (MGN), 8.8% for DPGN/crescentic GN, 6.5% for IgA nephritis, and 4.3% for focal PGN (4.3%). Secondary glomerulonephritis was due to systemic lupus erythematosus (SLE) in 57% of cases, post-infection in 11.3%, vasculitis in 5.9%, amyloidosis in 3.9%, RPGN in 2.3%, and HSP in 2.3%. Clearly, FSGS is the commonest type of primary glomerulonephritis seen in Saudi adults, with one study reporting the incidence as high as 40.8%.\(^2\) Membranous nephropathy has been found to be more prevalent in the western province\(^1\) whereas mesangial PGN was the commonest type in the southern region.\(^4\)

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**Membranous Nephropathy**

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Focal and Segmental Glomerulosclerosis (FSGS)  
Approximately 50% of adult patients present with asymptomatic proteinuria and 50% with nephrotic syndrome. Hypertension and microhematuria are common. Before diagnosing idiopathic FSGS it is important to rule out secondary causes such as narcotic abuse, HIV infection, vesico-uretral reflux, hyperlipidemia and morbid obesity. Recent studies show complete remission in 33% to 47% when prednisolone doses of 0.5-2.0mg/kg of body weight are administered for a prolonged period of six months. The rate of remission is higher with use of higher doses (>60 mg/day) for the first three months. Patients with asymptomatic proteinuria or who show a response to the initial course of steroid therapy had a better prognosis in our experience. On other hand, increased serum creatinine at diagnosis, hypertension, interstitial scaring and severe hypertensive changes on histology, and hyperlipidemia are poor prognostic signs. Such patients end up with end-stage renal failure within three to five years. Treatment with steroids and cytotoxic drugs should be avoided in those patients. The use of cyclosporine in steroid resistant cases at doses (5 mg/kg of body weight) to maintain serum levels at 150-300 µg/mL, has resulted in a more favourable course. However, if there is no response in three months the drug is unlikely to be effective. Relapse is common following abrupt withdrawal of cyclosporine; 6 to 12 months therapy followed by slow tapering is therefore recommended. Cyclosporine should be avoided in the presence of renal insufficiency or significant interstitial fibrosis. Early recurrence of FSGS in renal transplant patients should be promptly treated by plasmapheresis.

Membranous nephropathy (MN)  
Membranous nephropathy accounts for about 30% of nephrotic syndrome in adults. In approaching treatment, it is important to address whether nephropathy is primary or secondary. Several infective conditions (hepatitis B or C, malaria, filariasis, leprosy, schistosomiasis, and syphilis) can cause MN. Infective etiologies will require IF and immunohistochemical techniques for diagnosis. Similarly, therapy with captopril, penicillamine, NSAIDs, mercury and gold salts may be responsible for MN at times. MN has been seen in lupus nephritis, Wegener’s granulomatosis, lung and colon cancers, autoimmune diseases and diabetes. Adequate treatment of those conditions, with alpha interferon for hepatitis B/C and resection of colonic/lung cancer may ameliorate MN. It is important to know if the proteinuria is mild to moderate (<2 g/24 hrs) with absent leg edema. A “wait and watch” approach is preferred with such patients as they may have spontaneous remission. Poor prognostic factors include proteinuria with more than 5 g/24 hours, persistent proteinuria of more than 4 g, impaired renal function, male gender and association with DR3, DR5 and B37 HLA types.

Treatment. Evidence-based data has shown that corticosteroids alone are ineffective in MN, and therefore should not be tried as sole therapy. Azathioprine provides no extra benefit. However, cyclophosphamide and chlorambucil are both effective in treating MN. In view of the long-term toxicity, indications for these drugs are limited to patients with severe or prolonged nephrotic syndrome, declining renal function, or hypertension. The treatment regimen consists of methylprednisolone 1 g IV ×3 days, followed by oral prednisolone 0.4 mg/kg of body weight ×27 days at months 1, 3 and 5 alternated with chlorambucil 0.2 mg/kg/day for 28 days at months 2, 4 and 6. This treatment protocol is associated with better survival without developing nephrotic syndrome. An alternative protocol consisting of cyclophosphamide 1.5 mg/kg/day for 6 months and dipyridamole/warfarin for two years is associated with a higher rate of remission, although similar results have been reported with a cyclophosphamide (2 mg/kg/day) and prednisolone combination for one and half years. Cyclosporine has been found beneficial in patients who fail to respond to cytotoxic drug and prednisolone combinations. In a recent uncontrolled study, pentoxifylline was found effective in reducing proteinuria in 90% of MN patients who failed to respond to immunosuppressants and ACE inhibitors.

IgA nephritis (IgAN)  
IgAN is the commonest form of primary glomerulonephritis in Southeast Asia and the disease is seen worldwide. The pathogenesis of this condition is unclear. It may clinically manifest with asymptomatic hematuria and proteinuria, recurrent gross hematuria, acute glomerulonephritis, accelerated hypertension, or acute renal failure associated with glomerular crescents. No treatment has been found effective. End-stage renal failure eventually develops in 30% of patients of IgAN in 3 to 20 years. Patients having hypertension, persistent proteinuria and interstitial fibrosis on biopsy are at high risk of developing ESRD.
A recent meta-analysis recommended that if the patient has proteinuria of 1 g/24 hours, there is no need to intervene by giving a drug. If proteinuria is 1-3 g/24 hours and creatinine clearance (Cr) is normal, simple observation is all that is necessary. However, in the presence of renal insufficiency, fish oil (12 g/day) therapy is indicated. In patients having proteinuria more than 3 g/24 hour and Cr >70 mL/min, a course of prednisolone is justified. If Cr is <70 mL/min, only fish oil treatment is recommended. Fish oil is rich in long chain omega-3 polyunsaturated fatty acids (w-3-PUFA), namely eicosapentanoic acid (EPA) and docosahexanoic acid. These fatty acids act as substrates for both lipoxygenase and cyclooxygenase, which then produce less effective prostaglandins and leukotrienes, leading to reduced platelet aggregability and changes in cell membrane fluidity. Fish oil supplementation improves immune-mediated glomerular disease by reducing proteinuria and modifying the histological picture.

Tonsillectomy in cases of recurrent tonsillitis is mandatory and prompt antibiotic therapy for upper respiratory tract bacterial infection is recommended. Control of hypertension by ACE-inhibitors is preferable.

Rapidly progressive glomerulonephritis (RPGN)

Rapidly progressive GN is characterized by rapid onset of hematuria and proteinuria, with a marked decline in GFR manifesting often in oliguria. Biopsy onset of hematuria and proteinuria, with a marked decline in GFR manifesting often in oliguria. Biopsy reveals extensive crescent formation in about 50% or more glomeruli. Occasionally crescents may not be seen on initial biopsy and the only picture is that of a severe diffuse proliferative glomerulonephritis. Recovery in the absence of therapy is unlikely. Diverse and etiologically different glomerular diseases are associated with crescent formation. Immunopathologically, RPGN shows three types: immune complex glomerulonephritis (post infective, SLE), anti-GBM disease (Good Pasture Syndrome), and pauci-immune crescentic nephritis (vasculitis).

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS DUE TO IMMUNE COMPLEX GLOMERULONEPHRITIS.

The post-infectious form of RPGN with crescents has a better prognosis in children than in adults. Couser observed 50% recovery without specific therapy, while 18% underwent partial recovery and 32% developed end-stage renal failure. Idiopathic crescentic RPGN should be treated like pauci-immune RPGN. However, a large majority of these patients present in late stages when biopsy shows fibrous and fibro-cellar crescents and marked interstitial scarring implying a high chronicity index. Such patients should not be treated with corticosteroids or cytotoxic drugs as these have no beneficial value at that stage.

Anti-GBM antibody mediated RPGN. Early diagnosis is the key to successful treatment. Initial therapy consists of IV pulse of methylprednisolone 7 to 15 mg/kg/day to a maximum of 1 g/day for 3 days followed by oral prednisolone 60 mg daily for 7 days and thereafter tapered every week by 5 to 10 mgs over 7 to 8 weeks. A daily 4L plasma exchange (PE) for two weeks or until disappearance of anti-GBM antibody is recommended. Pulmonary hemorrhage is another indication for plasma exchange. However, PE should be deferred in totally anuric patients and when crescents involve more than 80% glomeruli. Plasma exchange therapy is to be continued until anti-GBM antibodies disappear.

Pauci-immune crescentic rapidly progressive glomerulonephritis. Although patients with this disease show variable features of systemic vasculitis, they are classified under one group (pauci-immune) because serologically they are recognized by antineutrophil cytoplasmic antibody (ANCA) positivity and immunopathologically share the common feature of absent or scanty scattered deposits. Clinically they manifest differently within the same spectrum, as renal limited vasculitis, for example, when only glomerular capillaries are involved; as microscopic polyangitis when kidney and peripheral microvessels are involved; as Churg-Strauss syndrome when the lungs are involved; or as Wegener's granulomatosis when kidney, lungs, and the upper respiratory tract are involved. Successful treatment is possible if physicians maintain a high index of suspicion and conduct prompt ANCA testing.

Treatment. Initially IV methylprednisolone pulse is given in dose of 15 mg/kg/day for three days followed by oral prednisolone 1 mg/kg/day for one month gradually tapered over 6 to 12 months. Cyclophosphamide should be given orally 3 mg/kg/day with monitoring of total lymphocyte count to avoid leucopenia (<3000 mL). Alternatively IV pulse cyclophosphamide is given (0.5 g/m2) every month. Cyclophosphamide should be continued for 3-6 months after which switching over to azathioprine for maintenance therapy is recommended. Plasmapheresis is considered for patients with lung hemorrhage or in non-responders to conventional...
therapy. Some of the newer treatments for renal vasculitis include intravenous immunoglobulin (2 g/kg IV in divided doses for 5 days) and humanized monoclonal antibodies against CD52 and CD4.28

Membranoproliferative glomerulonephritis (MPGN)
Idiopathic membranoproliferative glomerulonephritis is the least common among all glomerulonephritides. Complete diagnosis requires thorough exclusion of secondary causes like hepatitis B or C, HIV, and other infections, lupus nephritis and vasculitis. In recent years hepatitis C virus has been implicated as an important cause of MPGN.29 Virus has been demonstrated on immunohistochemical technique and electron microscopy of renal tissue although serology was negative. Hepatitis C-associated MPGN is best treated by interferon-alpha, resulting in serocconversion and reduction of proteinuria.30

In idiopathic MPGN with normal renal function and asymptomatic non-nephrotic range proteinuria, no specific therapy is required. Close follow-up of renal function, adequate control of blood pressure and proteinuria are all that is necessary. In children with MPGN presenting as nephrotic syndrome and/or impaired renal function, a trial of steroid (40 mg/m² on alternate days) for 6-12 months is recommended. The treatment should be discontinued if no benefit is observed on follow-up. In adults with proteinuria of more than 3 g/24 hours and/or impaired renal function, a trial of dipyridamole and aspirin combination treatment may be given.

Apart from specific therapy, three other aspects of the management of glomerulonephritis that need attention are hypertension, heavy proteinuria, hyperlipidemia, and stage of the disease. Their importance lies in retardation of progression to the chronic stage while specific therapy may be ineffective or unavailable in many cases. Diastolic blood pressure >90 mm Hg must be treated with ACE inhibitors or angiotensin receptor blocking agents. These drugs are renoprotective in nondiabetic glomerulopathies, as they reduce systemic pressure, intraglomerular capillary pressure and heavy proteinuria. Reduction of proteinuria reduces interstitial fibrosis. Total cholesterol and LDL are elevated in about one-third of patients with nephrotic syndrome and plasma lipoproteins are also increased.31 The pathologic role of hyperlipidemia on progressive glomerulonephritis has been demonstrated in several studies. Besides increasing cardiovascular morbidity, hyperlipidemia stimulates mesangial cell proliferation and the extracellular matrix. A recent meta-analysis showed a significant beneficial effect of antilipemic agents in slowing down progression of renal failure.32 Since patients with glomerulonephritis may present in the chronic stage with reduced glomerular filtration rate (<50 mL/min), dietary protein restriction helps stabilizing renal function.33

References