Acute Glomerulonephritis: Evidence-based Management

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INTRODUCTION
Numerous inflammatory and noninflammatory diseases affect the glomerulus and lead to alteration in glomerular permeability, structure and function. The term glomerulonephritis (GN) implies that there is an immune pathogenesis, and nonimmune-mediated conditions affecting the kidneys are also to be considered. Glomerulonephritis may be primary, restricted to the kidney, or may be part of a multisystem disease.

Chronic GN accounts for 13.3% cases of newly diagnosed chronic kidney disease (CKD) in India. Prompt identification and correct treatment of acute GN will help in preventing a large number of CKD cases being added to overburdened health care setting. Histological classification is based on different patterns of glomerular injury as seen on light microscopy, immunofluorescence (IF) and electron microscopy. Recently published guidelines by kidney disease improving global outcomes (KDIGO) attempt to unify treatment strategies, which vary among physicians in different regions of the world.

CLINICAL PRESENTATION
Presentation of GN varies widely:

- Asymptomatic non-nephrotic proteinuria: Proteinuria (150 mg to 3 g per day)
- Microscopic hematuria: More than 2 RBC per high power field in spun urine.
- Macroscopic hematuria: Brown or smoky urine.
- Nephrotic syndrome: Proteinuria greater than 3.5 g/day, hypoalbuminemia less than 3.5 g/dL, edema, hypercholesterolemia and lipiduria.
- Nephritic syndrome: Abrupt onset with oliguria, hematuria, proteinuria, azotemia, edema and hypertension.
- Rapidly progressive glomerulonephritis (RPGN): Proteinuria, hematuria and renal failure developing over days to a week.
- Chronic GN: Proteinuria, hypertension, renal failure and smooth contracted kidneys on ultrasonography (USG) examination.

DIAGNOSIS
Kidney biopsy is mandatory for all forms of GN except steroid-responsive nephrotic syndrome (NS) and poststreptococcal GN in children. Biopsy samples are tested by light microscopy for histopathology and by IF microscope to detect immune reactants. Electron microscopes are not widely available in India and not done routinely.

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES (KDIGO)
Clinical practice guidelines for GN were published in June 2012 after extensive review of literature by the working group members. The recommendations are graded as level 1, level 2 or not graded, depending on the strength of recommendation and further labeled as A, B, C, D based on the quality of supporting evidence.

GENERAL MANAGEMENT OF GLOMERULONEPHRITIS
Treatment of glomerular disease consists of generalized supportive treatment and disease-specific therapy.

Edema
Edema is controlled by salt-restricted diet (1-2 g/day), oral or intravenous (IV) loop diuretics alone or combined with thiazide or metolazone depending on the severity of edema and urgency of fluid removal. In resistant cases, IV albumin may be combined with loop diuretics. Elderly and children are prone to acute ischemic injury; hence fluid removal should be done gradually.

Proteinuria
Reduction of proteinuria below 0.3–1 g/day retards loss of kidney function. Angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blocker (ARB) drugs reduce proteinuria by up to 40–50% and are to be prescribed at the highest tolerable doses with monitoring of potassium, blood pressure and acute rise of creatinine. There is no evidence of superiority of one drug over the other and combination of ACE-I and ARB has shown no additional protection.

Hypercoagulability
The risk of thrombotic events occurs with severe hypoalbuminemia (albumin below 2 g/dL) and immobility. Anticoagulation with low molecular weight heparin or warfarin is mandatory if serum albumin is below 2 g/dL with one or more of the following: proteinuria greater than 10 g/day, body mass index greater than 35 kg/m², family history of thromboembolism, congestive heart failure, recent abdominal or orthopedic surgery or prolonged immobilization. Contraindications for anticoagulation are to be considered.

Hyperlipidemia
The risk of thrombotic events occurs with severe hypoalbuminemia (albumin below 2 g/dL) and immobility. Statins are well tolerated and effective in correcting lipid profile, but not proven to reduce cardiovascular events or reduce decline of glomerular filtration rate (GFR). Statin in combination with calcineurin inhibitor (cyclosporine) may cause myalgia/myositis.

Infection
The most common infections are spontaneous bacterial peritonitis, pneumonia, skin and soft tissue infections and tuberculosis. Parenteral antibiotics should be started at the first sign of infection.
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Treatment of Primary Focal Segmental Glomerulosclerosis (KDIGO Recommendation)

Initial treatment and relapses: Same as MCD.

Steroid-resistant Focal Segmental Glomerulosclerosis

Cyclosporine: 3–5 mg/kg/day in two divided doses (target 125–175 ng/ml) (2B); in case of remission, continue for 1 year and taper dose by 25% every 2 months (2D). Discontinue if no remission by 6 months

Or

Tacrolimus: 0.1–0.2 mg/kg per day in two divided doses (target level 5–10 ng/ml), taper like cyclosporine (2D).

Prednisolone: 0.15 mg/kg day for 4–6 months, then taper over 4–8 weeks.

Case reports and small observational studies have reported response to alkylation agents, sirolimus, rituximab and MMF.

Idiopathic Membranous Nephropathy

Membranous nephropathy is common in adults and presents as indolent NS progressing to CKD over few years. Diagnostic features include capillary wall thickening, normal cellularity, IgG and C3 along capillary wall in IF study. Secondary membranous nephropathy occurs due to chronic hepatitis B, lupus, drugs (nonsteroidal anti-inflammatory drugs, gold and mercury) and malignancy. Evaluation for exclusion of secondary causes should be done before treatment with immunosuppressives.

KDIGO Recommendations

Indication for immunosuppressive drugs:

Nephrotic syndrome with

- Proteinuria more than 4 g/day, which remains above 50% of baseline value and does not show progressive decline with antihypertensive and proteinuric drugs over 6-month-period (1B) and/or
- Severe disabling or life-threatening symptoms of NS (1C) and/or
- Rise of serum creatinine greater than 30%, but GFR greater than 25–30 mL/minute/1.73 m² (2C). Immunosuppressives not to be used if GFR less than 30 mL/minute and reduced kidney size on USG or severe infection.

Initial Therapy

Kidney disease improving global outcomes recommends alternate monthly cycle of steroid and cyclophosphamide (1B) as follows:

- Month 1: Intravenous methylprednisolone (1 g) daily for 3 days, then oral prednisolone (0.5 mg/kg/day) for 27 days.
- Month 2: Oral chlorambucil (0.15–0.2 mg/kg/day) or oral cyclophosphamide (2 mg/kg/day) for 30 days.
- Months 3 and 5: Same as month 1
- Months 4 and 6: Same as month 2.

Monitor total leucocyte count, serum creatinine, urine protein and serum albumin every fortnightly for 2 months, then every month for 6 months. Withhold cyclophosphamide or chlorambucil if count drops below 3,500/mm³.

In case of relapse, the same treatment can be repeated only once.

Alternative treatment for patients who choose not to receive steroid/alkylating agents or who have contraindications or resistance to the above drugs:

- Cyclosporine; 3.5–5 mg/kg per day in two divided doses with prednisolone 0.15 mg/kg/day for 6 months

Or

- Tacrolimus: 0.05–0.075 mg/kg/day orally in two divided doses without prednisolone for 6–12 months.

Other drugs like MMF, rituximab, corticosteroid monotherapy and adrenocorticotropic hormone have been tried but have low quality of evidence for recommendation.
In crescentic IgA nephropathy with RPGN, steroid and cyclophosphamide is suggested analogous to the treatment of Antineutrophil cytoplasmic antibodies (ANCA) vasculitis (2D).

**Not suggested are:** Azathioprine, mycophenolate, antiplatelet agents and tonsillectomy. Immunosuppressive therapy not suggested if GFR less than 30 ml/minute per 1.73 m².

**Lupus Nephritis**

Kidney involvement in systemic lupus is due to glomerular immune complex accumulation followed by interstitial involvement. The involvement of kidney is variable and depends on the class on histopathological examination but one class may transform to other.

**KDIGO Recommendations**

- **Class I lupus nephritis (LN) may be treated as dictated by extrarenal manifestations.**
- **Class II LN may be treated as dictated by extrarenal manifestations but corticosteroids or CNIs are suggested as described for MCD, if proteinuria greater than 3 g/day.**
- **Class III and IV lupus nephritis:** For initial therapy, a combination of corticosteroid (1A) with either cyclophosphamide (1B) or mycophenolate (1B) is recommended. An initial dose of oral prednisolone up to 1 mg/kg/day is recommended and tapered over 6–12 months, according to the response. Intravenous methyl-prednisolone is added initially for severe disease. Intravenous cyclophosphamide: at the dose of 0.5–1 g/m² monthly for 6 months.
- **Maintenance therapy:** Class III and IV LN, after initial therapy, should receive azathioprine (1.5 mg/kg/day) or mycophenolate (1–2 g/day) and low-dose corticosteroid (< 10 mg/day) (1B). Calcineurin inhibitor (cyclosporine or tacrolimus) with corticosteroids are suggested in patients who are intolerant to mycophenolate mofetil or azathioprine (2C). After remission, maintenance therapy should be continued for 1 year before tapering off the drugs (2D). If complete remission is not achieved after 1 year, consider rebiopsy (not graded). During maintenance, if kidney function deteriorates, or if the proteinuria worsens, previous level of immunosuppressants should be started (2D).
- **Class V lupus nephritis (membranous lupus nephritis):** Corticosteroids and immune suppressants are recommended for extrarenal manifestations of SLE and/or persistent nephritic range proteinuria (2D).
- **Class VI lupus nephritis:** Corticosteroid and immunosuppressives should be used as dictated by extrarenal manifestations (2D).
- **Relapse lupus nephritis:** The initial therapy which induced remission may be repeated (2B).
- **Resistant cases:** Biopsy to be repeated to exclude scarring. Rituximab, IV immunoglobulin, or calcineurin inhibitors may be considered (2D).
- **General treatment:** All patients should receive hydroxychloroquine³.

**Vasculitis**

Medium or small-vessel vasculitis involves the kidney as focal and segmental necrotizing and crescentic GN and present as RPGN with progression to ESRD within few weeks to months. Circulating ANCA directed to neutrophil granule protein myeloperoxidase or proteinase 3 is present in 90% of cases¹⁰ and extrarenal manifestations may affect respiratory tract, eyes, skin and nervous system.

**KDIGO Recommendations**

**Initial therapy:** Intravenous cyclophosphamide 0.75 g/m² q 3–4 weeks for 3–6 months or oral cyclophosphamide 1.5–2 mg/kg/day for 3–6 months with.
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- **Corticosteroid**: Intravenous methylprednisolone 500 mg OD × 3 days followed by prednisolone 1 mg/day, tapered over 3-4 months.
- Rituximab 375 mg/m² weekly × 4 doses with steroid as 2 if cyclophosphamide is contraindicated (2B).
- Plasmapheresis in diffuse pulmonary hemorrhage or patient with rapidly rising serum creatinine. Not given with pulse methylprednisolone.

*Maintenance Therapy for At Least 18 Months*

- Azathioprine: 1–2 mg/kg/day (1B)
- Mycophenolate mofetil: 0.5–1 gm twice daily in patients who do not tolerate azathioprine (2C)
- Methotrexate: 0.3 mg/kg/week (maximum 25 mg/week) in patients who do not tolerate azathioprine and MMF (1C)
- Trimethoprim-sulfamethoxazole as an adjunct in patients with upper respiratory-tract disease (2B)
  - Resistant disease: Rituximab (1C) or IV immunoglobulin (2C) or plasmapheresis (2D) as alternatives are suggested
- **Transplantation**: Delay transplantation until remission of extrarenal manifestation for 12 months (1C).

**Antiglomerular Basement Membrane Glomerulonephritis**

Antiglomerular basement membrane GN is a rare disease presenting as fulminant and rapidly progressive disease with lung hemorrhage (Goodpasture disease) or isolated GN and is caused by autoantibodies to the noncollagenous domain of the alpha 3 chain of type IV collagen. Kidney survival is poor due to delay in diagnosis and initiation of therapy.

**KDIGO Recommendations**

Immunosuppression with cyclophosphamide for 3 months and corticosteroid for 6 months plus plasmapheresis for 2 weeks for all patients except those who are dialysis-dependent and have 100% crescent in an adequate biopsy sample (1B).

Maintenance therapy is not recommended.

Kidney transplantation is deferred until antiGBM antibodies are undetectable for minimum of 6 months.

**CONCLUSION**

Glomerulonephritis encompasses a wide group of diseases of varied etiology and management, and hence a kidney biopsy examined by a renal pathologist is a prerequisite for most cases. Well-designed randomized control trials are required to resolve the issues of some of the recommendations of KDIGO based on low quality evidence. There is no uniformity in the quality of care for managing GN in India. Practical guidelines of KDIGO will be useful for optimal management of GN.

**REFERENCES**