Key Takeaways for Clinicians in the Management of C3 Glomerulopathy

**Diagnosis**

C3G is diagnosed on kidney biopsy with a membranoproliferative pattern of injury on light microscopy and C3 deposition at least 2 orders of magnitude greater than any other immune reactant on immunofluorescence.

- **Differential diagnosis of C3G:**
  - Infection related glomerulonephritis and post-infectious glomerulonephritis should be ruled out. In patients ≥ 50 years of age at presentation, evaluate for presence of monoclonal protein

- **Clinical phenotype of C3G:**
  - Usually follows a chronic indolent course with persistent alternative complement pathway activation

- **Extra-renal manifestations of C3G:**
  - Acquired partial lipodystrophy and retinal drusen are reported as direct consequence of complement activation.

- **Laboratory Investigations for C3G:**
  - Serum/plasma levels of complement proteins should be measured in all patients. Low C3 is seen in up to 75% cases of C3G. C3 nephritic factor, Factor H autoantibodies and free light chains should be assayed

- **Genetic analysis in C3G:**
  - No clear benefit of genetic analysis except in kidney transplantation for possible donor evaluation

**Treatment**

- **All patients should have optimal blood pressure control with renin angiotensin aldosterone system inhibitors. Adequate lipid control should be achieved.**

  - **For patients with moderate disease:**
    - Includes patients with 1) urine protein > 500 mg/24 hours despite supportive therapy, 2) moderate inflammation on biopsy, 3) Renal deterioration (increase in creatinine and/or proteinuria). Should be given prednisone and mycophenolate mofetil.

  - **For patients with severe disease:**
    - Includes patients with 1) urine protein > 2000 mg/24 hours despite supportive therapy and immunosuppression, 2) severe inflammation on biopsy, 3) Renal deterioration (increase in creatinine and/or proteinuria). For moderate-to-severe disease, such patients can be treated with MMF and glucocorticoids. If this fails, eculizumab should be considered. Non-responders should be considered for a clinical trial where available.

- **Kidney transplantation in C3G:**
  - No specific data available. Carries high risk of histological recurrence (90%) with no known preventive strategies.

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For funding and support information, see: https://www.isn.org/initiatives/toolkits/complement-mediated-kidney-disease-toolkit/#Support