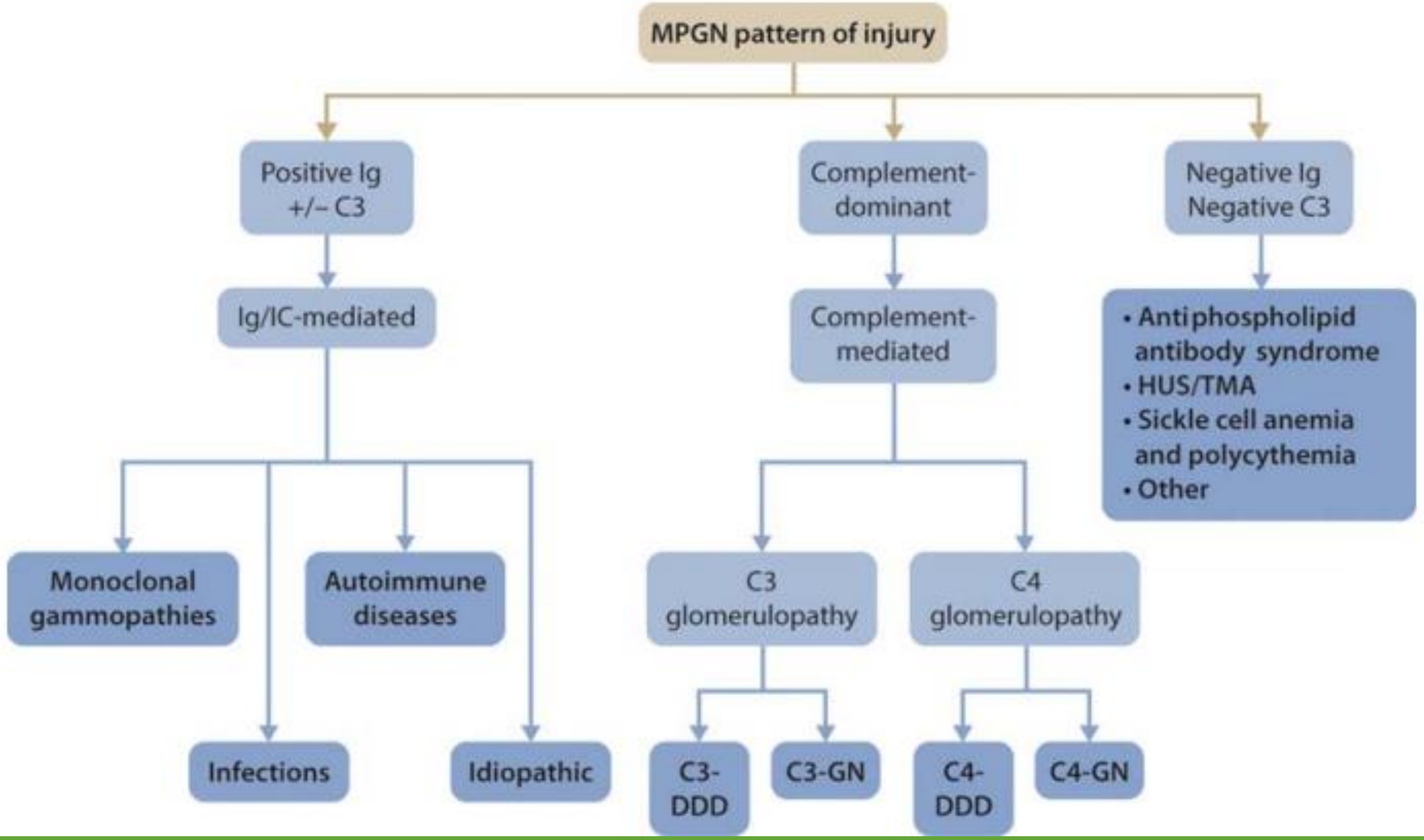
Membranoproliferative glomerulonephritis

Dr Pegah Hedayet
Assistant Professor Of Nephrology
Isfahan University Of Medical Sciences

Dr Reyhane Motamedi Fard
Assistant Professor Of Nephrology
Isfahan University Of Medical Sciences

Membranoproliferative glomerulonephritis

- MPGN is not a disease but a pattern of glomerular injury on kidney biopsy, including hypercellularity and thickening of GBM
- MPGN lesion derives from deposition of immunoglobulins and complement as either immune complexes (secondary to an underlying infection/autoimmune process), or monoclonal immunoglobulins, or is due to dysregulation of the alternative complement pathway


MPGN pattern of injury
Positive Ig +/– C3
Complement-dominant
Negative Ig Negative C3
Ig/IC-mediated
Complement-mediated
• Antiphospholipid antibody syndrome
• HUS/TMA
• Sickle cell anemia and polycythemia
• Other
Monoclonal gammopathies
Autoimmune diseases
C3 glomerulopathy
C4 glomerulopathy
Infections
Idiopathic
C3-DDD
C3-GN
C4-DDD
C4-GN

CLINICAL PRESENTATION

- The clinical presentation is not specific, and patients commonly present with

proteinuria hypertension, glomerular hematuria, and abnormal kidney function

- Hypocomplementemia (C3 and/or C4) is often, but not always, present

CLINICAL FEATURES

- Hematuria, typically with dysmorphic red cells and occasionally with red cell casts
- Proteinuria
- Serum creatinine may be normal or elevated
  - Such patients may have a bland urine sediment with a variable degree of proteinuria and elevation in serum creatinine

The diagnosis is made by kidney biopsy

CLINICAL FEATURES
Hypocomplementemia

- In immune complex/monoclonal immunoglobulin-mediated MPGN:
  - normal or mildly decreased serum C3 concentration and a low serum C4 concentration
- In complement-mediated MPGN:
  - low serum C3 and normal C4 levels due to activation of the alternate pathway

Complement-mediated MPGN is not excluded by a normal serum C3 concentration

Diagnosis

1. Evaluate patients with ICGN for underlying disease
2. Evaluate patients with GN and monoclonal immunoglobulin deposits for a hematologic malignancy
3. Rule out infection-related GN or postinfectious GN prior to assigning the diagnosis of C3G
4. Evaluate for the presence of a monoclonal protein in patients who present for the first time with a C3G diagnosis at 50 years of age

Evaluate patients with ICGN for underlying disease

First:

consider infection such as HBV and HCV infection, chronic bacterial infection (e.g., endocarditis, shunt nephritis, abscesses), fungal, and particularly in the developing world, parasitic infections (e.g., schistosomiasis, echinococcosis, malaria)

Streptococcal serology should be performed in patients with recent history of infection

Evaluate patients with ICGN for underlying disease….

Second:

consider autoimmune disorders such as SLE (particularly in the chronic phase of LN) and, less often, Sjögren's syndrome or rheumatoid arthritis

ICGN may be associated with malignancy; therefore, age-appropriate cancer screening may be warranted

Evaluate patients for a hematologic malignancy

Patients with PGNMID, should undergo a complete evaluation for a hematologic malignancy :

(i) serum and urine protein electrophoresis

(ii) serum and urine immunofixation

(iii) measurement of serum-free light chain levels

(iv) hematology consultation to further evaluate for the presence of an underlying B cell/plasma cell clone producing the monoclonal immunoglobulin

GENERAL MEASURES IN ALL PATIENTS

Dietary sodium and protein restriction

- Antihypertensive therapy
- Renin-angiotensin system inhibition
- Lipid lowering
- Treatment of edema

Approach to common clinical presentations

Mild disease

In patients who present with mild disease, characterized by normal kidney function, non-nephrotic-range proteinuria (<3.5 g/day), and no significant hematuria (arbitrarily defined as <10 red blood cells [RBC]/high-power field [HPF]), we suggest conservative therapy (including renin-angiotensin system inhibition) alone

Approach to common clinical presentations

Mild disease….

- Monitor serum creatinine, urine protein excretion (24-hour urine or spot urine protein-to-creatinine ratio), and a urinalysis at three and six months
- If spot urine protein-to-creatinine ratio is used for routine follow-up, a 24-hour urine protein collection should be performed at least once every 6 to 12 months since

Approach to common clinical presentations

Mild disease….

- If kidney function and proteinuria remain stable or improve, we continue conservative therapy indefinitely with follow-up every six months
- If the patient develops increasing proteinuria, worsening hematuria, or worsening kidney function despite conservative therapy, it is reasonable to perform a repeat kidney biopsy to evaluate disease activity and chronicity
- If the biopsy shows evidence of ongoing active glomerulonephritis immunosuppressive therapy may be warranted

Approach to common clinical presentations

Nephrotic syndrome with normal kidney function

In patients who present with nephrotic syndrome and normal (or near-normal) kidney function, with or without an active urinary sediment (arbitrarily defined as >10 RBC/HPF), we suggest immunosuppressive therapy in addition to conservative therapy, rather than conservative therapy alone

Approach to common clinical presentations

Nephrotic syndrome with normal kidney function …

- The optimal immunosuppressive therapy is not known
- Our preferred initial therapy is a three to six month course of oral glucocorticoids
- For patients who cannot or do not wish to receive glucocorticoids, treatment with a CNI for six months is a reasonable alternative

Approach to common clinical presentations

Nephrotic syndrome with normal kidney function….

If oral glucocorticoids are used:

- prednisone 1 mg/kg per day (maximum dose 60 to 80 mg/day) for four weeks….
- 40 mg/day for four weeks
- 30 mg/day for two weeks,
- 20 mg/day for two to four weeks (total of 12 to 14 weeks)

Approach to common clinical presentations

Nephrotic syndrome with normal kidney function….

- If cyclosporine is used, we start with 2 to 4 mg/kg per day (given in two divided doses) or approximately 75 to 100 mg twice daily, → trough level between 100 and 175 ng/mL

- If tacrolimus is used, we start with 0.1 mg/kg per day (given in two divided doses) or approximately 2 to 4 mg twice daily, → trough level between 5 and 10 ng/mL

Approach to common clinical presentations

Nephrotic syndrome with normal kidney function….

We monitor serum creatinine, 24-hour urine protein excretion (or spot urine protein-to-creatinine ratio), and a urinalysis every two to three months to assess the response to treatment

Approach to common clinical presentations

Nephrotic syndrome with normal kidney function….

Patients who respond with a ≥30 percent reduction in proteinuria after 12 to 14 weeks are considered to have a satisfactory response to therapy

If the patient is receiving prednisone, we gradually taper prednisone to 10 mg/day for four weeks, 5 mg/day for four weeks, and then discontinue

Approach to common clinical presentations

Nephrotic syndrome with normal kidney function….

- If the patient is receiving a CNI, we continue treatment for at least 12 months before discontinuing the CNI

- We continue to monitor serum creatinine, 24-hour urine protein excretion (or spot urine protein-to-creatinine ratio), and a urinalysis every three to six months, indefinitely

Approach to common clinical presentations

Nephrotic syndrome with normal kidney function….

- Patients who respond with a <30 percent reduction in proteinuria after 12 to 14 weeks are considered to have an unsatisfactory response to therapy
- If the patient is receiving prednisone, we decrease prednisone to 10 mg/day and add a CNI (cyclosporine or tacrolimus) for six months

Approach to common clinical presentations

Nephrotic syndrome with normal kidney function….

- We continue to monitor serum creatinine, 24-hour urine protein excretion (or spot urine protein-to-creatinine ratio), and a urinalysis every three to six months, indefinitely
- Patients who do not respond to second-line treatment with a CNI plus low-dose prednisone are considered to have resistant disease

Approach to common clinical presentations

Abnormal kidney function (without rapidly progressive crescentic disease)

- In patients with an eGFR ≥30 and <60 mL/min/1.73 m2 who have evidence of active glomerulonephritis and no significant chronic changes (ie, severe tubulointerstitial fibrosis) on kidney biopsy, we suggest immunosuppressive therapy in addition to conservative therapy, rather than conservative therapy alone

Approach to common clinical presentations

Abnormal kidney function (without rapidly progressive crescentic disease)…

- In patients with an eGFR ≥30 and <60 mL/min/1.73 m2 who have no evidence of active glomerulonephritis or have significant chronic changes on kidney biopsy, we treat with conservative therapy alone

- In most patients with an eGFR <30 mL/min/1.73 m2, we treat with conservative therapy alone, unless the patient has another indication that could benefit from the use of immunosuppression

Approach to common clinical presentations

Abnormal kidney function (without rapidly progressive crescentic disease)….

- If the decision is made to initiate immunosuppressive therapy, our preferred initial therapy is a three to six month course of oral glucocorticoids

- For patients who cannot or do not wish to receive high-dose glucocorticoids, treatment with mycophenolate mofetil (MMF), with or without low-dose prednisone (10 mg/day), for 6 to 12 months is a reasonable alternative

Approach to common clinical presentations

Abnormal kidney function (without rapidly progressive crescentic disease)….

- If oral glucocorticoids are used, we administer prednisone 1 mg/kg per day (maximum dose 60 to 80 mg/day) for four weeks, then reduce the dose to 40 mg/day for four weeks, 30 mg/day for two weeks, and 20 mg/day for two to four weeks (total of 12 to 14 weeks)

Approach to common clinical presentations

Abnormal kidney function (without rapidly progressive crescentic disease)….

- If MMF is used, we start MMF at 500 mg twice daily for three days and increase the dose up to 1000 mg twice daily as tolerated.
- We aim for a mycophenolic acid trough level of 1 to 3 ng/Ml
- We monitor serum creatinine, 24-hour urine protein excretion (or spot urine protein-to-creatinine ratio), and a urinalysis every two to three months to assess the response to treatment

Approach to common clinical presentations

Abnormal kidney function (without rapidly progressive crescentic disease)….

- Patients who respond with stabilization or improvement in kidney function or ≥30 percent reduction in proteinuria after 12 to 14 weeks are considered to have a satisfactory response to initial therapy

- If the patient is receiving prednisone as first-line therapy, we gradually taper prednisone to 10 mg/day for four weeks, 5 mg/day for four weeks, and then discontinue

Approach to common clinical presentations

Abnormal kidney function (without rapidly progressive crescentic disease)….

- If the patient is receiving MMF as first-line therapy, we continue MMF until proteinuria reaches its nadir and hematuria disappears
- If the patient has persistent low-grade proteinuria and significant hematuria we continue MMF indefinitely or until hematuria resolves
- We continue to monitor serum creatinine, urinalysis, and 24-hour urine protein excretion every three to six months

Approach to common clinical presentations

Abnormal kidney function (without rapidly progressive crescentic disease)….

- Patients who respond with worsening kidney function and <30 percent reduction in proteinuria after 12 to 14 weeks are considered to have an unsatisfactory response to initial therapy
- If the patient is receiving prednisone as first-line therapy, we decrease prednisone to 10 mg/day and add MMF as second-line therapy for 6 to 12 months
- We continue to monitor serum creatinine, 24-hour urine protein excretion (or spot urine protein-to-creatinine ratio), and a urinalysis every two to three months

Approach to common clinical presentations

Abnormal kidney function (without rapidly progressive crescentic disease)….

- If there is no improvement in kidney function, proteinuria, or hematuria after 6 to 12 months of first-line therapy with MMF or second-line therapy with MMF and low-dose prednisone, we discontinue these agents

- In such patients, it is reasonable to repeat a kidney biopsy to reevaluate disease activity and chronicity

Approach to common clinical presentations

Abnormal kidney function (without rapidly progressive crescentic disease)….

- If the repeat kidney biopsy shows primarily signs of chronic damage without evidence of active glomerulonephritis we do not give additional immunosuppressive therapy, since it is unlikely to be of benefit

- If the repeat kidney biopsy shows evidence of ongoing active glomerulonephritis, cyclophosphamide and rituximab are reasonable alternative treatment options

Approach to common clinical presentations

Abnormal kidney function (without rapidly progressive crescentic disease)….

- If cyclophosphamide is used, we administer daily oral cyclophosphamide (2 mg/kg per day, maximum dose of 200 mg/day) together with prednisone 10 to 20 mg/day for three to six months
- We typically reduce the cyclophosphamide dose by 25 percent in older adults (age >60 years) and adjust the dose appropriately in patients with impaired kidney function
- We use a maximum cumulative cyclophosphamide dose of 16 g

Approach to common clinical presentations

Abnormal kidney function (without rapidly progressive crescentic disease)….

- If rituximab is used, we give 1 g followed 14 days later by another 1 g. We repeat the same regimen at six months

- Patients who do not respond to treatment with either cyclophosphamide or rituximab are considered to have resistant disease; in such patients, we discontinue immunosuppressive therapy, continue general supportive measures, and refer for kidney transplantation when appropriate

Approach to common clinical presentations

Rapidly progressive crescentic disease

- Patients presenting with a rapidly progressive crescentic MPGN should receive immunosuppressive therapy without delay since they are at high risk for progression to ESKD if untreated
- We treat such patients with pulse IV methylprednisolone followed by daily oral prednisone and cyclophosphamide (oral or IV) using a regimen similar to that used for patients with antineutrophil cytoplasmic antibody-associated vasculitis
- We do not use plasma exchanges in these cases

Treatment ICGN

- When the cause of ICGN is determined, the initial approach to treatment should focus on the underlying pathologic process
- Indolent ICGN, whether idiopathic or linked to a primary disease process, is best managed with supportive care and carefully considered use of immunosuppression
- For patients with idiopathic ICGN and proteinuria <3.5 g/d, the absence of the nephrotic syndrome, and a normal eGFR, we suggest supportive therapy with RAS inhibition alone

TREATMENT OF INFECTION-ASSOCIATED MPGN

- Initial therapy should focus on successful treatment of the primary infection, such as antiviral therapy for MPGN due to hepatitis C or B virus

- Immunosuppressive therapy is both unnecessary and potentially deleterious in patients with hepatitis, except in selected conditions such as severe HCV-associated mixed cryoglobulinemia or rapidly progressive glomerulonephritis

TREATMENT OF INFECTION-ASSOCIATED MPGN....

- Patients with MPGN associated with chronic bacterial (eg, endocarditis, shunt nephritis, abscesses), fungal, or parasitic (eg, schistosomiasis, echinococcosis) infections should be treated with appropriate antimicrobial therapy for these infections

TREATMENT OF MPGN associated with an autoimmune disorder

- Patients with MPGN associated with an autoimmune disorder should receive treatment for their underlying disorder as appropriate, which usually involves the use of immunosuppression
- The type and duration of immunosuppressive therapy depends upon the aggressiveness of the autoimmune disorder

TREATMENT OF MPGN associated with Monoclonal gammopathies

- Patients with MPGN associated with a malignant hematologic disorder such as multiple myeloma or a lymphoproliferative disorder should be referred to an appropriate specialist and treated for the underlying malignancy

TREATMENT OF MPGN associated with Monoclonal gammopathies

- The treatment of MPGN in patients with a nonmalignant or premalignant plasma cell or B cell clone such as PGNMID, should target the underlying pathogenic clone, whenever possible
- We suggest treating patients with a non-immunoglobulin M (IgM) MGRS with a regimen targeting a plasma cell clone, similar to what is used to treat multiple myeloma
- In patients with an IgM MGRS, we suggest a regimen used to treat Waldenström macroglobulinemia

C3 glomerulopathy

- In the absence of a monoclonal gammopathy, C3G in patients with moderate-to-severe disease should be treated initially with MMF plus glucocorticoids, and if this fails, eculizumab should be considered

RECURRENT MPGN AFTER KIDNEY TRANSPLANTATION

- ICGN is less likely to recur after kidney transplantation
- MPGN due to PGNMID has a high risk of recurrence, which occurs in 70 percent of the cases
- Transplantation of such patients is generally not advised unless a plan to address the underlying plasma cell disorder has been established

PROGNOSIS

- As with other glomerular diseases, patients with MPGN who present with non-nephrotic proteinuria (less than 3.5 g/day, no hypoalbuminemia, and no edema), normal serum creatinine or eGFR, absence of hematuria, and normal blood pressure have a benign prognosis as long as the kidney manifestations do not become more prominent

PROGNOSIS

Poor prognostic signs at presentation include

1. Nephrotic syndrome
2. Elevated serum creatinine
3. Hypertension (or blood pressure well above the patient's previous baseline)
4. On kidney biopsy, crescents

Patients with non-nephrotic proteinuria and normal blood pressure appear to have an excellent long-term kidney prognosis

Greater degrees of hematuria (eg, 50 or more versus 5 to 20 red blood cells [RBC]/high-power field [HPF]) suggest more inflammation, but there is no evidence of an independent effect on prognosis

PROGNOSIS

- Another important adverse prognostic sign on kidney biopsy is tubulointerstitial disease (interstitial inflammation, fibrosis, and tubular atrophy)
- The risk of progression usually correlates more closely with the severity of the tubulointerstitial injury than with the degree of glomerular damage

Thank you!