Management of Membranous Nephropathy

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AJKD

Core Curriculum

Membranous Nephropathy: Core Curriculum 2021

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The understanding and management of membranous nephropathy, a common cause of nephrotic syndrome that is more frequently encountered in adults than in children, has rapidly evolved over the past decade. Identification of target antigens has allowed for more precise molecular diagnoses, and the ability to monitor circulating autoantibodies has added a new vantage point in terms of disease monitoring and decisions about immunosuppression. Although immunosuppression with alkylating agents combined with corticosteroids, or with calcineurin inhibitor–based regimens, has been the historical mainstay of treatment, observational and now randomized controlled trials with the B-cell–depleting agent rituximab have moved this agent to the forefront of therapy for primary membranous nephropathy. In this Core Curriculum, we discuss the typical features of primary and secondary disease; highlight the target antigens such as the phospholipase A_2 receptor, thrombospondin type 1 domain-containing 7A, neural epidermal growth factor-like 1, and semaphorin-3B; describe the relationship between the immunologic and clinical courses of disease; and review modern management with supportive care or immunosuppressive treatment based on these composite parameters.

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Introduction

b) Duplex ultrasonography of her renal vessels
c) Titer of phospholipase A_2 receptor (PLA_2R)

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KDIGO executive conclusions

Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases

OPEN

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- In contrast to the KDIGO 2012 guidelines, a kidney biopsy is no longer required to confirm the diagnosis of MN in patients with NS and a positive anti-M-type phospholipase A2 receptor (PLA2R) antibody test.
- Nevertheless, a kidney biopsy can provide important additional information even under these circumstances.
- Patients with MN should be evaluated for associated conditions (e.g., malignancy, infections, lupus, drugs), regardless of whether anti-PLA2R antibodies and/or anti–thrombospondin type-1 domain-containing 7A (THSD7A) or other antibodies are present or absent.
- Clinical and laboratory criteria should then be used to assess the risk of progressive loss of kidney function.

Clinical criteria for assessing risk of progressive loss of kidney function

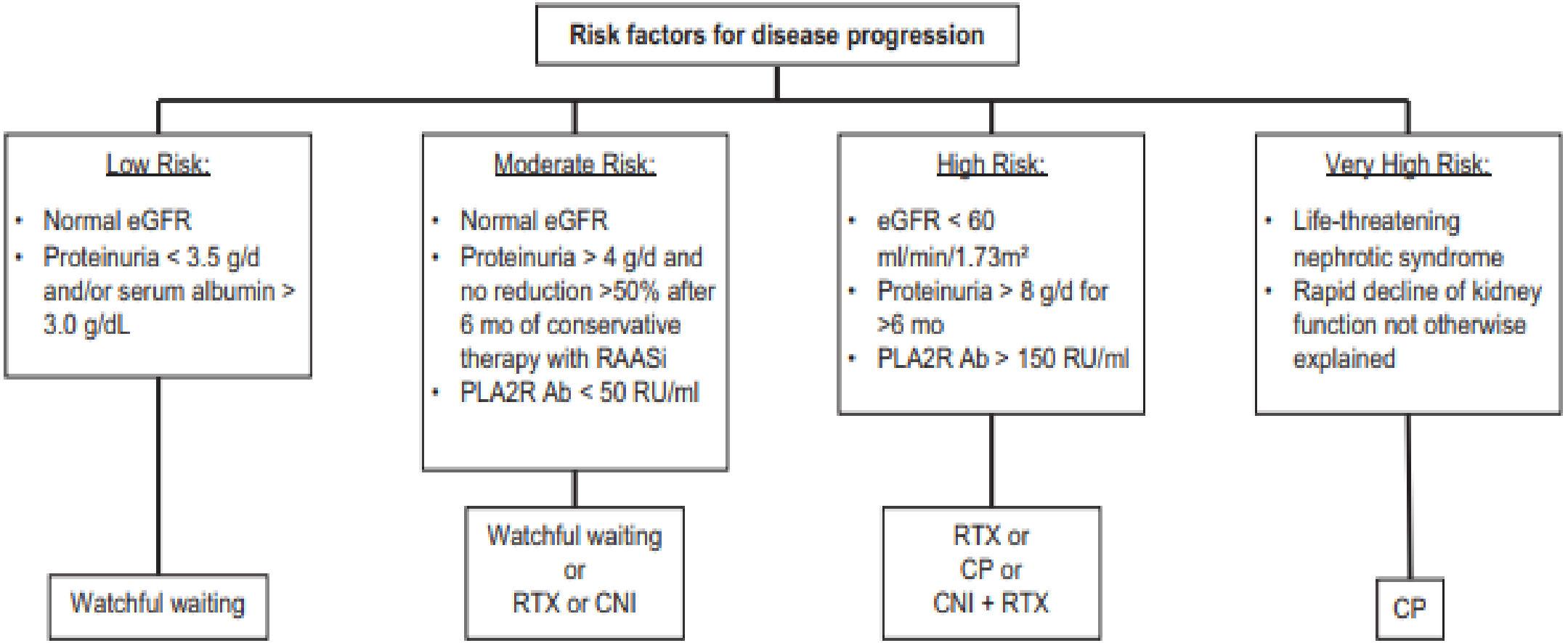
Low risk	Moderate risk	High risk	Very high risk
• Normal eGFR, proteinuria <3.5 g/d and serum albumin >30 g/l OR • Normal eGFR, proteinuria <3.5 g/d or a decrease >50% after 6 months of conservative therapy with ACEi/ARB	• Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND • Not fulfilling high-risk criteria	• eGFR <60 ml/min/1.73 m^{2}* and/or proteinuria >8 g/d for >6 months OR • Normal eGFR, proteinuria >3.5 g/d and no decrease >50% after 6 months of conservative therapy with ACEi/ARB AND at least one of the following: • Serum albumin <25 g/l† • PLA2Rab >50 RU/ml‡ • Urinary α_1-microglobulin >40 µg/min • Urinary IgG >1 µg/min • Urinary β_2-microglobulin >250 mg/d • Selectivity index >0.20§	• Life-threatening nephrotic syndrome OR • Rapid deterioration of kidney function not otherwise explained

Table 3 | **Risk classification of patients with membranous nephropathy**

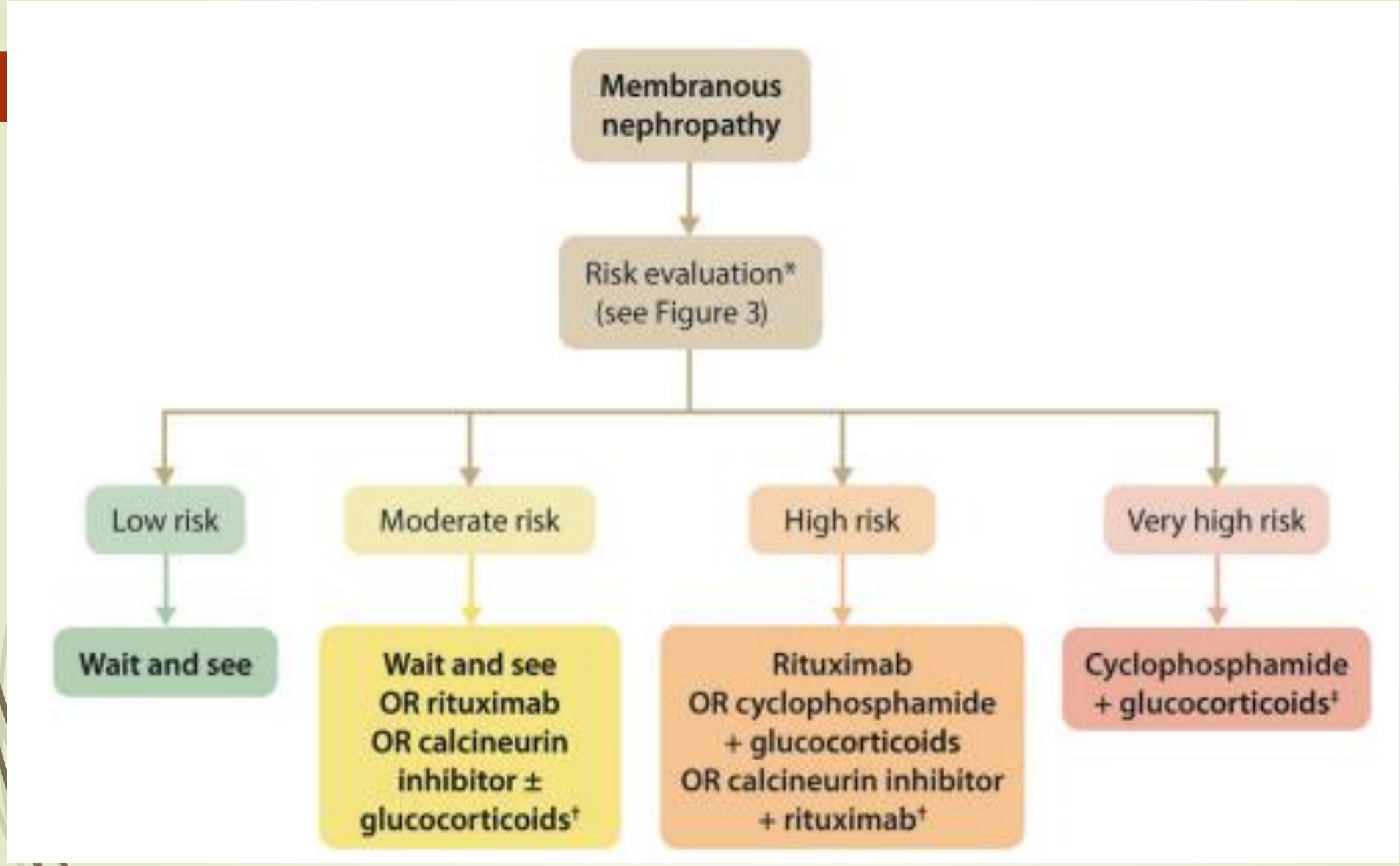
Risk category	Definition	Remarks
Low risk	Normal eGFR, proteinuria <3.5 g/day and serum albumin >30 g/l	Non-nephrotic, progression preceded by the development of overt nephrotic syndrome; serum albumin measured by BCP or immunoassay
	Normal eGFR and proteinuria decrease >50% in 6–12 months	Unlikely to progress; high likelihood of remission
Moderate risk	Normal eGFR; proteinuria >4 g/day for >6 months; proteinuria decrease <50% in 6 months; not fulfilling high-risk criteria	Likelihood of spontaneous remission ~40%
High risk	Serum creatinine <1.5 mg/dl, proteinuria >4 g/day for >6 months; proteinuria decrease <50% in 6 months AND at least one of the following: Toronto risk score >80%; proteinuria >8 g/day for >6 months; eGFR <fifth percentile (age adjusted); PLA2R antibody levels >50 RU/ml; urinary α_1M >40 µg/min; urinary β_2M >1 µg/min; urinary IgG >250 mg/day	Prefer using serum creatinine criteria over eGFR; when using eGFR consider the age-dependent decrease of eGFR; Toronto risk score combines proteinuria, eGFR and eGFR change; risk score denotes chance (%) of progression; PLA2R antibody levels need validation
Very high risk	Serum creatinine >1.5 mg/dl; eGFR decrease >20% attributed to membranous nephropathy; severe nephrotic syndrome; high risk AND PLA2R antibody >150 RU/ml	Severe nephrotic syndrome: untreatable oedema, dyspnoea due to pleura effusion; serum albumin <15 g/l; PLA2R antibody >150 RU/ml: low rate of response using standard-dose rituximab

Clinical criteria for assessing risk of progressive loss of kidney function

- SCr values >1.5 mg/dl (133 mmol/l) are often used to define kidney insufficiency. An eGFR value of 60 ml/min per 1.73 m2 defines kidney insufficiency in a young adult. It is important to realize that eGFR decreases with age, and an SCr value of 1.5 mg/dl (133 mmol/l) reflects an eGFR of 50 ml/min per 1.73 m2 in a 60-year-old male patient and 37 ml/min per 1.73 m2 in a 60-year-old female patient. Thus, when using eGFR in risk estimation, age should be taken into account.
- Anti-PLA2R antibodies should be measured at 3–6-month intervals, the shorter interval being performed in patients with high anti-PLA2R antibodies levels at baseline. Changes in anti-PLA2R antibodies levels during follow-up likely add to risk estimation.
- Disappearance of anti-PLA2R antibodies precedes clinical remission and should lead to refraining from additional therapy.
- § Selectivity index is calculated as clearance of IgG/clearance of albumin.


Risk factors for disease progression
Low Risk:
• Normal eGFR
• Proteinuria < 3.5 g/d and/or serum albumin > 3.0 g/dL
Watchful waiting
Moderate Risk:
• Normal eGFR
• Proteinuria > 4 g/d and no reduction >50% after 6 mo of conservative therapy with RAASi
• PLA2R Ab < 50 RU/ml
Watchful waiting or RTX or CNI
High Risk:
• eGFR < 60 ml/min/1.73m²
• Proteinuria > 8 g/d for >6 mo
• PLA2R Ab > 150 RU/ml
RTX or CP or CNI + RTX
Very High Risk:
• Life-threatening nephrotic syndrome
• Rapid decline of kidney function not otherwise explained
CP

- Immunosuppressive therapy should be considered when at least one risk factor for disease progression is present or when serious complications of NS (e.g., AKI, infections, thromboembolic events) have occurred.
- Longitudinal monitoring of anti-PLA2R antibody levels after starting therapy may be useful for evaluating treatment response in patients with MN, and can be used to guide adjustments to therapy.


Membranous nephropathy
Risk evaluation* (see Figure 3)
Low risk
Moderate risk
High risk
Very high risk
Wait and see
Wait and see OR rituximab OR calcineurin inhibitor ± glucocorticoids†
Rituximab OR cyclophosphamide + glucocorticoids OR calcineurin inhibitor + rituximab†
Cyclophosphamide + glucocorticoids‡

- † Calcineurin inhibitor (CNI) monotherapy is considered less efficient.
- Treatment with CNI for 6–12 months with rapid withdrawal is associated with a high relapse rate.
- Still, its use may be considered in patients with normal eGFR and moderate risk of progression, since many of these patients will develop a spontaneous remission. The use of CNI will shorten the period of proteinuria.
- In patients with high risk of progression, addition of rituximab after 6 months of treatment with CNI is advised, with the possible exception of patients with documented disappearance of antiPLA2R antibodies after CNI treatment.
- ‡in very high rirk of progression, There is insufficient evidence that rituximab used in standard doses prevents development of kidney failure.
- If eGFR falls below 50 ml/min per 1.73 m2 , the doses of cyclophosphamide should be halved. In patients who do not tolerate or can no longer use cyclophosphamide, rituximab could be offered.

- In patients who are classified as high or very high risk because of abnormal or declining kidney function at presentation or rapidly declining kidney function due to MN, suggest combination treatment with glucocorticoids and a cytotoxic agent (preferably cyclophosphamide) rather than rituximab or other therapies. Such patients have a higher urgency for initiating treatment, and cytotoxic therapy appears to provide the best protection against progressive kidney disease.
- We prefer cyclophosphamide, rather than chlorambucil, because it is associated with fewer adverse effects. In patients who wish to avoid cytotoxic therapy, treatment with rituximab may be a reasonable alternative.
- In addition, patients with MN who experience a rapid decline in kidney function should be evaluated for other potential causes of worsening kidney function, such as crescentic GN, acute hypersensitivity interstitial nephritis, or acute bilateral renal vein thrombosis.

- In patients who are classified as high or very high risk and have stable kidney function, we suggest treatment with rituximab rather than cytotoxic therapy or other therapies.
- Such patients have a lower urgency for initiating treatment than those with progressive kidney failure, and rituximab, which has less treatment-related toxicity, may be preferable.
- We prefer rituximab to a CNI; because of the more prolonged remission with rituximab and higher relapse rate of CNIs after therapy has been discontinued.
- However, either a CNI or combination therapy with glucocorticoids plus a cytotoxic agent is a reasonable alternative to rituximab in patients who are antiPLA2R antibody negative.
- We do not give glucocorticoids alone to high-risk patients, as this has not been shown to be effective.

- in moderate-risk patients who show a progressive increase in proteinuria over the observation period, we recommend treatment with immunosuppressive therapy and continued general supportive measures, rather than continued general supportive measures alone.
- In moderate-risk patients who show stable proteinuria over the observation period, we suggest immunosuppressive therapy and continued general supportive measures, rather than continued general supportive measures alone.
- However, some clinicians would continue to withhold immunosuppressive therapy beyond six months in such patients if they are doing well, especially if serum albumin is increasing, anti-PLA2R antibody levels (if initially positive) are low or decreasing, or if the patients are at high risk of having an adverse event with immunosuppressive therapy.

- In moderate-risk patients who show a progressive decline in proteinuria over the observation period, we withhold immunosuppression and continue general supportive measures.
- Preferred first-line immunosuppressive therapies for moderate-risk patients with primary MN include rituximab, combination therapy with glucocorticoids plus a cytotoxic agent (preferably cyclophosphamide), or a CNI (cyclosporine or tacrolimus).
- The choice among these regimens depends upon several factors, including clinician and patient preference, drug availability and cost, efficacy, toxicity, and tolerability

- In most moderate-risk patients who require immunosuppressive therapy, we suggest rituximab rather than glucocorticoids plus cytotoxic therapy or a CNI.
- If rituximab is unavailable, either combination therapy with glucocorticoids plus a cytotoxic agent or CNI monotherapy is a reasonable alternative.
- Some experts prefer cytotoxic therapy in moderate-risk patients with evidence of disease progression (eg, decreasing eGFR, increasing proteinuria, or decreasing serum albumin), given the higher relapse rates and potential for nephrotoxicity with CNIs .
- In patients with more stable disease, however, some experts prefer CNIs over cytotoxic therapy given their comparable shortterm efficacy and better overall safety profile.
- If cytotoxic therapy is chosen, we prefer cyclophosphamide over chlorambucil since chlorambucil has more side effects.

- We do not routinely use mycophenolate mofetil (MMF), natural adrenocorticotropic hormone (ACTH) gel, or synthetic ACTH as initial therapy in moderate-risk patients. However, such agents may be considered in patients who do not respond to all of the first-line therapies.

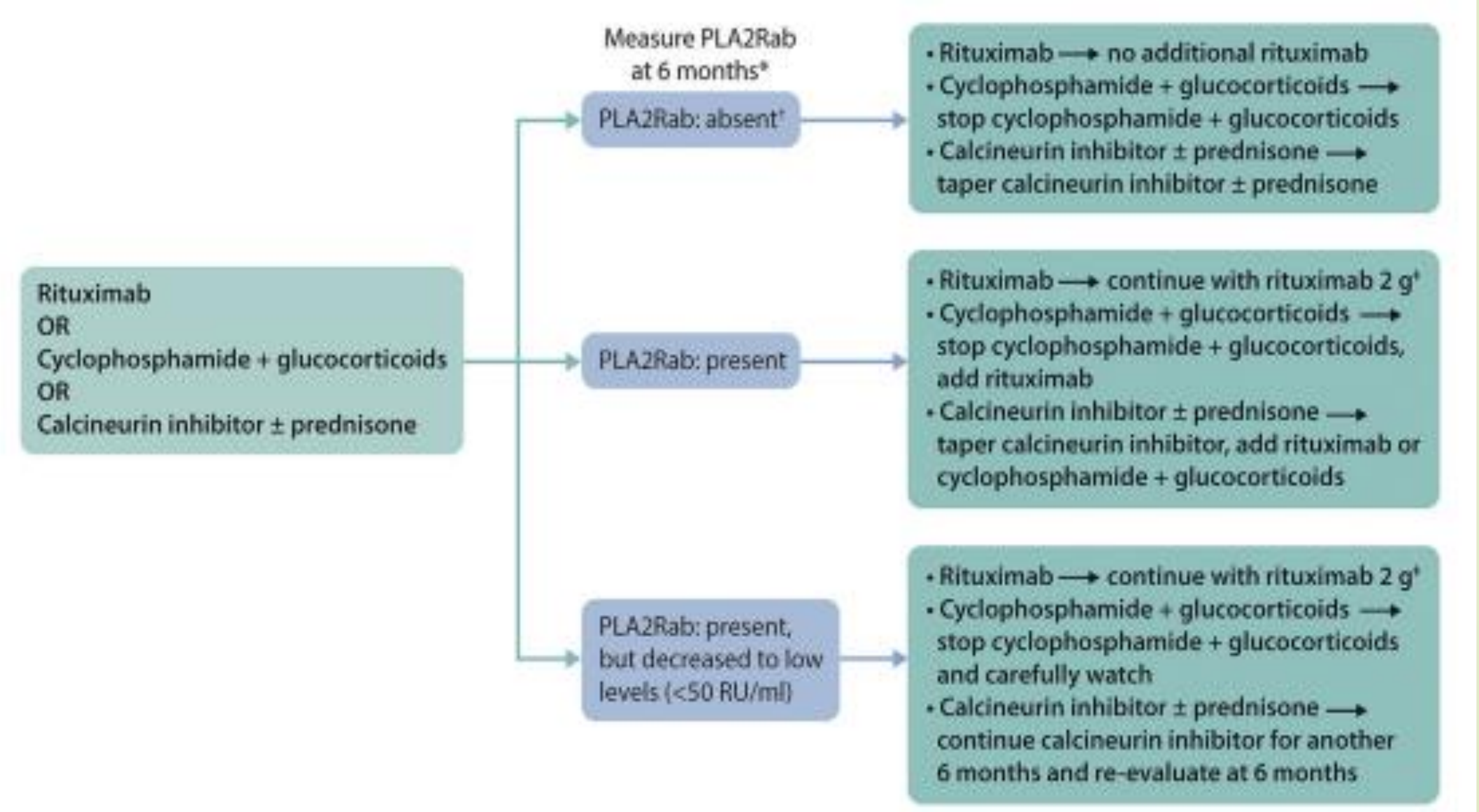
- The optimal dosing regimen for rituximab is uncertain. We administer rituximab using the dose that was given in the MENTOR trial , specifically 1 g initially followed 14 days late by another 1 g dose.
- Some experts use an alternative regimen, administering 375 mg/m weekly for four weeks or a B cell-driven approach in which a second dose of 375 mg/m is given if ≥5 circulating B cells/microL are detected by flow cytometry one week after treatment.
- The rationale for two additional doses is to induce a more profound B cell depletion. However, there are no controlled trials that have compared the efficacy of the various rituximab regime.
- In patients treated with an initial dose of rituximab of 2 g, we do not routinely check peripheral B cell counts.
- However, in centers that are used to administering lower doses (eg, 375 mg/m , one or two doses), we suggest checking peripheral blood B lymphocyte counts (by monitoring CD19-positive cells) one week after the last rituximab dose to ascertain B cell depletion.
- We administer an additional dose of rituximab (1 g) if B cell depletion is not complete.

- If a cyclosporine-based approach is chosen, the preferred regimen is treatment for at least six months at a dose of 3 to 5 mg/kg per day in two divided doses to maintain whole blood trough levels of 120 to 200 ng/mL; some clinicians would also initiate therapy with prednisone given every other day (maximum 10 mg every other day).
- If a tacrolimus-based approach is chosen, the preferred regimen is 0.05 to 0.1 mg/kg per day for at least six months in two divided doses to maintain whole blood trough levels between 3 and 5 ng/mL. The dose may be increased to achieve a higher trough level between 5 and 8 ng/mL if there is no reduction in proteinuria by two months, provided that kidney function has not worsened.

Immunologic response

- In patients with PLA2R-associated primary MN, serial assessment of serum anti-PLA2R antibody levels can be used to monitor the immunologic activity of the disease.
- Immunologic remission is defined as depletion of anti-PLA2R antibodies, as evidenced by anti-PLA2R antibody titers below the cut-off value for a positive result and/or a negative indirect immunofluorescence test.

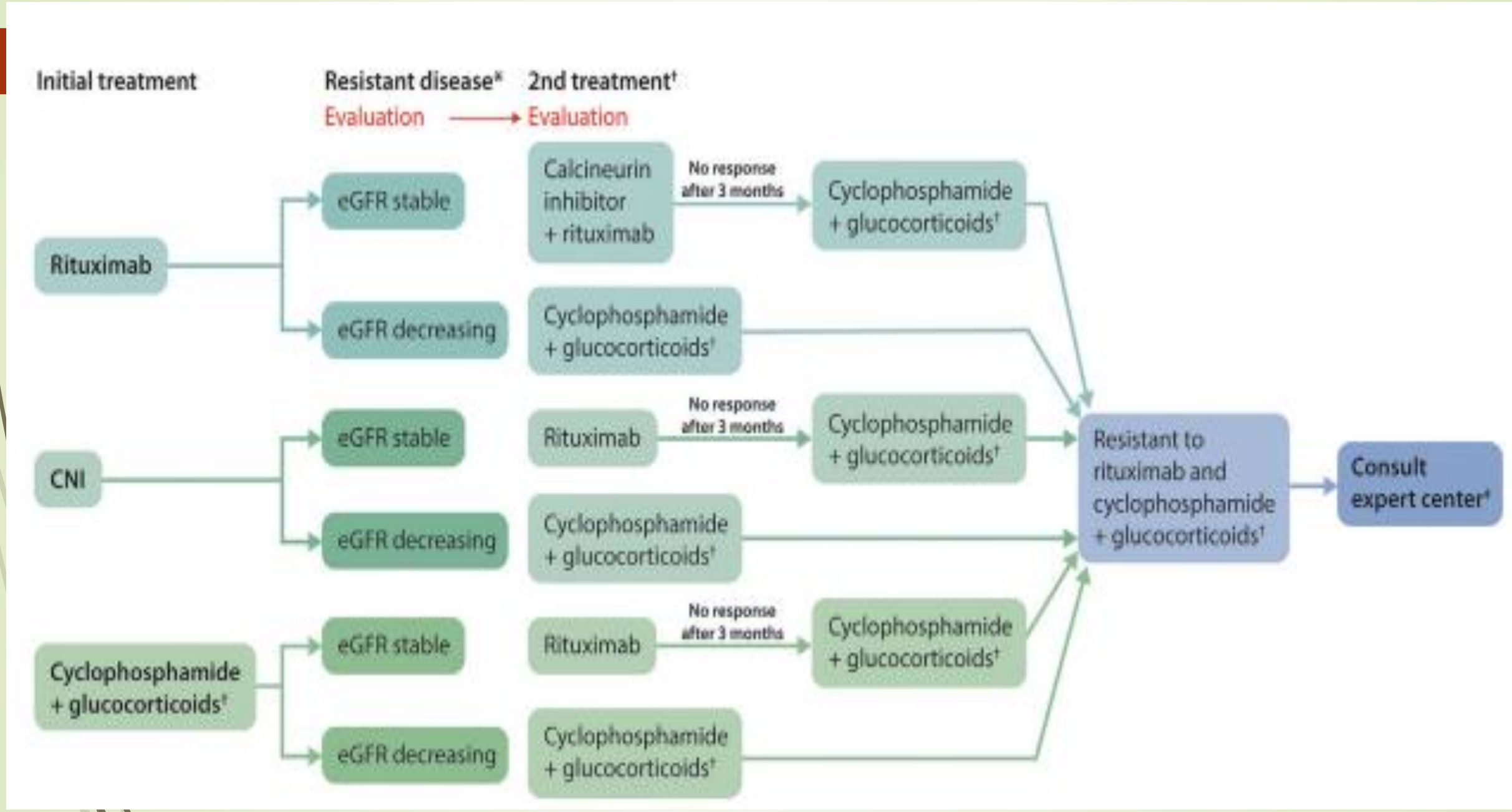
Immunologic monitoring in MN after start of therapy



Immunologic monitoring in MN after start of therapy

- The cumulative dose of cyclophosphamide should not exceed 36 g in view of the risk of malignancy. To stay on the safe side, we usually limit the cumulative dose to 25 g (in an 80 kg male: 6 months cyclical cyclophosphamide at a dose of 2.5 mg/kg/d equals 18 g and 6 months daily cyclophosphamide at a dose of 1.5 mg/kg/d equals 22 g). Lower doses (maximum 10 g) must be used in patients who wish to conceive.
- CNIs are unlikely to induce late immunologic remission; in patients with persistent anti-PLA2R antibodies, these drugs may be used in combination with rituximab. B cell depletion is insufficient to judge the efficacy of rituximab therapy; extra doses may be considered even if B cells in the peripheral blood are absent or very low.
- eGFR should be stable; if not, then it is always necessary to evaluate for other causes; and if eGFR decrease is attributed to MN activity, always provide additional therapy.
- *Some centers will measure antiPLA2R antibodies at month 3, and adapt treatment at that time. In most patients, response occurs within 3 months after start of therapy.
- † A negative immunofluorescence test indicates immunologic remission. If measured by enzyme-linked immunosorbent assay, a cutoff value of 2 RU/ ml should be used to define complete immunologic remission.
- ‡ Retreatment with rituximab should be given similarly to the initial treatment with 1 or 2 infusions of 1 g rituximab each administered 2 weeks apart (Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. N Engl J Med. 2019;381:36–46).

Management of resistant disease in MN

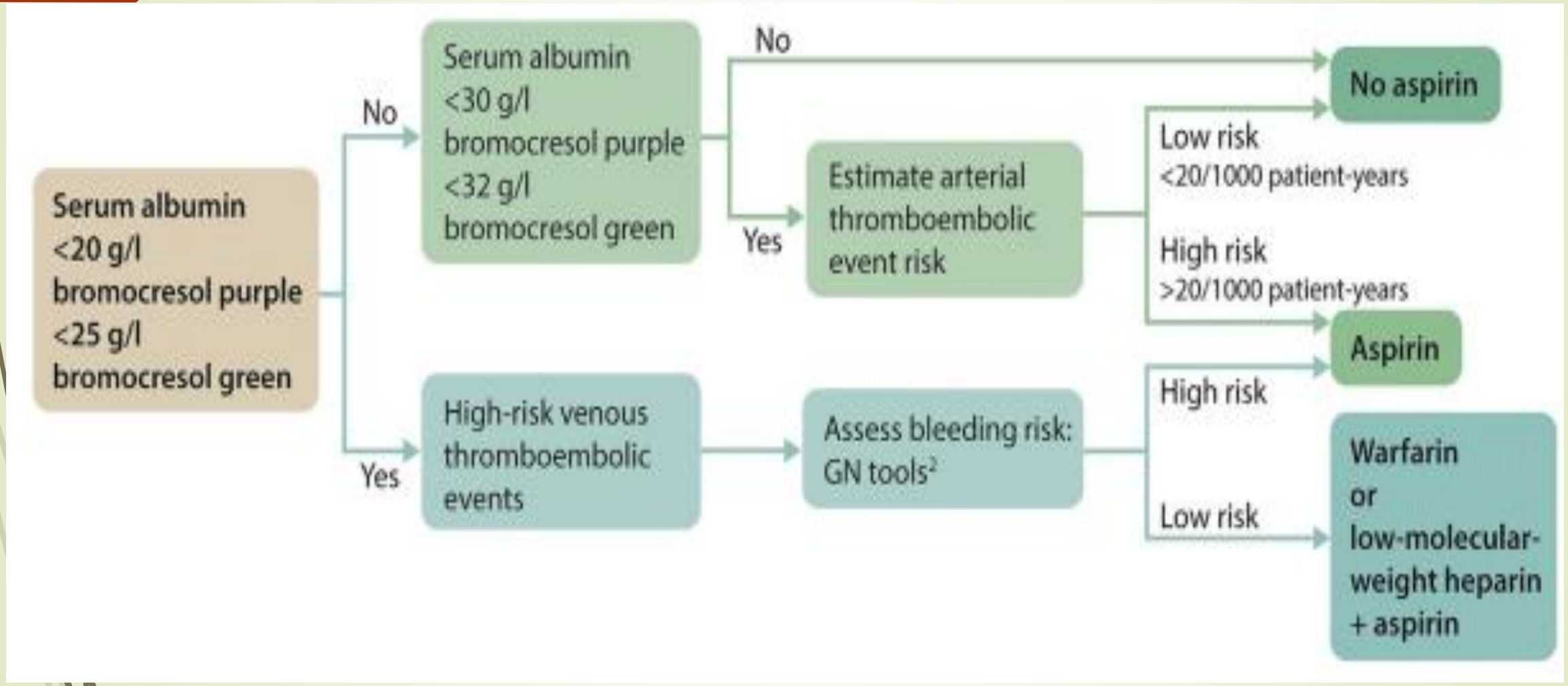


- In patients with MN and initial relapse of the NS after therapy, the initial therapy can be repeated or treatment may be switched to rituximab in those initially treated with CNIs or cyclophosphamide

Management of resistant disease in MN

- Evaluaion: In patients with resistant disease, compliance should be checked and efficacy monitored (e.g., B-cell response, antirituximab antibodies, IgG levels, leukocytopenia during cyclophosphamide, CNI levels).
- Persistent proteinuria is not sufficient to define resistance. If proteinuria persists, while serum albumin has increased, one should also consider secondary FSGS. This would be further supported by the disappearance of anti-PLA2R antibodies.
- In patients with persistent proteinuria with normal or near-normal serum albumin levels or patients with persistent proteinuria despite loss of anti-PLA2R antibodies, a kidney biopsy should be considered to document active MN.
- † Second treatment is dependent on the severity of deterioration of eGFR as indicated. When rituximab is chosen as second treatment, the response of proteinuria and anti-PLA2R antibodies should be evaluated after 3 months
- Cyclophosphamide treatment should take into account the maximal tolerable dose: The cumulative dose should not exceed 10 g if preservation of fertility is required. The cumulative dose should not exceed 36 g to limit risk of malignancies. Expert centers may still use more, based on weighing risk and benefits.
- ‡ Patients who did not respond to rituximab or cyclophosphamide should have a consultation with an expert center. These centers may choose experimental therapies (bortezomib, anti-CD38 therapy, and belimumab) or a higher dose of conventional immunosuppressive therapy.

Anticoagulant therapy in patients with MN



Anticoagulant therapy in patients with MN

- 1. The risk of thrombotic events is related to the level of serum albumin. It is important to note that there is a large difference among the serum albumin assays. A serum albumin concentration of 25 g/l [2.5 g/dl] with bromocresol green (BCG) equals a concentration of w20 g/l [2.0 g/dl] with bromocresol purple (BCP), or immunonephelometry. It is likely that most studies have used the BCG assay. Consider using 25 g/l [2.5 g/ dl] as a threshold when using BCG and 20 g/l [2.0 g/dl] when using BCP or immunonephelometry.
- 2. Assess risk of venous thrombosis and risk of bleeding (http://www.med.unc.edu/gntools/).
- 3. The risk of arterial thrombotic event (ATE) is dependent on age, history of previous events, diabetes, estimated glomerular filtration rate (eGFR), smoking, and severity of nephrotic syndrome (NS). Risk assessment can be done using the Framingham risk score, and including previous events and proteinuria.
- 4. Use of aspirin is insufficient to prevent venous thromboembolism (VTE); use of warfarin is sufficient to prevent ATE.
- 5. Treatment with warfarin: There is more INR variability in patients with NS and low eGFR; there is increased risk of thrombosis immediately after starting high-dose warfarin. Consider starting anticoagulation therapy with low-dose low-molecularweight heparin and then folding in warfarin and, when therapeutic, stopping the heparin. A good alternative is to use low-dose lowmolecular-weight heparin þ aspirin for a period of 3 months before switching to warfarin, allowing for judgment on the course of proteinuria.
- 6. Glucocorticoids increase the risk of thrombosis; thus, anticoagulant therapy should not be omitted in patients who start prednisone therapy.
- 7. ATE risk is estimated using the Framingham risk score, with added risk in case of low eGFR or higher proteinuria. The Framingham risk score takes into account age, smoking, serum cholesterol, and blood pressure.

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- Evaluation of a kidney transplant recipient with MN should include maximal efforts to ascertain if MN is associated with PLA2R antibodies, including staining the native kidney biopsy for PLA2R expression in immune deposits (enhanced PLA2R staining). The risk of recurrence increases if PLA2R antibodies persist in the circulation despite kidney failure. After transplantation, patients with known PLA2R antibodyassociated MN should be monitored for the kinetics of antibody levels every 1–3 months with a liberal transplant biopsy in case of increasing antibodies. Rituximab can be used in case of documented recurrent MN.

Table 1. Clinical and Pathologic Features That Distinguish Recurrent from De Novo MN

Category	Recurrent MN	De Novo MN
Epidemiology	• 10%-45% recurrence rate (higher rates in centers with protocol biopsies) • Clinically apparent by 13-15 mo, but proteinuria can begin within months of transplantation	• 1%-2% posttransplant with increasing incidence with time; reported as ~5.3% at 8 y • Higher incidence in pediatric population, reaching ~9%
Pathogenesis	• Anti-PLA_2R at time of transplantation is a risk factor • Can appear years later with reemergence of autoantibodies when transplant immunosuppression decreased	• Not fully known • Has been associated with chronic and/or antibody-mediated rejection
Clinical presentation	• Similar to primary MN • May be detected earlier with lower amounts of proteinuria due to heightened surveillance (especially with protocol biopsy)	• Can be asymptomatic or with various degrees of proteinuria many years after transplantation
Diagnosis	• MN present on biopsy of native kidney • Presence of anti-PLA_2R can support recurrent MN if native diagnosis not known • Positive PLA_2R staining within deposits in 70%-80% • IgG4 is the dominant or codominant IgG subclass	• Diagnosis other than MN in biopsy of native kidney • Typically not associated with anti-PLA_2R antibody or PLA_2R staining of deposits • Evidence of chronic and/or antibody-mediated rejection • IgG1 is predominant IgG subclass
Treatment	• Can closely follow if low titer anti-PLA_2R, subnephrotic proteinuria, stable kidney function • Transplant immunosuppression may cause decrease and disappearance of autoantibodies • Heightened concern warranted as process already resulted in loss of native kidneys • Rituximab for worsening disease in setting of transplant immunosuppression	• Unknown natural history but 50% graft loss has been reported • Treat underlying rejection and implement antiproteinuric therapy • Increase maintenance immunosuppression, consider plasmapheresis if chronic rejection is present • Consider rituximab or cyclophosphamide if kidney function is rapidly declining

IgG, immunoglobulin G; MN, membranous nephropathy; PLA_2R, phospholipase A_2 receptor

- MN, when it occurs in the kidney allograft, can represent a recurrence of the same disease that occurred in the native kidneys (ie, recurrent MN) or as de novo disease in a recipient who experienced kidney failure due to other causes. The features of these two forms are quite different (Table 1)

Recurrent MN

- The development of recurrent MN likely recapitulates the earliest stages of MN in the native kidney, when circulating autoantibodies have started to target intrinsic podocyte proteins (eg, PLA2R) in the donor kidney and form immune deposits of increasing size. Although the humoral response is typically quite mature by the time someone has progressed to kidney failure and requires transplantation, transplant immunosuppression itself can mitigate the humoral response and is sometimes able to cause decrease and disappearance of circulating antibodies. Knowledge of autoantibody status in the peritransplantation period is critical. In those with low antibody titers, transplantation can often proceed, with careful monitoring of autoantibody titer after transplantation; the answer to question 4 is therefore (c). In those with high titers, it is less likely that transplant immunosuppression alone will fully treat the autoimmune process before clinically significant recurrent disease can occur and potentially threaten the allograft. In this case, consideration should be given to treatment before transplantation.

De Novo MN

- It has been proposed that de novo MN occurs as a result of multiple triggers that all lead to formation of antigenantibody complexes in the subepithelial space of the GBM, resulting in podocyte injury and MN. These antigens are exposed as a result of a prior episode of rejection or planted in the subepithelium as a result of an infection in an immunocompromised host. It has also been proposed that episodes of rejection can lead to disturbance in the GBM architecture, rendering it susceptible to formation of subepithelial deposits.