Updates on Membranous nephropathy

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Introduction:

- Membranous nephropathy (MN) represents a histologic pattern of glomerular injury characterized by an accumulation of electron-dense deposits in the subepithelial region of the glomerular basement membrane, composed of immunoglobu lins and complement components
- Membranous nephropathy (MN) is a common cause of adult nephrotic syndrome and is seen less commonly in children. It is the main cause of NS in White adults and almost twice more frequent in men.

Classification:

primary:

- The subtypes of disease in which there is a humoral autoimmune response to a normal podocyte antigen in the absence of secondary features or etiologies of disease.
- The identification of target autoantigens in adult idiopathic MN, starting with the description in 2009 of anti- bodies against the M-type PLA2R, was a turning point in our understanding of this disease and rapidly led to new methods for diagnosis and monitoring.

Secondary :

- The cases that arise in the setting of systemic processes such as infection, malignancy, or drug exposure in which treatment of the underlying disorder is expected to lead to the resolution of the MN.

Alloimmune MN:

- Alloimmunity develops when there is a discrepancy between host and recipient antigens and is characterized by an immune response to a previously unfamiliar antigen.

❖antenatal

❖ de novo post transplantation MN

Primary MN is a kidney-specific autoimmune glomer ular disease caused by circulating podocyte-targeted autoantibodies, mainly anti-PLA2R (70%75%). Recently, novel autoantibodies and podocyte antigens have been described using laser-capture microdissec-tion/mass spectrometry

Box 1. Common Causes of Primary, Secondary, or Alloimmune MN

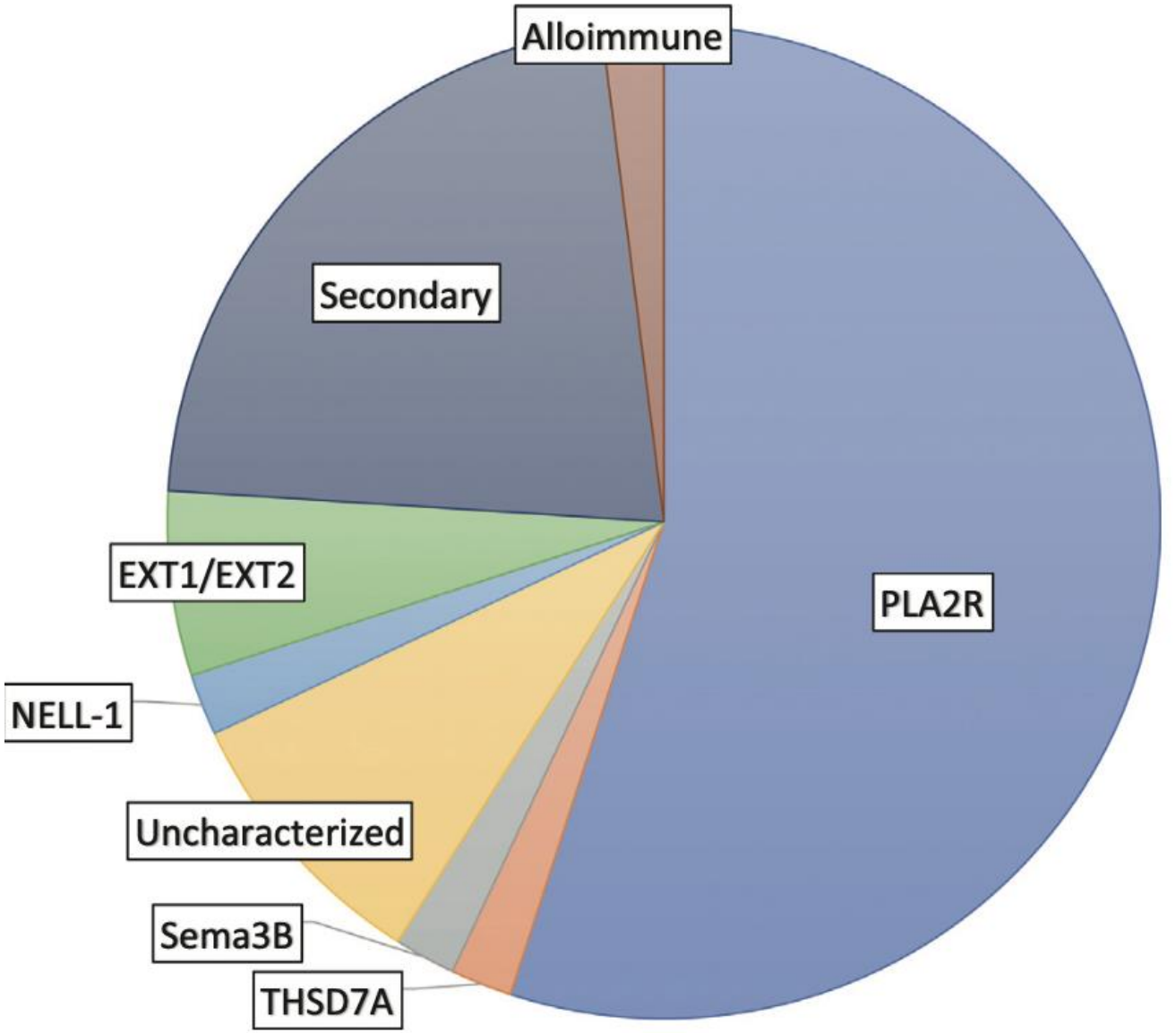
Primary MN[a]
- PLA_2R-associated
- THSD7A-associated
- NELL-1–associated
- Sema3B-associated
- Uncharacterized

Secondary MN
- Autoimmune/collagen-vascular disease: SLE and mixed connective tissue disease (includes EXT1/EXT2-associated), Sjogren's, thyroiditis, sarcoidosis, dermatitis herpetiformis
- Infection: HBV and HCV, malaria, secondary or congenital syphilis, leprosy
- Drugs, toxins, other adulterants: NSAIDs, gold salts, penicil-lamine, mercury, cationic bovine serum albumin (infant formula)
- Malignancy: more commonly solid-organ carcinomas (lung, breast, colon, and kidney), NHL, leukemia; rarely associated with THSD7A expression in tumor; NELL-1–associated MN linked to underlying malignancy

Alloimmune MN
- Antenatal alloimmune MN caused by anti-NEP antibodies
- De novo MN in kidney allograft
- Graft-vs-host disease

AJKD, Membranous Nephropathy: Core Curriculum 2021

Spectrum of disease within the larger pathologic clas sification of MN according to the observation that secondary entities represent approximately 30% of all MN. The percentages of MN associated with the newer antigens NELL-1, Sema3B, and EXT1/EXT2 are estimates, and larger cohorts are needed to determine the true prevalence of these subtypes of MN. The uncharacterized group reflects those cases of presumed primary MN in which the target antigen has yet to be described.



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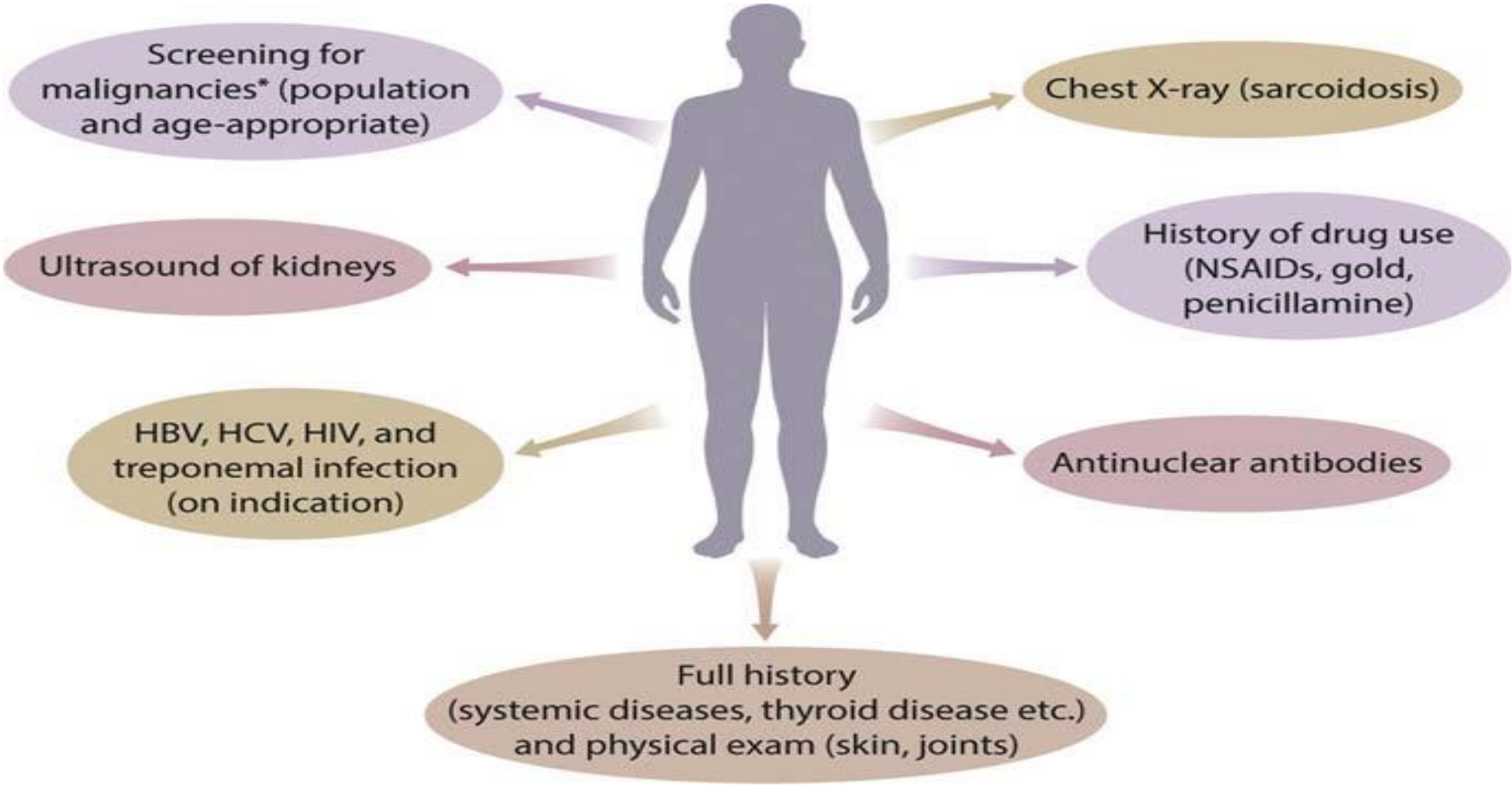
Patients with MN should be evaluated for associated conditions, regardless of whether anti-PLA2R antibodies and/or anti-THSD7A antibodies are present or absent



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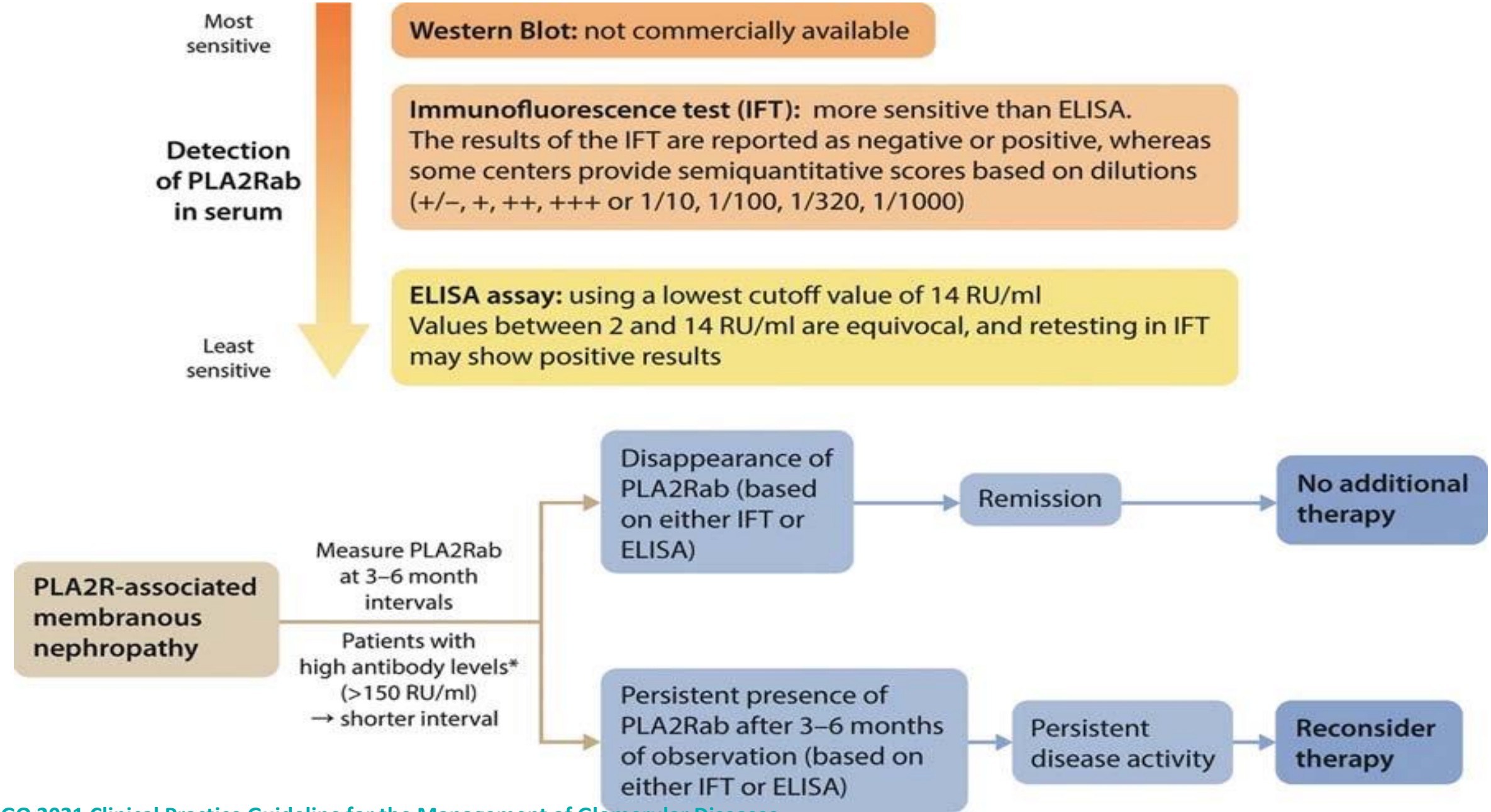
PLA2R

- PLA2R is a 180-kDa transmembrane glycoprotein expressed by the human podocyte, where its precise function is not clear.
- PLA2R-associated MN is typically more common in male patients, although some of the more recently described subtypes such as THSD7A- or NELL-1–associated MN may have less of a male predominance.

- A kidney biopsy is not required to confirm the diagnosis of membranous nephropathy (MN) in patients with nephrotic syndrome and a positive anti- PLA2R antibody test.



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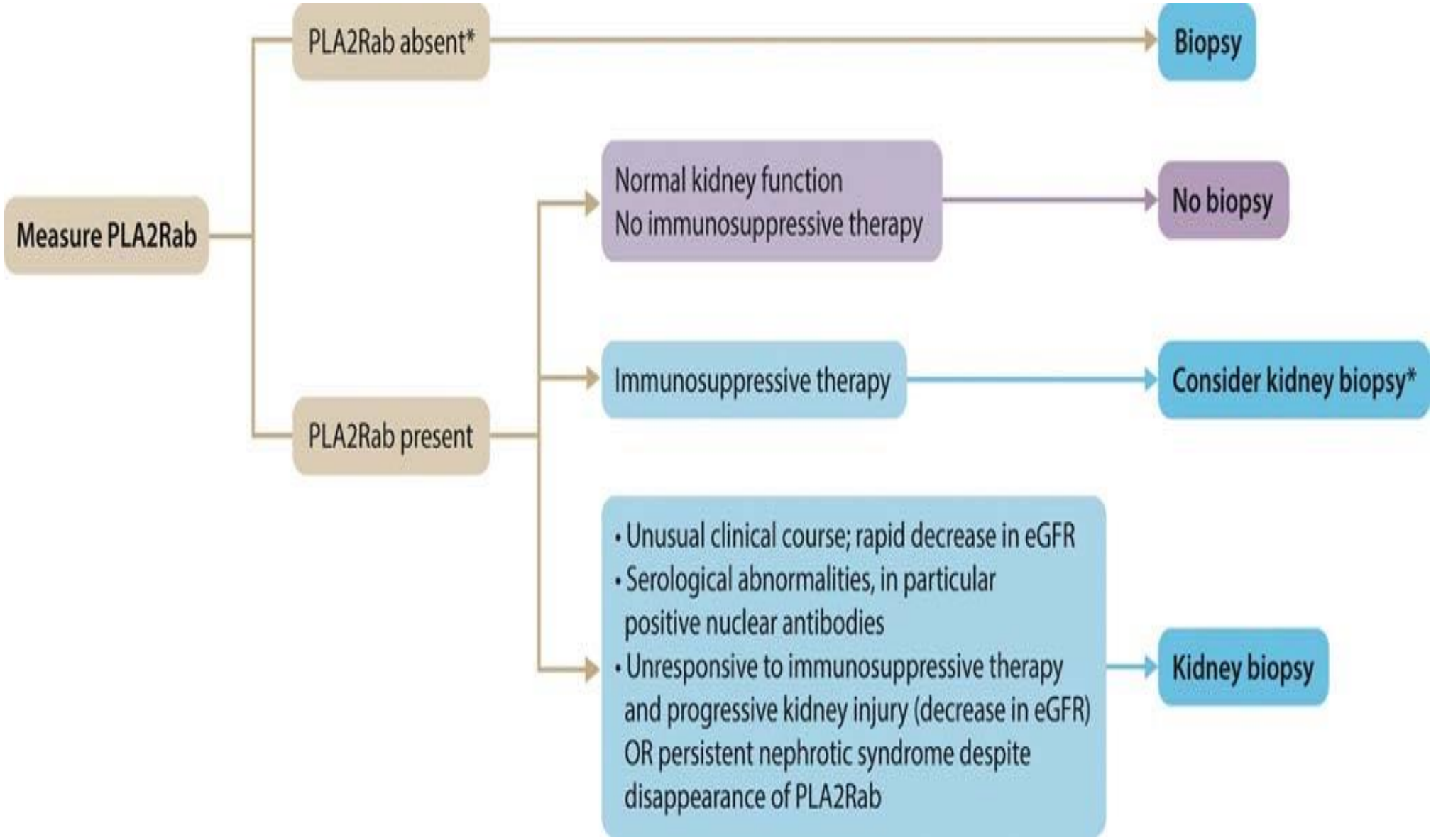
When to consider a kidney biopsy in a patient who is anti-PLA2R antibody-positive:



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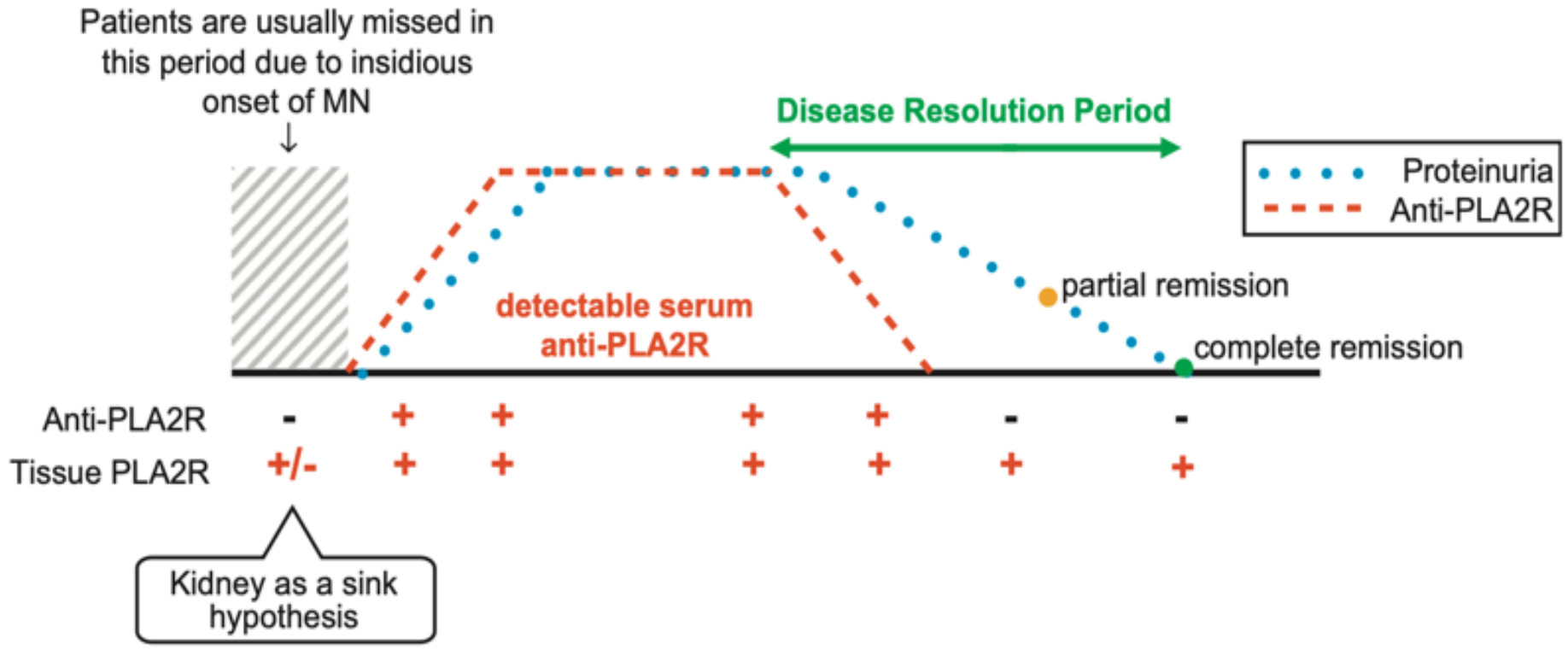

Schematic representation of the immunologic and clinical courses of disease in PLA_2R-associated MN.

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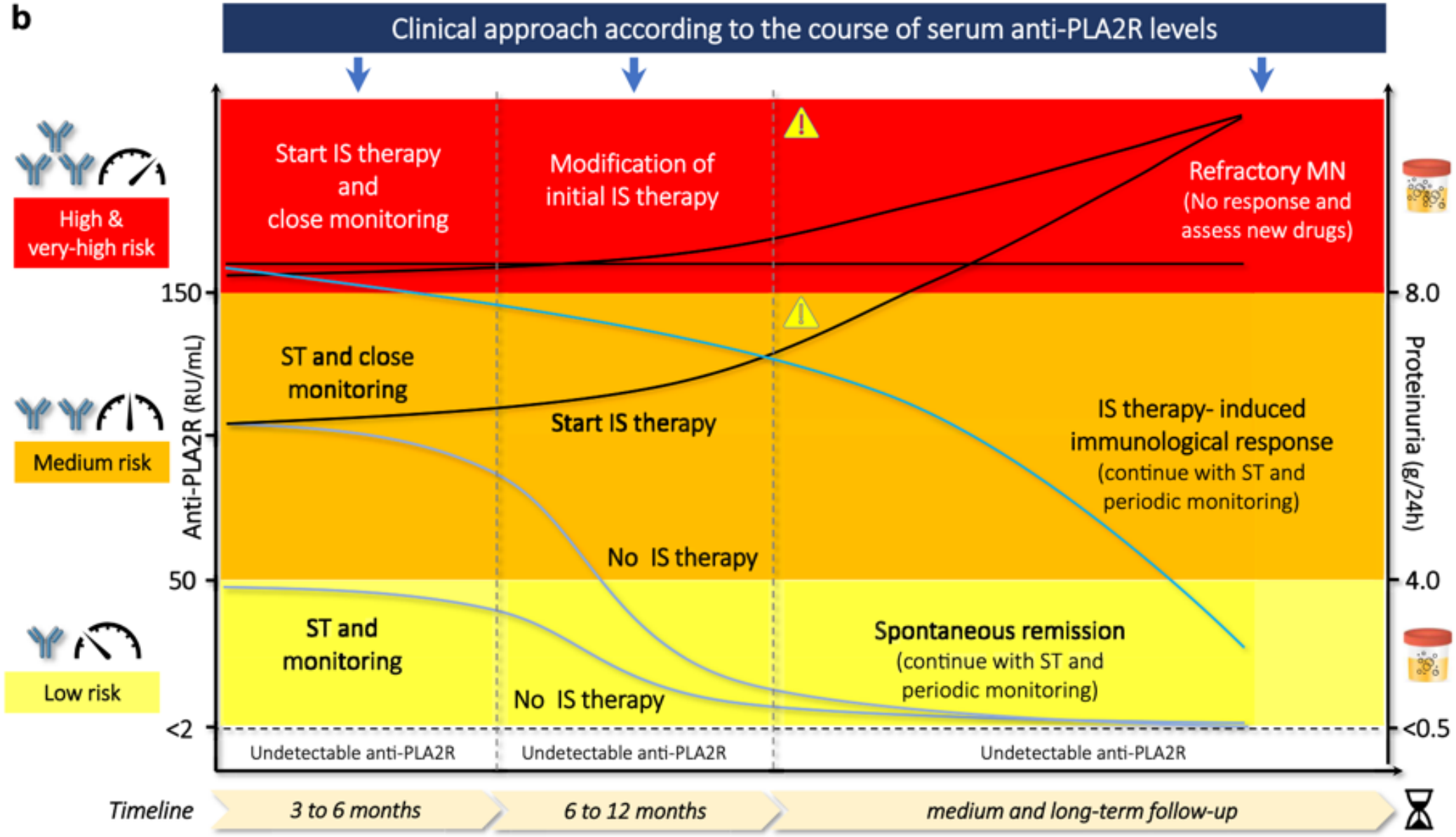
Understanding that autoantibody levels must decrease and disappear before any significant clinical remission can occur is the reason why high anti-PLA2R titers are associated with increased severity of disease, adverse kidney outcomes, and decreased likelihood of remission.



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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

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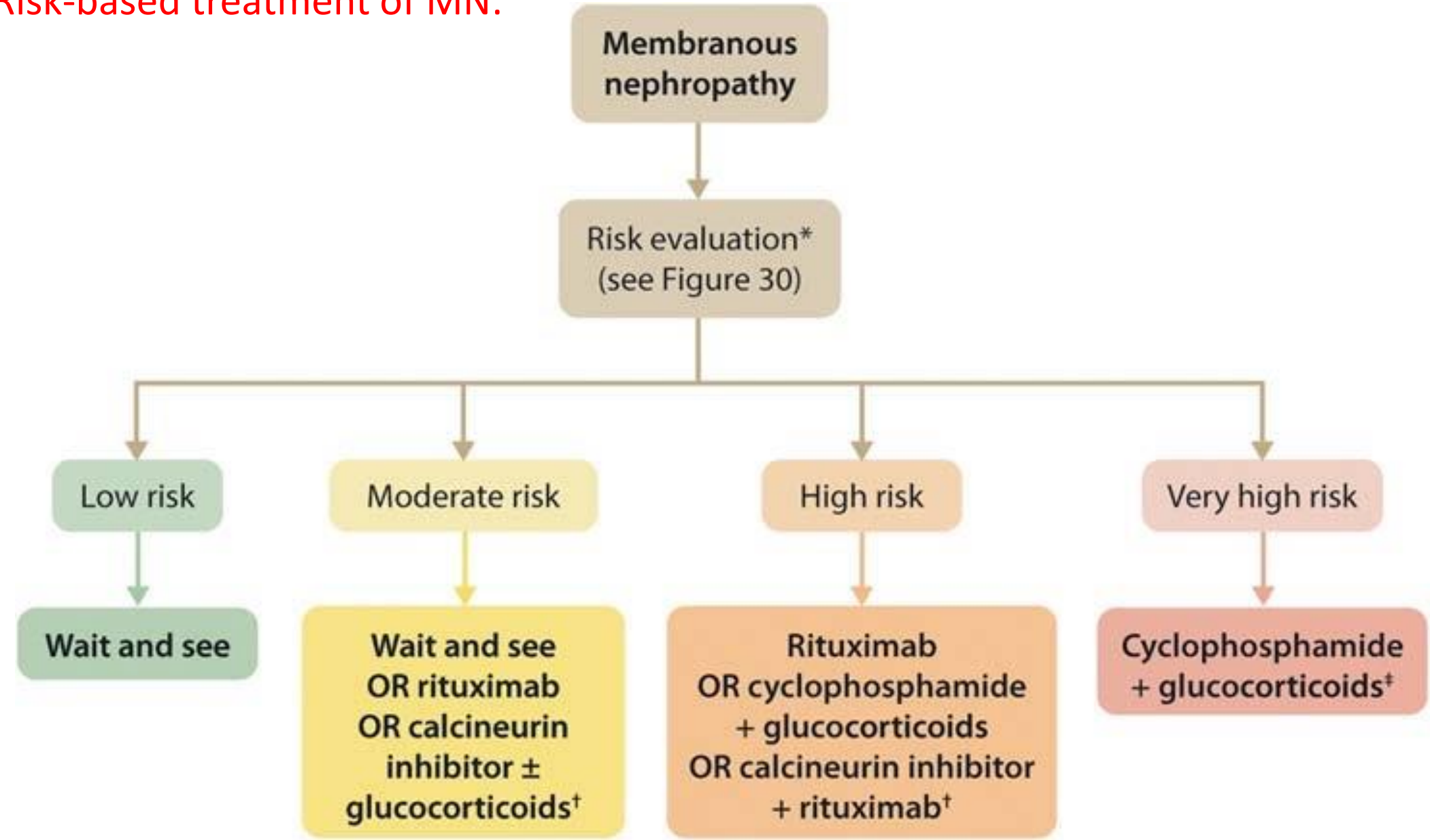
Selectivity index is calculated as clearance of IgG/clearance of albumin.

Risk-based treatment of MN:



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Rituximab: the First Option for Most Patients

- According to 2021 KDIGO guidelines, for moderate- high risk MN, the first option is rituximab (+/-CNIs).
- Rituximab is an anti-CD20 chimeric IgG1 monoclonal antibody that depletes CD20þ pre-B/mature B cells for at least 6 to 12 months through complement-dependent cytotoxicity, antibody- dependent cellular cytotoxicity, and apoptotic cell death.
- Rituximab may also protect podocytes by stabilizing sphingomyelin-phosphodiesterase-acid-like-3b expression and preventing downregulation of acid- sphingomyelinase activity, thereby decreasing actin cytoskeleton disruption and apoptosis.

- GEMRITUX : did not show better efficacy of rituximab versus conservative anti- proteinuric therapy at the 6-month end point, but long- term follow-up for a median of 17 months showed higher remission rates in the rituximab arm.

- MENTOR trial: designed as a noninferiority trial that compared the use of rituximab and cyclosporine in primary MN, demonstrated not only equal efficacy at 12 months, but superiority of rituximab at achieving and maintaining remission at 24 months. This trial lends strong support for the use of rituximab as first-line treatment for primary MN.

- STARMEN trial: It is recently published and compares 24-month remission rate after sequential therapy with tacrolimus and rituximab versus the modified Ponticelli regimen in primary MN. Treatment with corticosteroids–cyclophosphamide induced more complete or partial remissions at 24 months, as compared with tacrolimus– RTX (84% vs 58%). In addition, the rate of complete remissions was significantly greater in the former as compared with the latter (60% vs 26%). Remarkably, the number of relapses were also lower in the group of patients treated with corticosteroids– cyclophosphamide.
- Thus, the STARMEN trial failed to support the hypothesis that the tacrolimus–RTX regimen was superior to corticosteroids–cyclophosphamide

- The rationale for dual therapy is to administer rituximab prior to tapering the tacrolimus in an attempt to reduce the rate of relapse that is otherwise common in this setting.
- Because of the more limited adverse effects of rituximab, it may be considered in patients with advanced chronic kidney disease and immunologically active MN, as successful treatment of the MN may help to preserve remaining GFR.

Commonly used treatment regimens for patients with MN :

Cyclophosphamide (cyclical)	• Methylprednisolone 1 g i.v. for 3 consecutive days at start of month 1, 3, and 5 • Prednisone 0.5 mg/kg/d in months 1, 3, and 5 • Cyclophosphamide 2.5 mg/kg/d in months 2, 4, and 6‡
Cyclophosphamide (continuous)	• Methylprednisolone 1 g i.v. for 3 consecutive days at start of month 1, 3, and 5 • Prednisone 0.5 mg/kg/d every other day in months 1–6, with taper thereafter • Cyclophosphamide 1.5 mg/kg/d in months 1–6‡
Rituximab	• Rituximab 1 g i.v. administered twice within 2 weeks* • Rituximab 375 mg/m^2 given 1–4 times at weekly intervals
Tacrolimus	• Tacrolimus 0.05–0.1 mg/kg/d, target trough level 3–8 ng/ml (3.7–9.9 nmol/l), duration 12 months†
Cyclosporine	• Cyclosporine 3.5 mg/kg/d, target trough level 125–225 ng/ml (104–187 nmol/l)†

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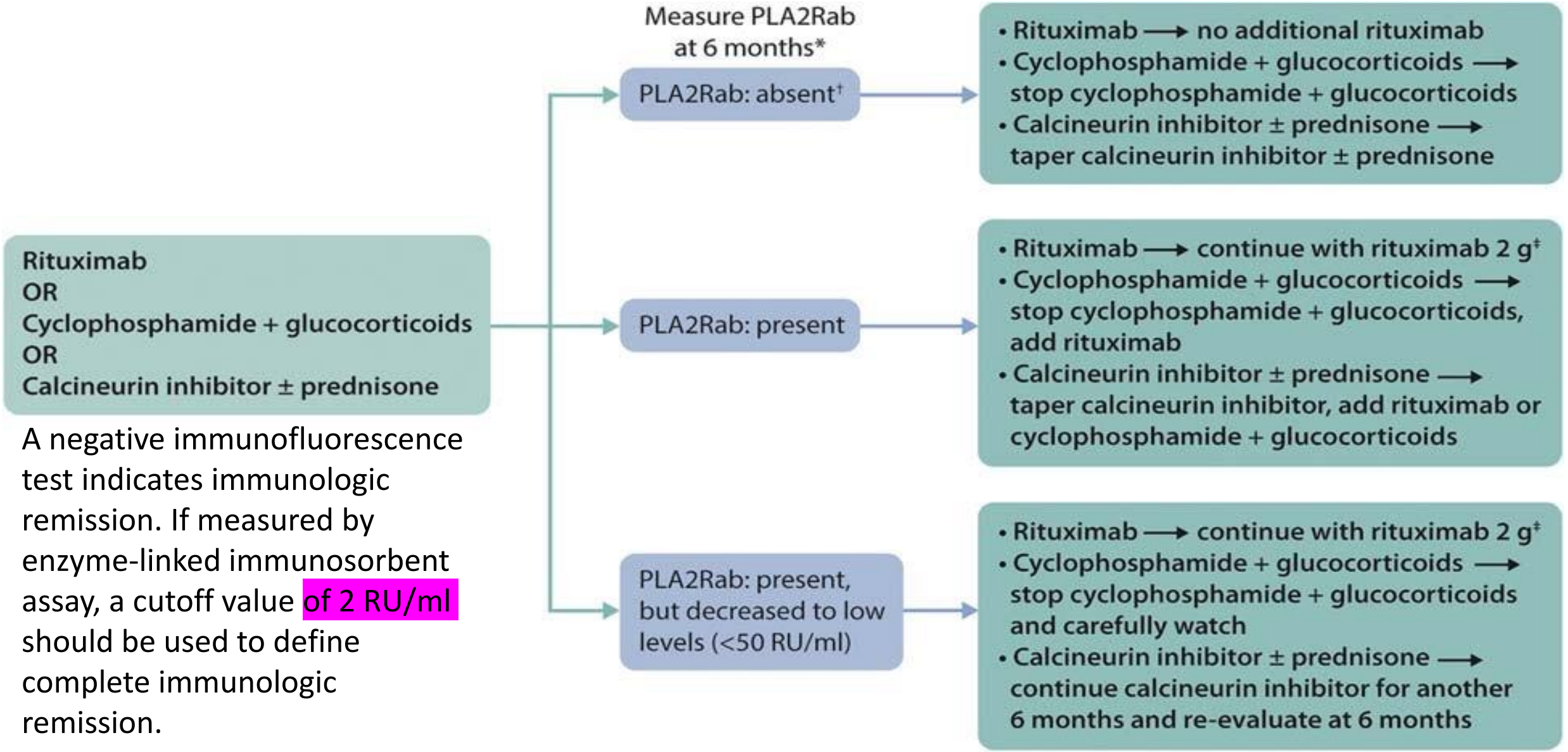
Longitudinal monitoring of anti- PLA2R antibody levels after start of therapy:



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.

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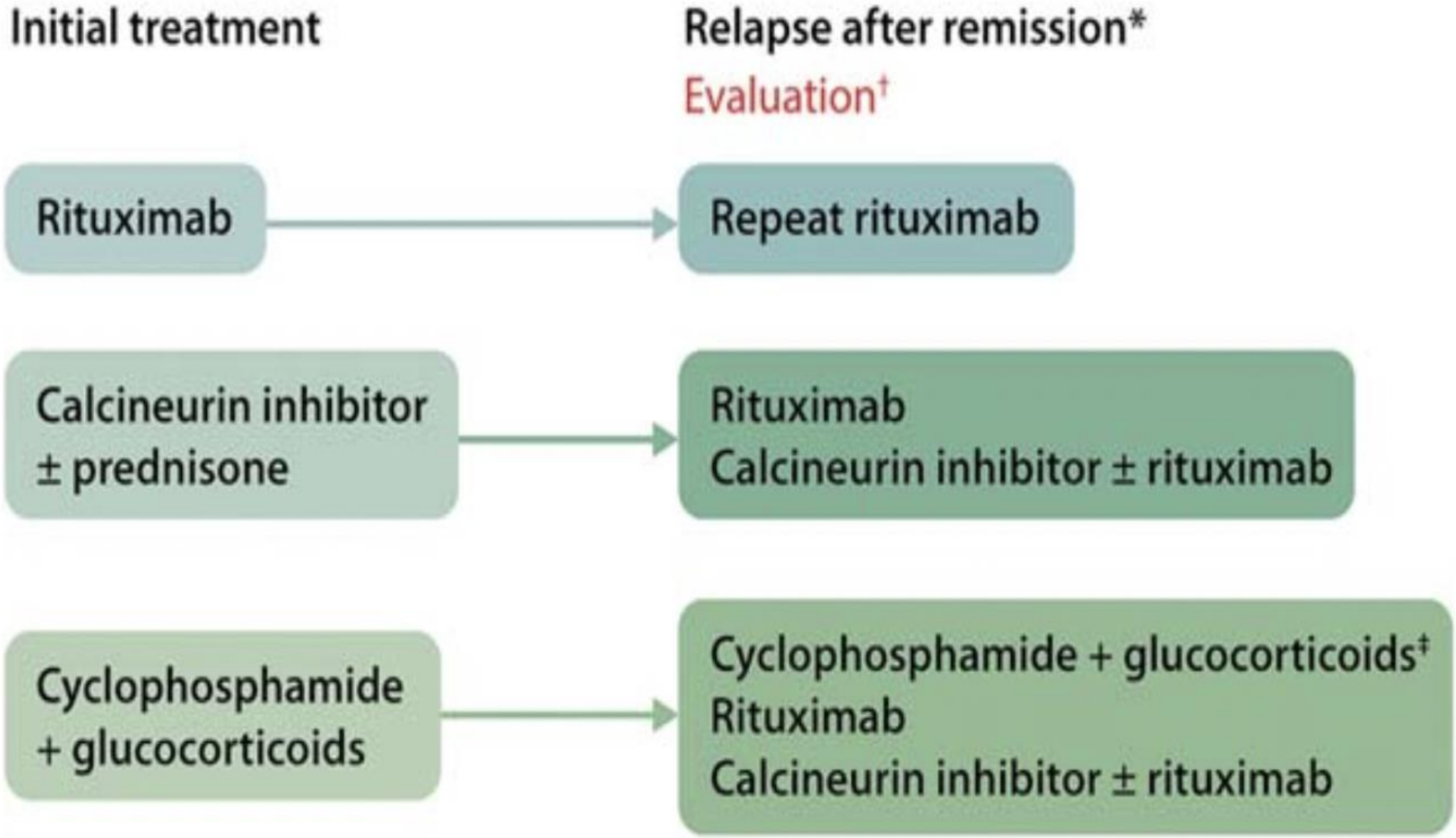
Relapse:

Definition:

- The definition of relapse is variable. Some authors define relapse after remission as an increase in proteinuria >3.5 g/d in patients who developed a partial or complete remission.
- KDIGo suggests that the course of serum albumin and PCR should be used in the evaluation.
- In patients with a partial remission (characterized by normalization of serum albumin), a relapse should be defined by an increase of proteinuria paralleled by a decrease in serum albumin levels.

- Immunologic monitoring is of particularly great value in these situations. If, in the period of “clinical remission,” anti-PLA2R antibodies were still positive, this would be evidence for resistant disease.
- Therefore, in patients with positive anti-PLA2R antibodies, it is advised that anti-PLA2R antibodies be evaluated at the time of remission and relapse. The course of anti-PLA2R antibodies should precede the clinical course.
- In patients with very early relapse, it is important to consider reasons for the failure of the previous therapy (e.g., compliance, low drug levels, insufficient B cell depletion, presence of anti-rituximab antibodies).

Management of initial relapse after therapy in MN:



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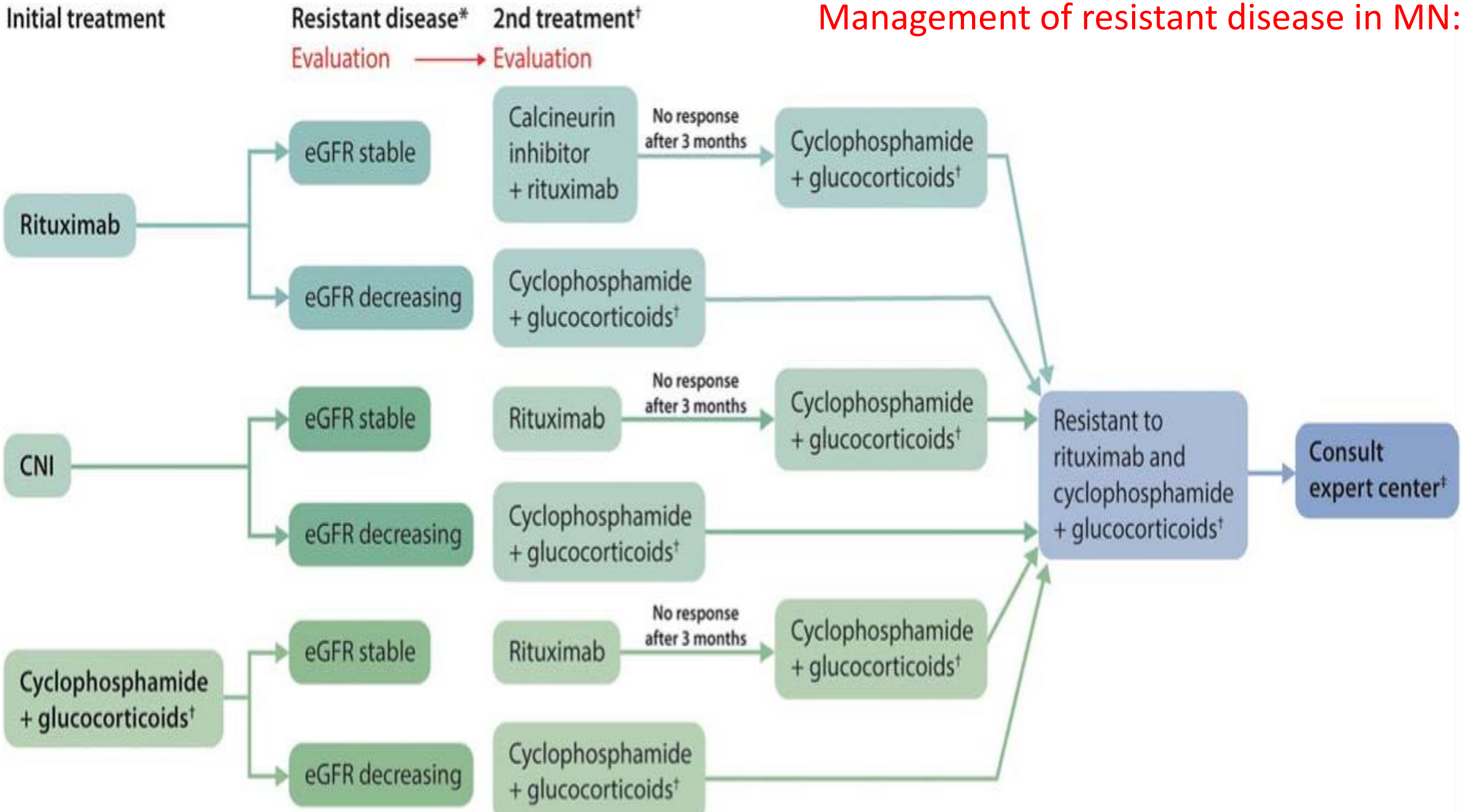
Resistance MN

Definition:

- KDIGO has no accepted definition of resistant disease. In patients with MN, with measurable anti-PLA2R antibodies at the start of therapy, resistant disease can be defined by the persistence of anti-PLA2R antibodies at high or unchanged levels after 1 line of immunosuppressive therapy (of sufficient dose and duration). The persistence of moderate proteinuria should not be used to define resistant disease, as proteinuria can persist for 12–24 months after the start of therapy.
- Obviously, defining resistance is more difficult in patients who are anti-PLA2R antibody–negative.

Management of resistant disease in MN:



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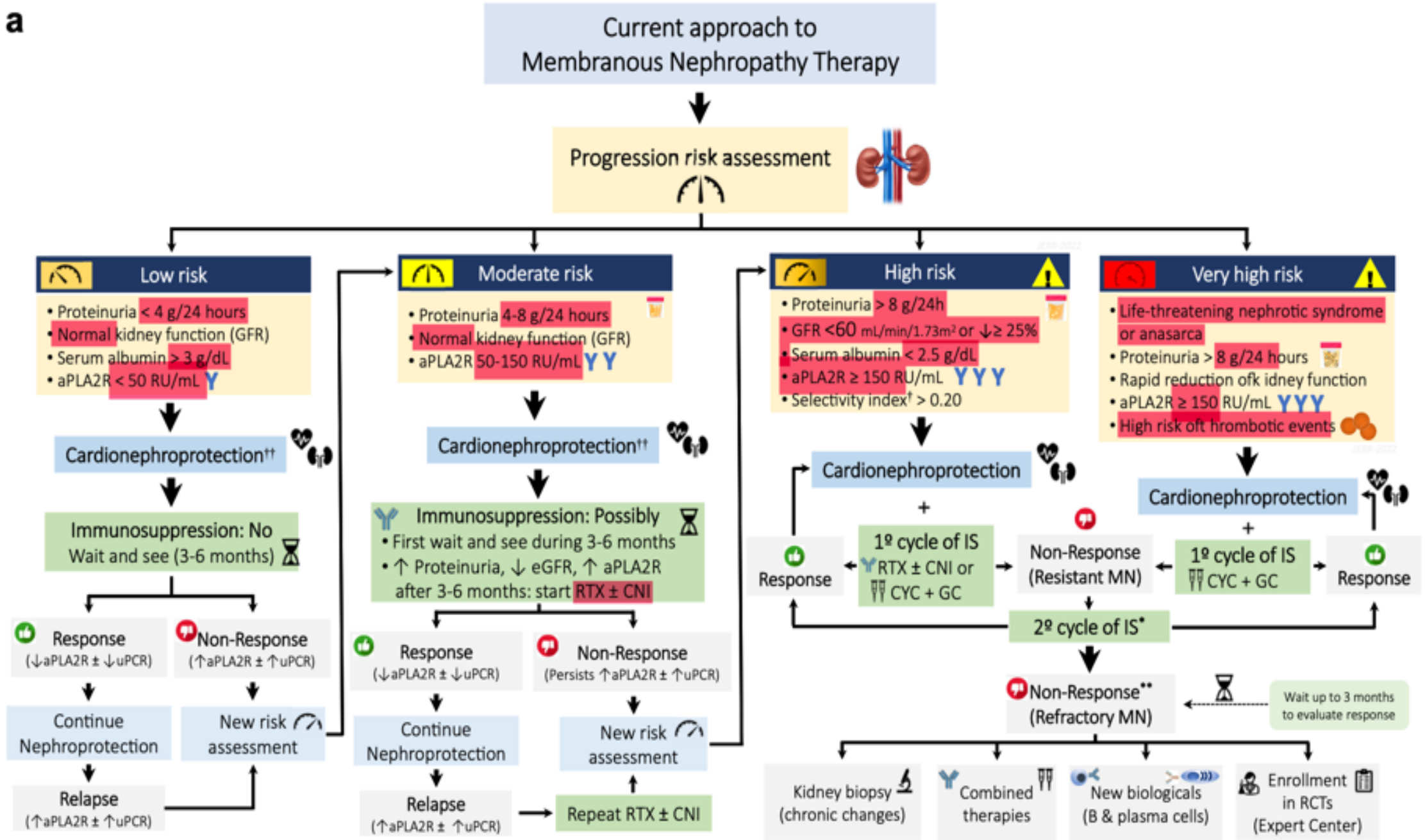

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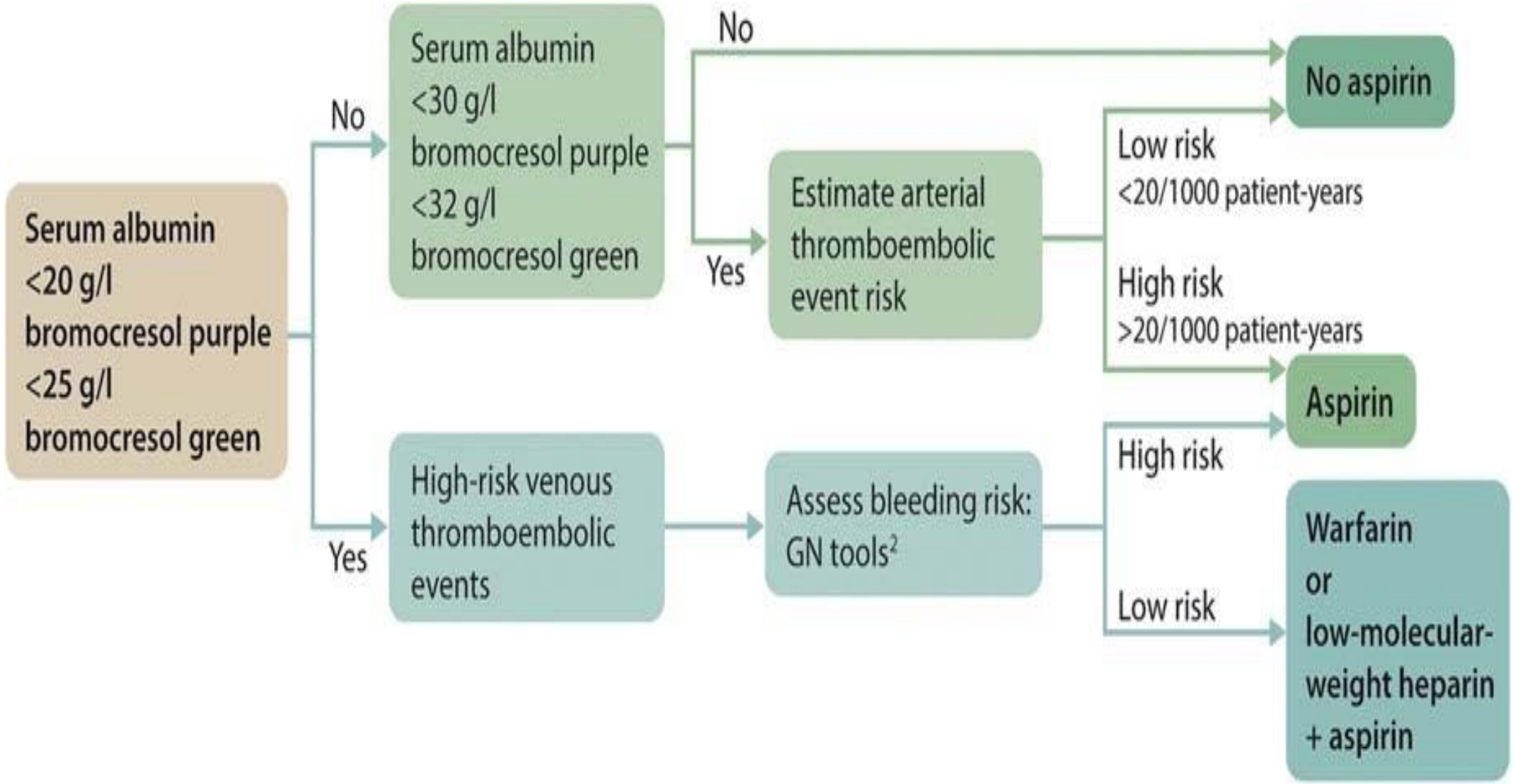
Anticoagulant Therapy:

- Nephrotic syndrome is associated with an increased risk of VTE and ATE. Patients with MN have the greatest risk. The risk of thrombosis is particularly increased in the first 6–12 months after onset of disease.

- Prophylactic anticoagulant therapy in patients with MN and nephrotic syndrome should be based on an estimate of the risk of thrombotic events and the risk of bleeding complications

Anticoagulant therapy in patients with MN:



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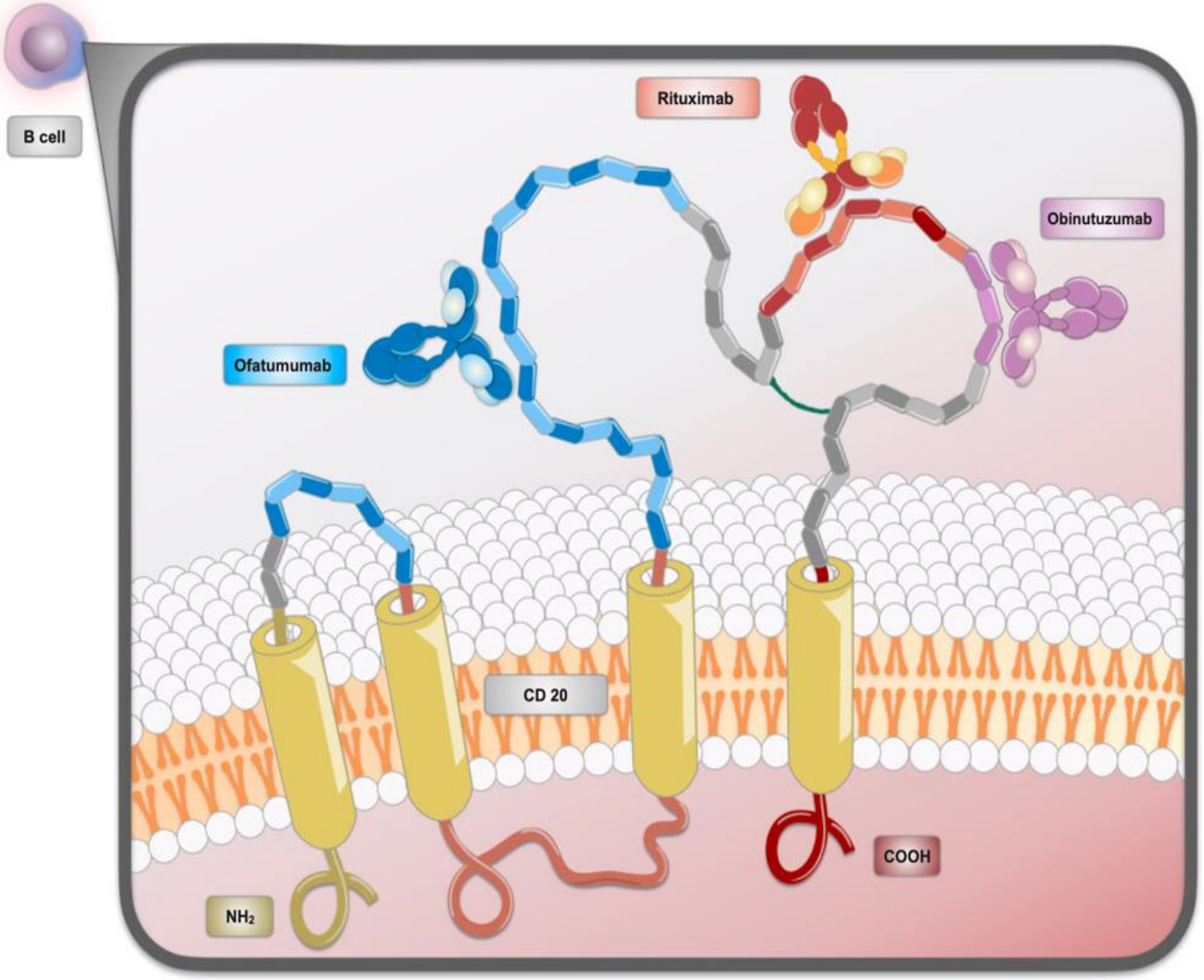
- Use of aspirin is insufficient to prevent venous thromboembolism (VTE); use of warfarin is sufficient to prevent ATE.
- There is more international normalized ratio (INR) variability in nephrotic syndrome and low eGFR; there is increased risk of thrombosis immediately after starting high-dose warfarin. Consider starting anticoagulation therapy with low-dose low-molecular- weight heparin and then folding-in warfarin and, when therapeutic, stopping the heparin. A good alternative is to use low-dose low-molecular-weight heparin +aspirin for a period of 3 months before switching to warfarin, allowing for judgment on the course of proteinuria.
- Glucocorticoids increase the risk of thrombosis; thus, anticoagulant therapy should not be omitted in patients who start prednisone therapy.

Novel Treatment:

- **NEWER ANTI-CD20**
- **PROTEASOME INHIBITORS**
- **ANTI-CD38**
- **ANTI-COMPLEMENT THERAPIES**
- **BELIMUMAB**

NEWER ANTI-CD20 :

B-cell lymphocytes have been shown to play a key role in the pathogenesis underlying MN . CD20 is composed of four membrane-spanning domains with the amino- and carboxyterminal domains located within the cytoplasm . The extracellular part of CD20 consist of two loops formed between position 72–80 and 142–182, and represent the main targets of anti-CD20 monoclonal antibodies .



CKJ REVIEW 2023
Future landscape for the management of membranous nephropathy Fernando Caravaca-Fontán et al

ofatumumab (OFA)

Case report

Ofatumumab for multirelapsing membranous nephropathy complicated by rituximab-induced serum-sickness

Manuel Alfredo Podestà,[1,2] Barbara Ruggiero,[1,3] Giuseppe Remuzzi,[1] Piero Ruggenenti[1,2]

OFA recognizes both small and large loops of CD20, whereas RTX only binds to the large loop of the distal epitope . Furthermore, OFA has a binding site for C1q, which results in improved complement-mediated cytotoxicity .

The efficacy of OFA in MN was reported in a patient with a multiple relapsing disease requiring repeated infusions of RTX, in whom rescue treatment with OFA achieved a persistent re mission of nephrotic syndrome for 2 years

Obinutuzumab (OBI)

EXCEPTIONAL CASE

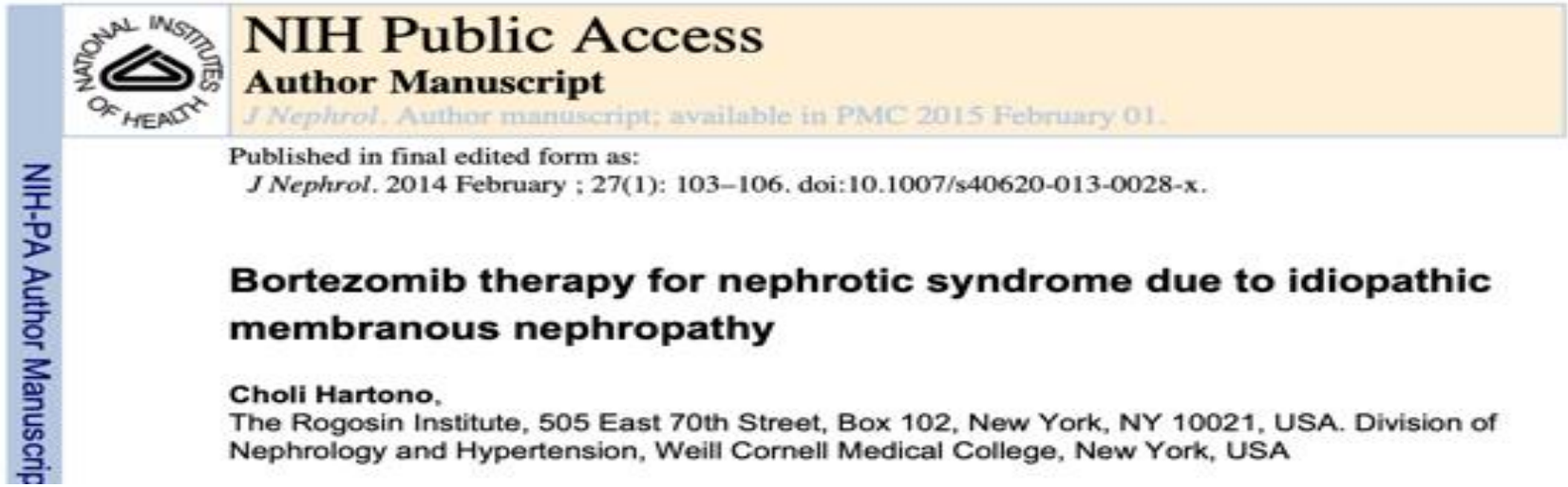
Membranous nephropathy associated with immunoglobulin G4-related disease successfully treated with obinutuzumab

Noemi E. Ginthör[1], Katharina Artinger[1], Marion J. Pollheimer[2], Martin H. Stradner[3] and Kathrin Eller[1]

[1]Division of Nephrology, Medical University of Graz, Graz, Austria, [2]Institute of Pathology, Medical University of Graz, Graz, Austria and [3]Division of Rheumatology and Immunology, Medical University of Graz, Graz, Austria

- OBI has demonstrated superiority in the depletion of B cells in whole blood samples, and also triggers a deeper depletion of B cells in spleen and lymph nodes, compared with RTX . All these characteristics provide a strong pathophysiological rationale for its use in resistant MN patients aimed at preventing the production of antibodies against certain podocyte antigens, and the deposition of immune complexes

PROTEASOME INHIBITORS



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J Nephrol. 2014 February ; 27(1): 103–106. doi:10.1007/s40620-013-0028-x.

Bortezomib therapy for nephrotic syndrome due to idiopathic membranous nephropathy

Choli Hartono,
The Rogosin Institute, 505 East 70th Street, Box 102, New York, NY 10021, USA. Division of Nephrology and Hypertension, Weill Cornell Medical College, New York, USA

First generation :Bortezomib

Second generation : carfilzomib, ixazomib , delanzomib,

Successful use of bortezomib in MN has been reported in the literature , including an early recurrence after kidney transplantation refractory to RTX

Anti CD38:

Long-lived plasma cells play a major role in the sustained production of antibodies in autoimmune diseases . As such, tar geting them represents a therapeutic challenge because, un- like short-lived plasmablasts (CD19+CD20–), long-lived plasma cells (CD19−CD20−CD38+CD138+) reside in survival niches in in flamed tissue and bone marrowSplenic and bone marrow plasma cells highly express CD38 and therefore, the use of anti-CD38 agents represents an attractive option in autoimmune diseases

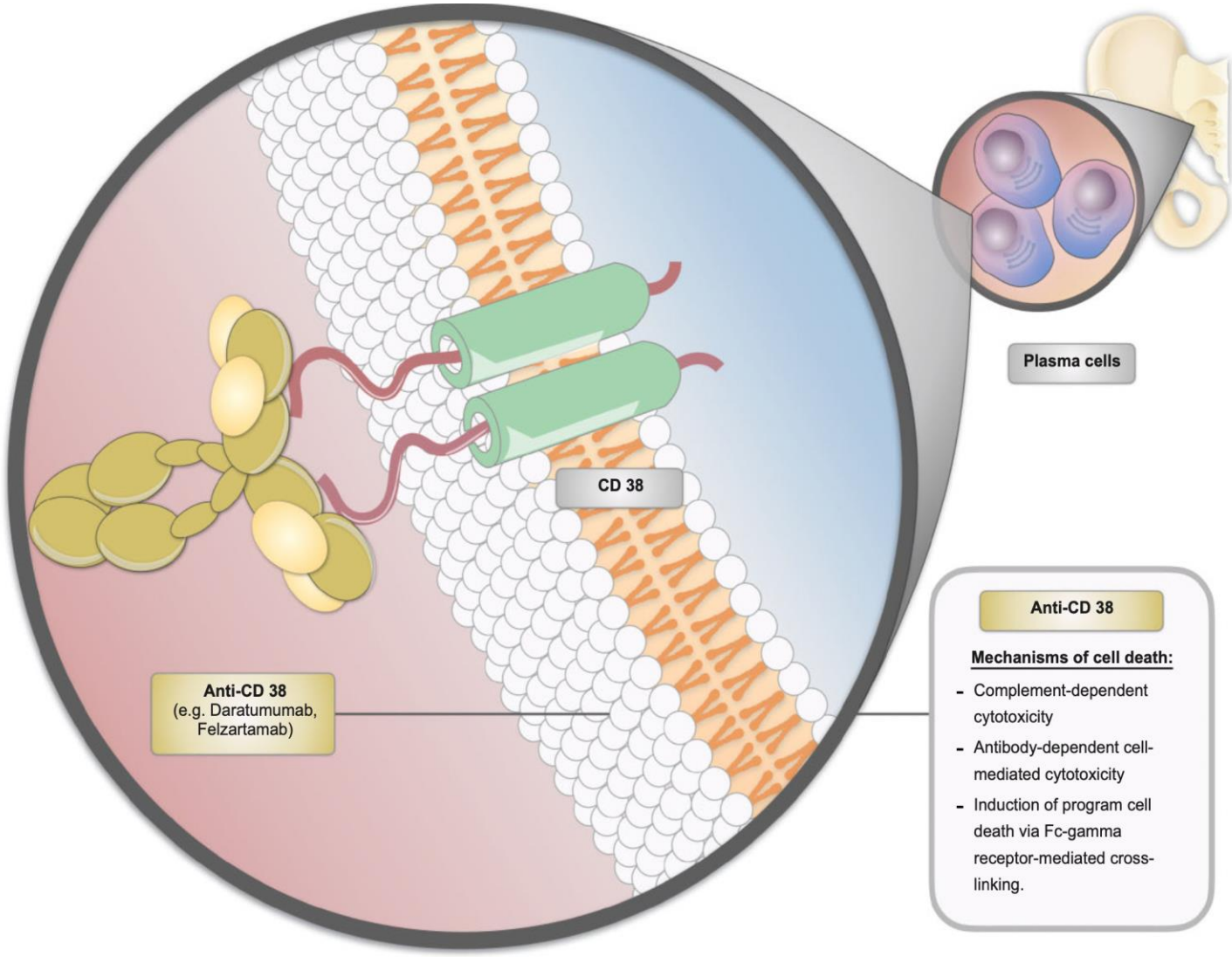

Figure 3: Schematic representation of CD38 and the mechanisms of cell death of anti-CD38 antibodies (e.g. daratumumab, felzartamab).

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Future landscape for the management of membranous nephropathy ,Fernando Caravaca-Fontán et al

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Advance Access publication 26 June 2019

ndt
Nephrology Dialysis Transplantation

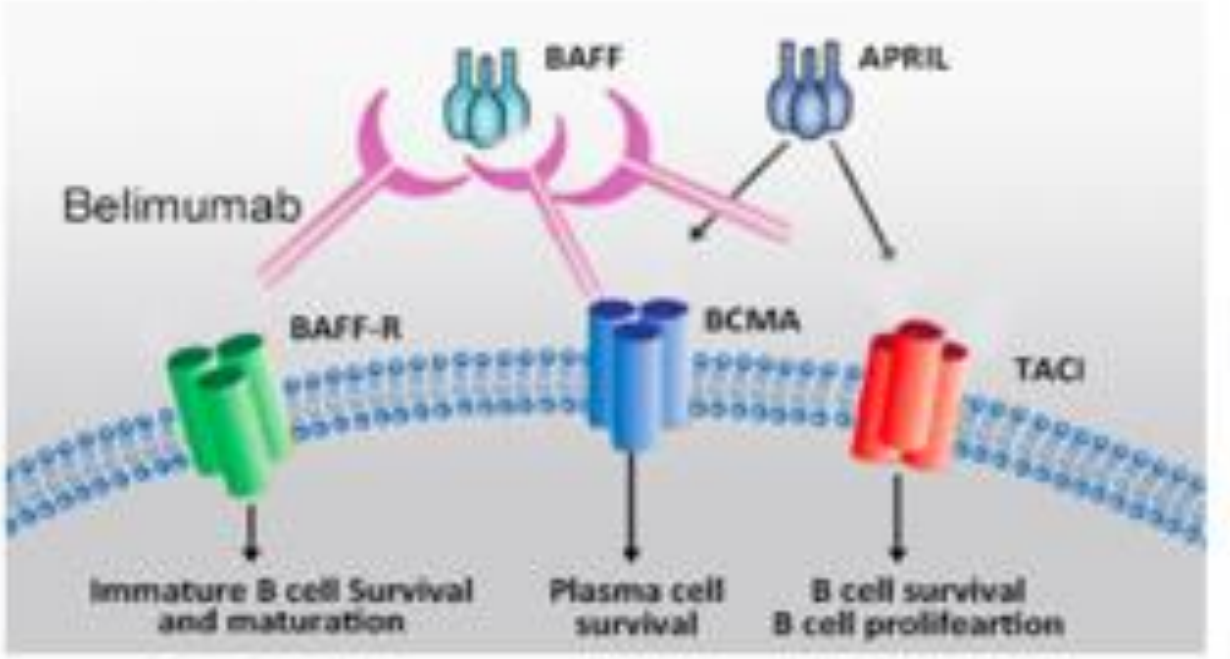
Effect of belimumab on proteinuria and anti-phospholipase A2 receptor autoantibody in primary membranous nephropathy

Christine Barrett[1], Lisa C. Willcocks[2], Rachel B. Jones[2], Ruth M. Tarzi[1], Robert B. Henderson[1], Gengqian Cai[3], Sophie I. Gisbert[4], Alexandra S. Belson[1] and Caroline O. Savage[1]

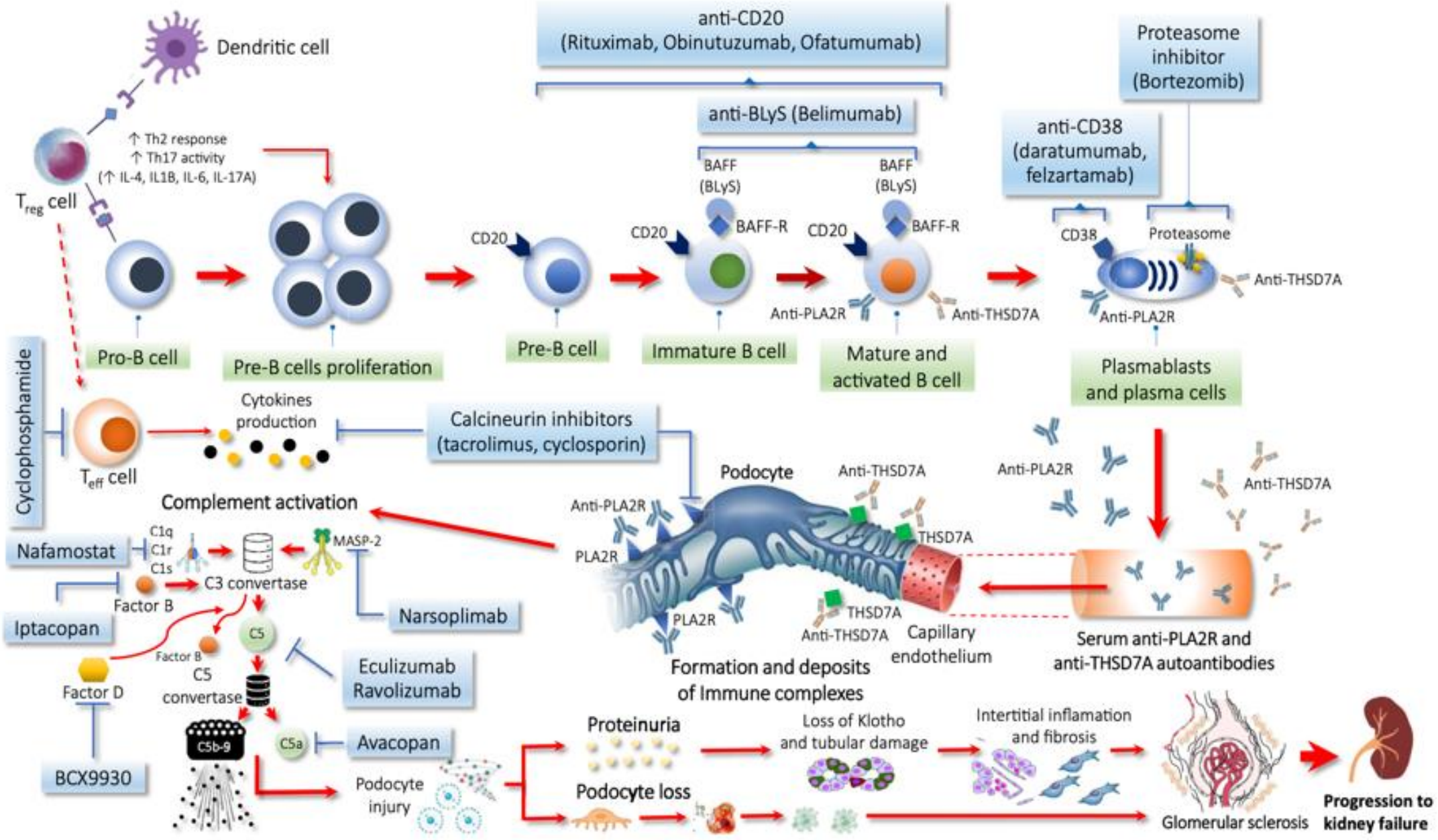
[1]Experimental Medicine Unit, GlaxoSmithKline R&D, UK, [2]Renal Unit, Addenbrooke's Hospital, UK, [3]Quantitative Sciences, GlaxoSmithKline R&D, USA and [4]GlaxoSmithKline R&D, UK

Belimumab:

- The mechanism is the inhibi tion of autoreactive B cells by targeting B-lymphocyte stimulator (BLyS), which promotes its apoptosis and prevents the differen tiation and survival of B cells



Biomedical Research 2018, Belimumab: therapeutic mechanism and current status of clinical trials. Dhilleswara Rao Vana



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Thanks