Membranous Nephropathy one of immune complex CMKD

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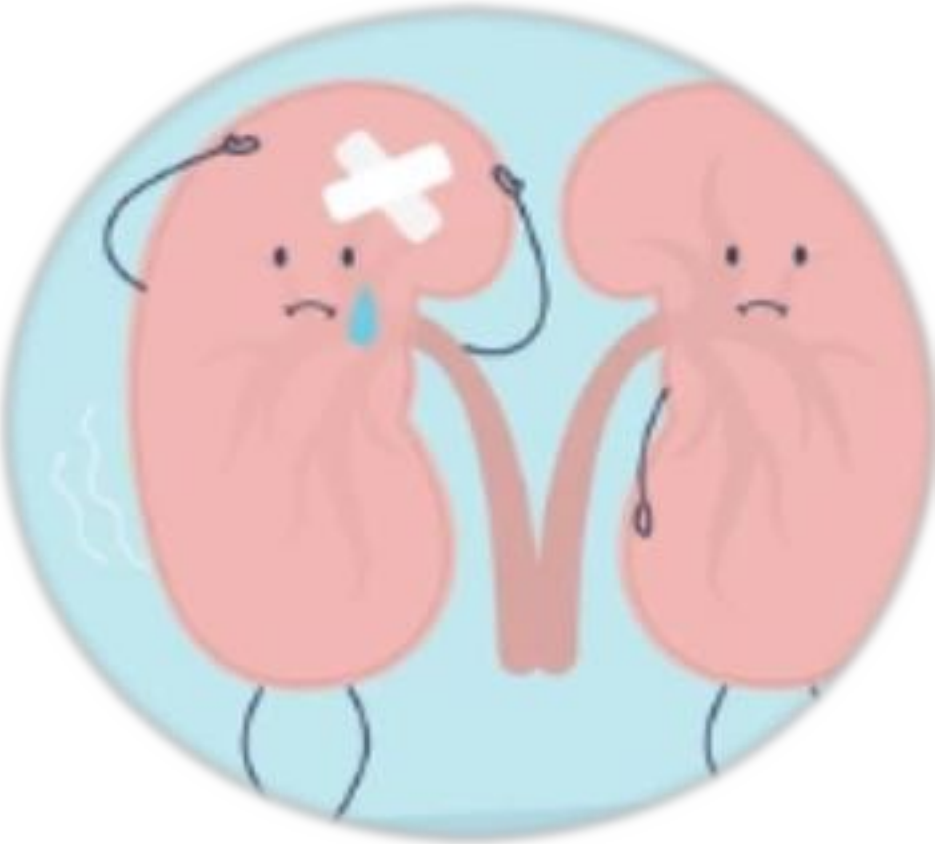
Agenda

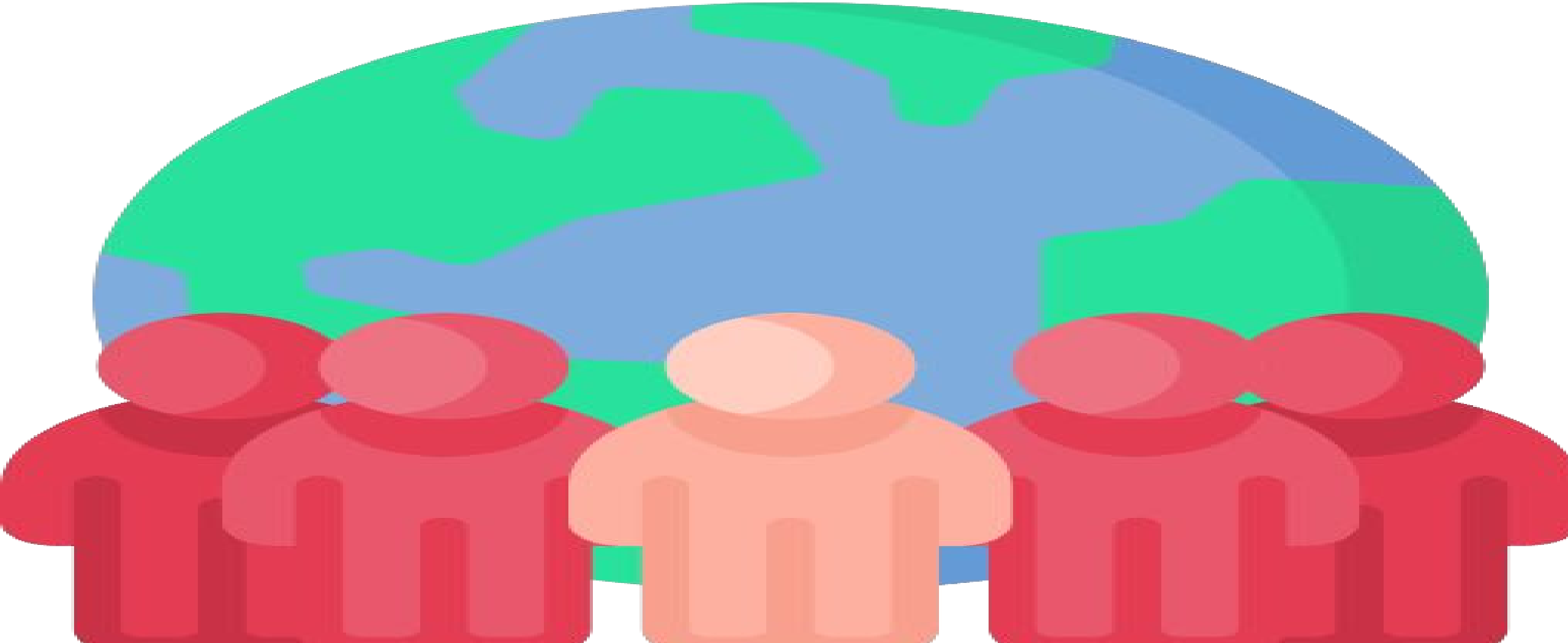
- Epidemiology of MN
- Pathophysiology of MN
- Clinical manifestations
- Diagnosis
- Recommendations for Management
- Prognosis

Definition of MN

- A glomerulopathy, which main affected target is the podocyte, and has consequences on the glomerular basement membrane.



EPIDEMIOLOGY



- Studies with large population are rare worldwide, especially in pediatrics.
- So exact data regarding the prevalence of MN remains unclear
- Male : Female ratio of 2:1 .
- Mean age : of 50-60 years old.

Pediatric Epidemiology

- MN is uncommon in pediatric population(about 0.1 cases per 100,000 per year) and is mainly secondary
- No specific gender distribution in pediatric patients
- Median age at presentation has a wide range between 7 and 15 years
- Prevalence of MN is highly different between children<12 years old (3%) and adolescents (18.5%)

- However, the frequency of MN is likely to be underestimated in children less than 12 years as those children are commonly treated with empirical glucocorticoids without biopsy.

Percentage of MN in pediatric kidney biopsies:

- During the past two decades. The proportion of pediatric MN increased from 3% (2004- 2007) to 7% in (2012-2014) reported from a 11-year national study in China.
- Similar data acquired from Turkey, Pakistan and India.
- It is not sure whether the incidence of MN has really increased or because of the increase of kidney biopsies in pediatrics
- The factors related to the environment are likely to increase the genetic propensity for pMN within the contaminated areas.

Pathophysiology of MN

In the last 55 years there are advances in its understanding so Dr. William Couser said “Membranous nephropathy: a long road but well-travelled”

IN 1959,

- Knowledge of the mechanisms involved in MN increased, when the experimental model of Heymann's nephritis was developed in rats.
- There was "in situ" formation of the immune complex in the subepithelial space with need for complement system activation for the development of proteinuria
- In this experimental model, the target antigen was megalin
- However, this antigen does not exist on podocytes in humans, and so , human MN remained without target antigen for 40 years .

Target antigens identification in humans

- Great advances in the identification of potential target antigens have occurred in the last twenty years:

IN 2002 ,

- Knowledge of target antigens in humans began with the identification of the neutral endopeptidase protein (NEP)

- In this case, a newborn with nephrotic syndrome due to MN, had subepithelial immune deposits of IgG and C3

- Mother was genetically deficient for the NEP protein. The pregnant woman had been alloimmunized in a previous pregnancy and in the following pregnancy there was placental transfer of maternal anti-NEP antibodies to the fetus.

IN 2009 ,

- "M-type phospholipase-A2 receptor" (PLA2R was described as an autoantigen
- It has circulating anti-PLA2R antibody and corresponds to 70% to 80% of MN
- It is expressed on the podocyte processes and the apical surface with little known function.
- Although PLA2R was initially considered the major target of pMN in adults, subsequent studies have indicated positive staining for it in pediatric patients.
- Adolescents exhibited similar positive rate of PLA2R staining in comparison with adults, with a higher rate than young pediatric patients

SINCE 2014 ,

- Other target antigens have been discovered (THSD7A, EXT1/2, NELL1, Sema3B, NCAM1, PCDH7, HTRA1 and NTNG1).

- Some of these antigens have shown associations with some features

  - Sema3B predominating in children
  - THSD7A in some neoplasms
  - EXT1/2 with SLE and autoimmune diseases.

- Although the discovery of different autoantibodies have highlighted the role of B cells in MN
- Suboptimal response or even resistance to B cell-directed therapies occurs, suggesting that other pathophysiological mechanisms are involved.

There is evidence from animal and human models, as well as patients, implicating complement activation in the pathogenesis of proteinuria and kidney injury.

However, many questions remain about how and which complement pathways are involved.

J Clin Invest. 1980 Dec;66(6):1339-50. doi: 10.1172/JCI109987.

A new role for complement in experimental membranous nephropathy in rats

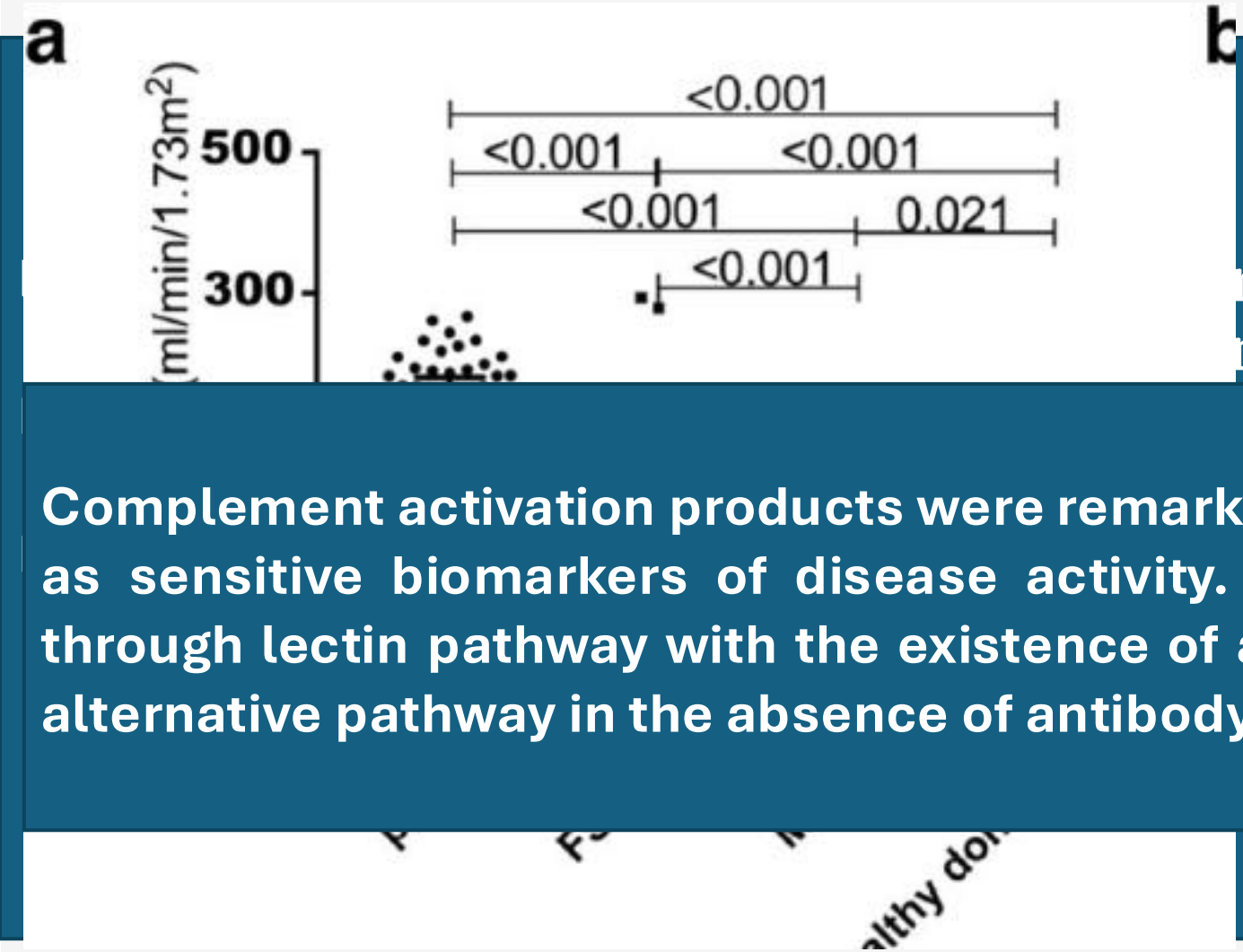
D J Salant, S Belok, M P Madaio, W G Couser

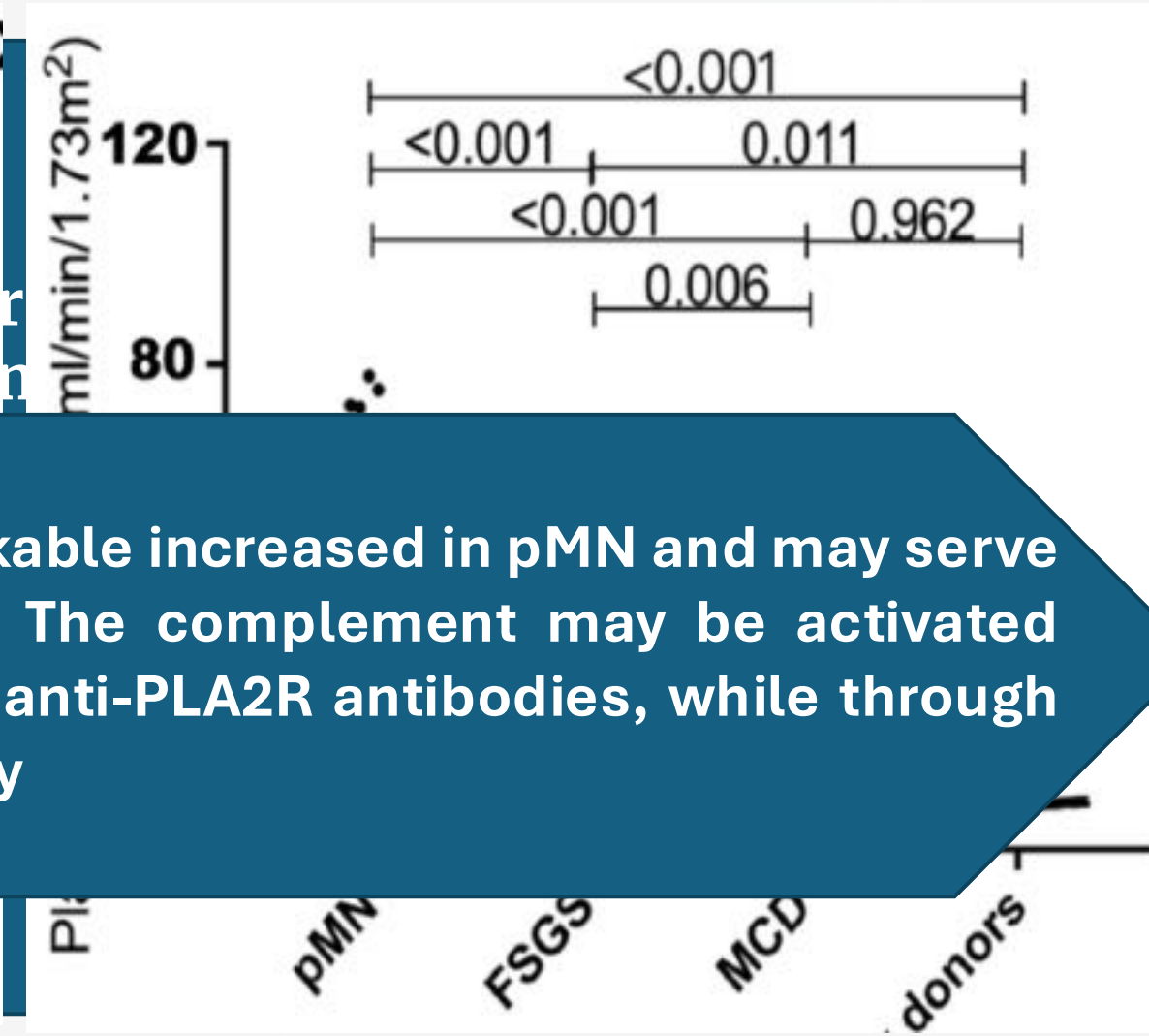
PMID: 7440718 PMCID: PMC371620 DOI: 10.1172/JCI109987

In the passive model of Heymann nephritis, pretreatment with cobra venom factor to maintain undetectable circulating C3 levels prior to induction of nephritis resulted in development of subepithelial immune deposits without C3, and without manifestation of any degree of proteinuria

> BMC Nephrol. 2019 Aug 9;20(1):313. doi: 10.1186/s12882-019-1509-5.

Complement activation products in the circulation and urine of primary membranous nephropathy





Complement activation products were remarkable increased in pMN and may serve as sensitive biomarkers of disease activity. The complement may be activated through lectin pathway with the existence of anti-PLA2R antibodies, while through alternative pathway in the absence of antibody

Proteomic Analysis of Complement Proteins in Membranous Nephropathy (MN)

Cohort

Methods

Laser Microdissection & Mass Spectrometry

Analysis

Complement Proteomic Analysis

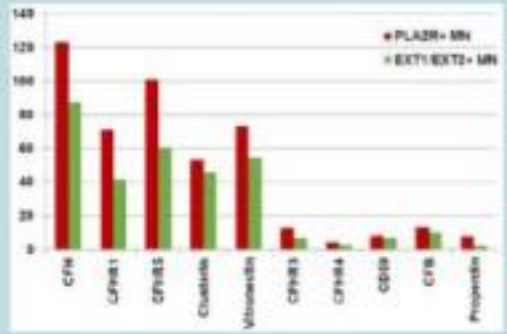
Results

Data Suggest Ongoing Complement Activation

PLA2R+ MN, N=7

EXT1/EXT2 + MN, N=21

High spectral counts of complement proteins (C3, C4, C5, C9) & complement regulators (FH, FHR1, FHR5, Clusterin, Vitronectin)



EXT = Exostosin

CONCLUSION:

Significant complement activation including complement regulatory pathways are present in PLA2R+ MN and EXT1/EXT2+ MN.

KI REPORTS

KIReports.org

Ravindran A, et al. 2020

Complement C3a and C3a Receptor Activation Mediates Podocyte Injuries in the Mechanism of Primary Membranous Nephropathy

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

MN patients
C3aR staining in glomeruli
Correlation analysis

Podocytes
Exposure to MN plasma containing high level of C3a
C3aR blockade

Passive Heymann nephritis rats
C3aR antagonists treatment (SB290157 or JR14a)

OUTCOME

- C3aR staining was strong in MN patients and merged well with podocin.
- The intensity of C3aR staining correlated positively with proteinuria, serum creatinine and no-response to treatments.

- PLA2R ↑, C3aR ↑, Wnt/β-catenin ↑, synaptopodin ↓, migration function ↓, cell viability ↓
- These effects could be blocked by the C3aR antagonists.

- C3aR blockade attenuated proteinuria, electron dense deposition, foot process width and GBM thickening in glomeruli.
- The increased plasma C3a levels and over-expression of C3aR in glomeruli were alleviated.
- Specific IgG, but not total IgG, was decreased, with less deposition of rat IgG in glomeruli and subsequent reduction of C1q, factor B, and C5b-9.

Conclusion
C3a anaphylatoxin is a crucial effector of complement mediated podocyte damage in MN. The C3aR antagonist may be a potentially viable treatment for this disease.

doi: 10.1681/ASN.2021101384

The role of the classical complement pathway in MN

- In humans, primary MN is mediated primarily via IgG4 immunoglobulins including the anti-PLA2R .
- IgG4 cannot directly activate the classical pathway.
- olved
- n

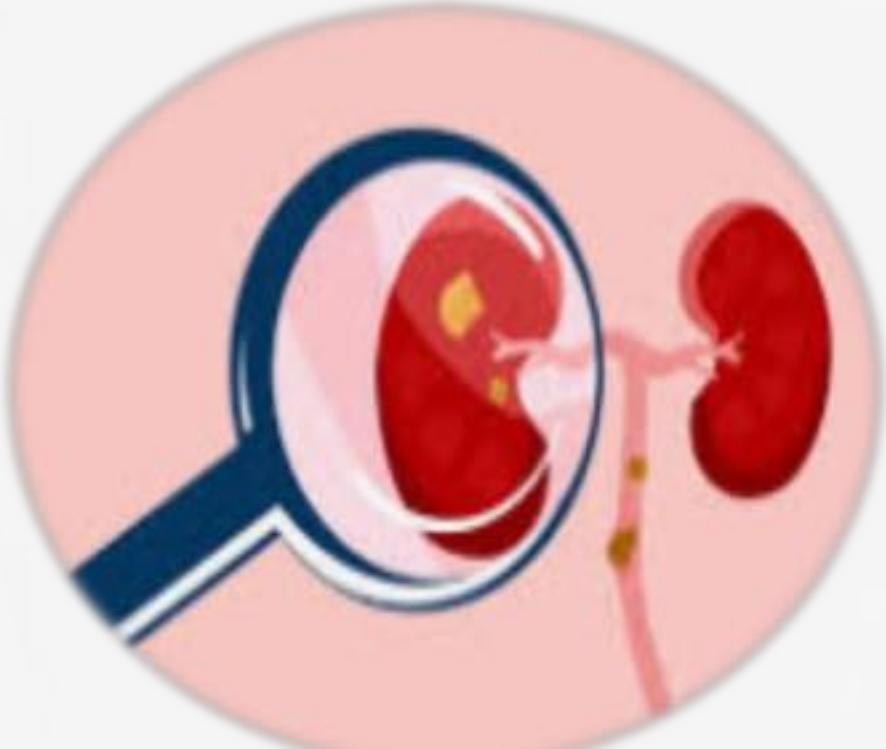
- There is compelling evidence of that the mannose-binding lectin (MBL) and alternative pathways are particularly implicated in MN.

TABLE 1 Complement pathways implicated in various kidney diseases.

Disease	Classical pathway	Alternative pathway	Lectin pathway	Complement regulator proteins
Immune-mediated kidney diseases				
Lupus nephritis	✓	✓	✓	✓
IgA nephropathy	–	✓	✓	✓
Primary membranous nephropathy	–	✓	✓	✓
C3 glomerulonephritis	–	✓	–	✓
ANCA-associated vasculitis	–	✓	–	–
Thrombotic microangiopathies	–	✓	–	✓

✓, involvement of the complement pathways in the disease specified.

Pathology



- There is deposition of immune complexes in the subepithelial space of the glomerular capillary loop.
- The immune deposits are formed of :

- **Podocyte target antigen :**

(PLA2R, SEMA-3B, THSD7A, among others),

- **Immunoglobulins G :** usually with a predominance of the IgG4
- **complement fractions:**

Table 1 Histopathology changes caused by membranous nephropathy

Microscopy → Stage ↓	LM	IF	EM
Stage 1	Normal GCL	IgG fine granular in GCL	Subepithelial electron-dense deposits
Stage 2	Thick GCL with GBM spikes (MSS)	IgG granular in GCL	Subepithelial electron-dense deposits with spikes
Stage 3	Thick GCL and with chain links (MSS)	IgG granular in GCL	Subepithelial electron-dense deposits involved by the GBM
Stage 4	Thick GCL with variable changes (MSS)	IgG granular and GCL variable	GBM with variable irregularities

LM: light microscopy; IF: immunofluorescence microscopy; EM: electron microscopy; GCL: glomerular capillary loop; MSS: methenamine silver stain; GBM: glomerular basement membrane.

- Classically, MN is categorized into primary or secondary forms.

Secondary MN :

underlying malignancy, an autoimmune disease (SLE), a chronic infection (HBV, HCV), or drugs (NSAIS)

Primary MN: was used to describe cases that were thought to be idiopathic before era of new antigens

- **There are several features which distinguish between pMN and sMN:**

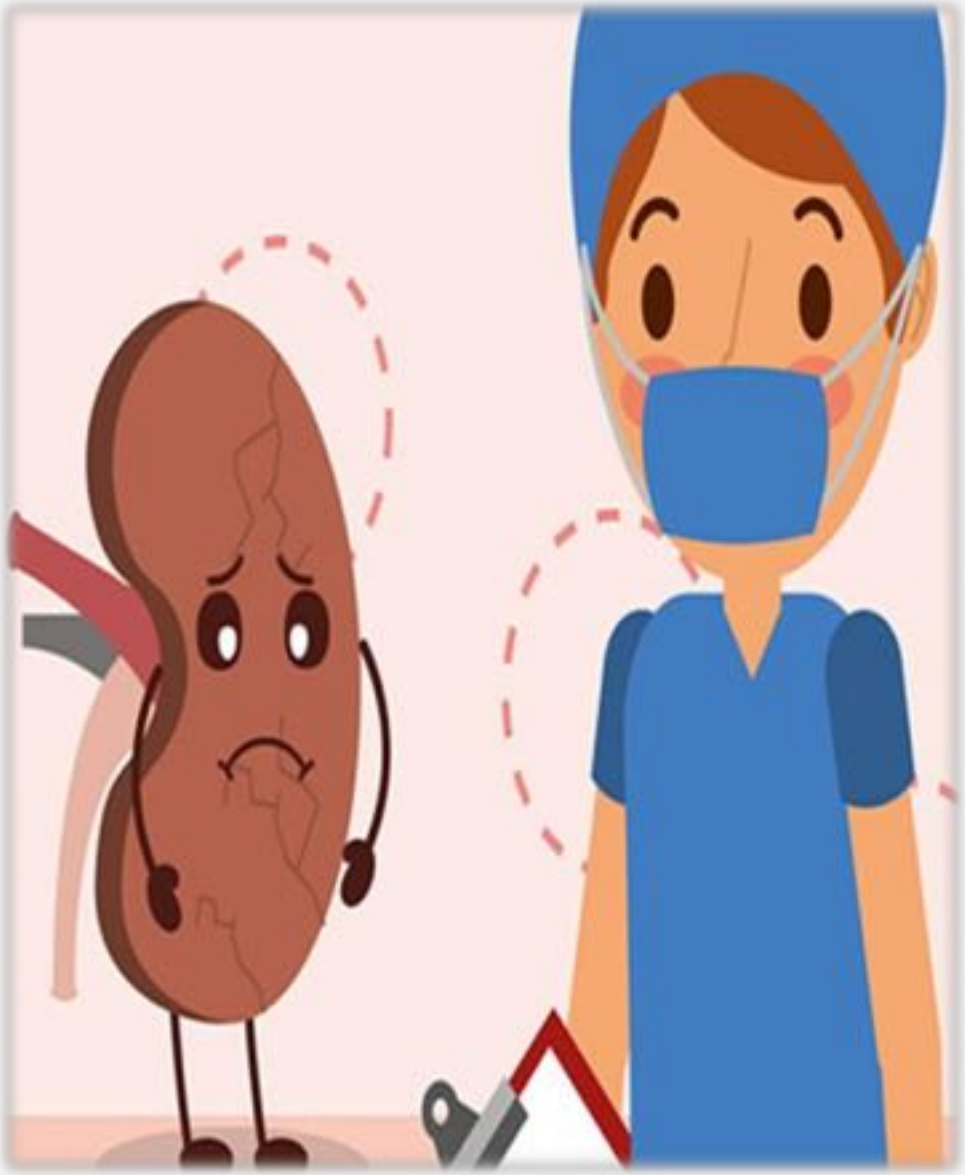
- **Mesangial or endocapillary proliferation are mainly in secondary MN**

- **Staining for IgG1, IgG2, and IgG3 primarily deposit in class V lupus nephritis, whereas IgG4 predominates in PLA2R- and THSD7A related pMN.**

- **The classification of MN in primary or secondary forms has several limitations:**

- **The discovery of novel antigens has challenged this traditional classification.**
- **Because the above novel antigens could present both in primary and secondary disease.**
- **The pathophysiology, clinical features, laboratory findings, pathological biopsy characteristics and effect of treatment differ in each specific antigen-related MN .**
- **So new classification proposals have been presented that associates MN to the respective antigen.**

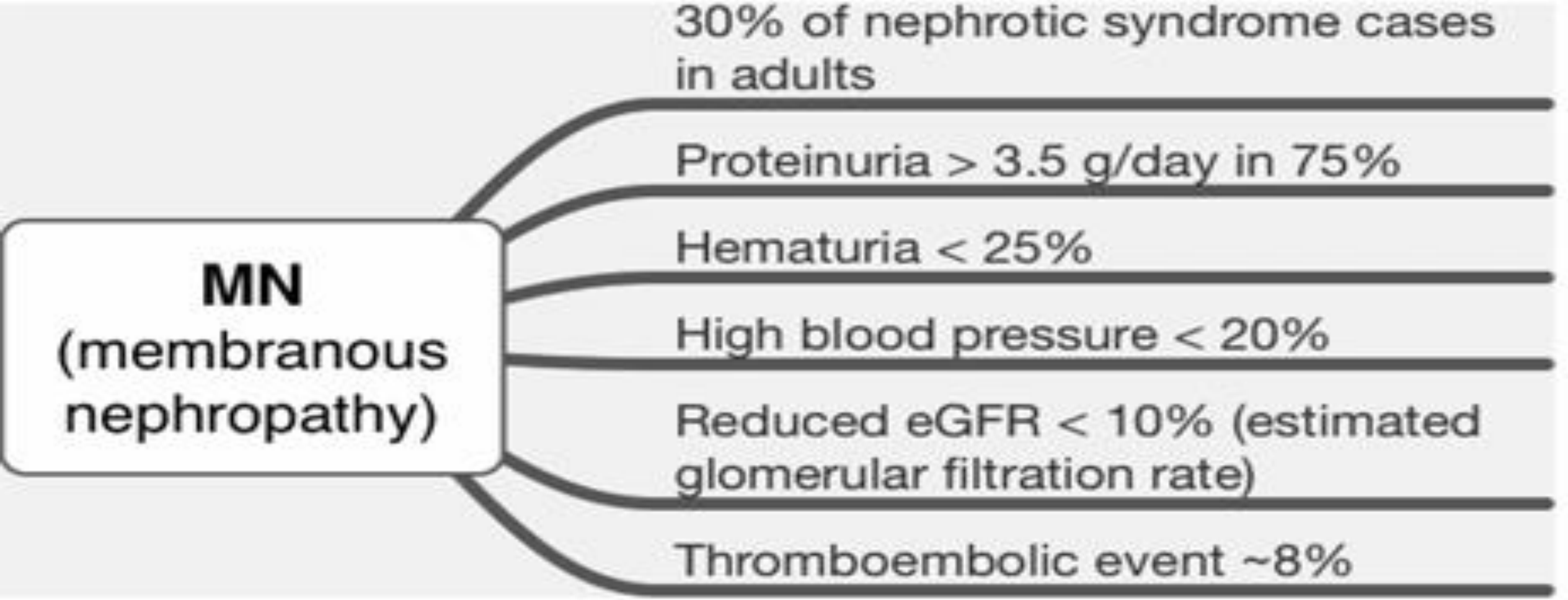
Clinical Presentation



- nephrotic syndrome

- Many cases can evolve with asymptomatic non-nephrotic proteinuria.

Frequency of clinical features at the presentation of membranous nephropathy.



Diagnosis

• Indications for renal biopsy in MN patients

- ❑ Given the high specificity of PLA2R antibodies, deferral of a kidney biopsy has been suggested in adult patients with nephrotic syndrome and PLA2R antibodies.

- ❑ This is supported by the KDIGO 2021 guideline

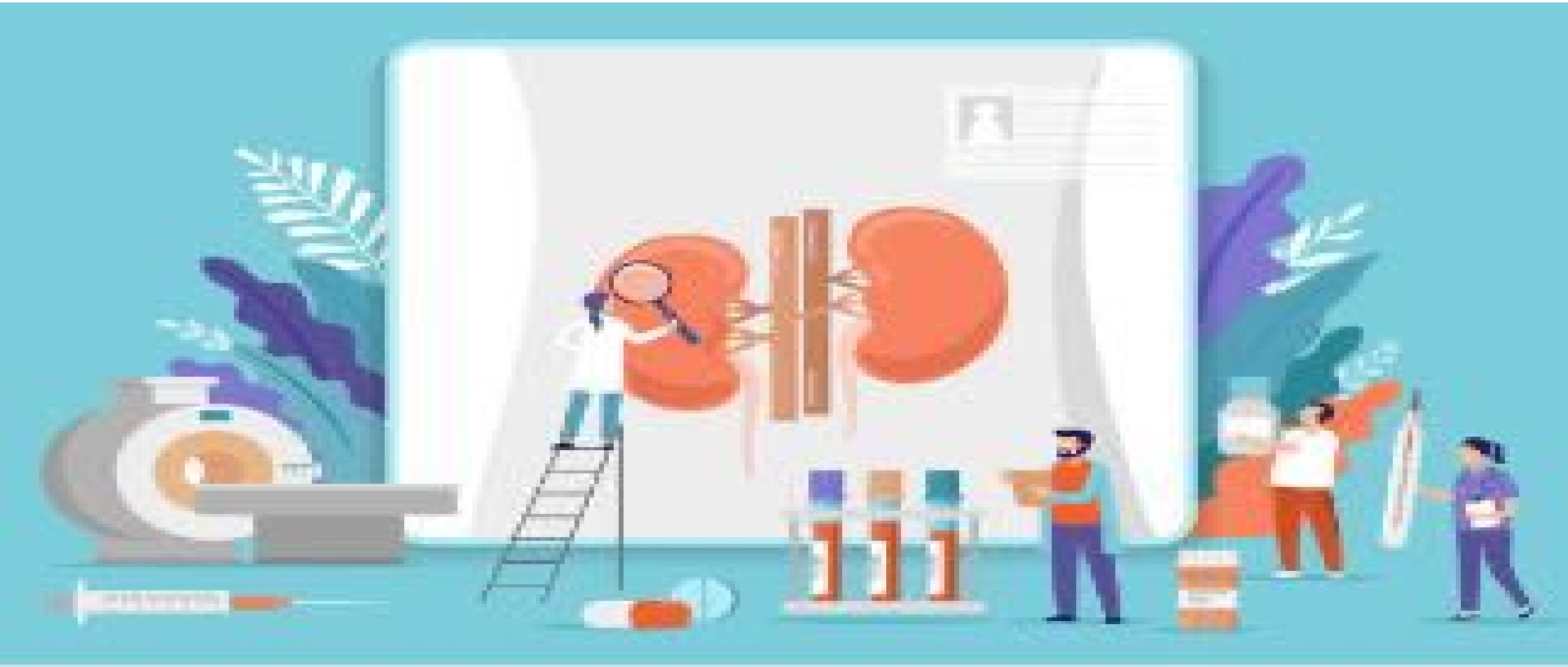
- **However, in comparison with adults , Pediatric MN patients are somewhat different :**

- ❑ **Children with NDNS should receive daily steroid for 4 weeks**
- ❑ **KDIGO 2021 guideline recommended that PLA2R antibody may be performed in SRNS patients before a renal biopsy when secondary causes or persistent abnormal renal function are ruled out.**
- ❑ **When the patient has the positive PLA2R antibody serology, deferral of a renal biopsy is suggested.**

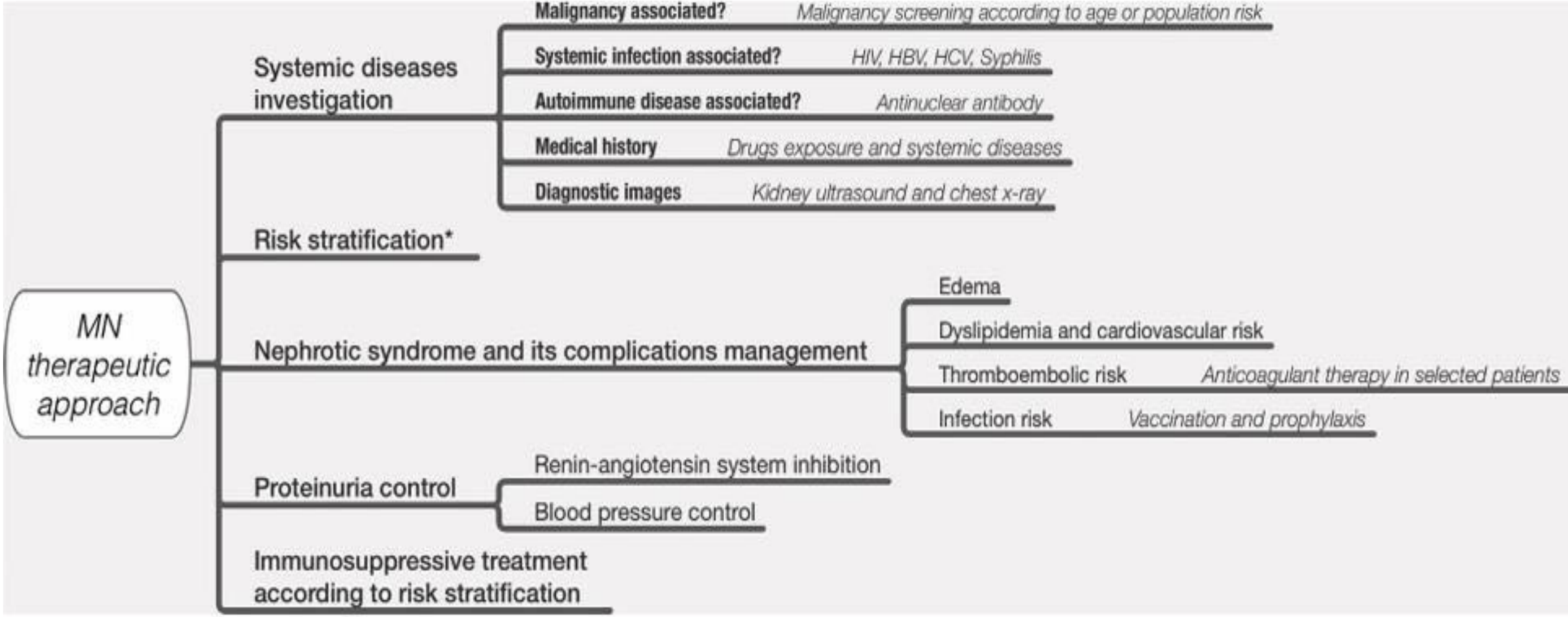
Other Investigations

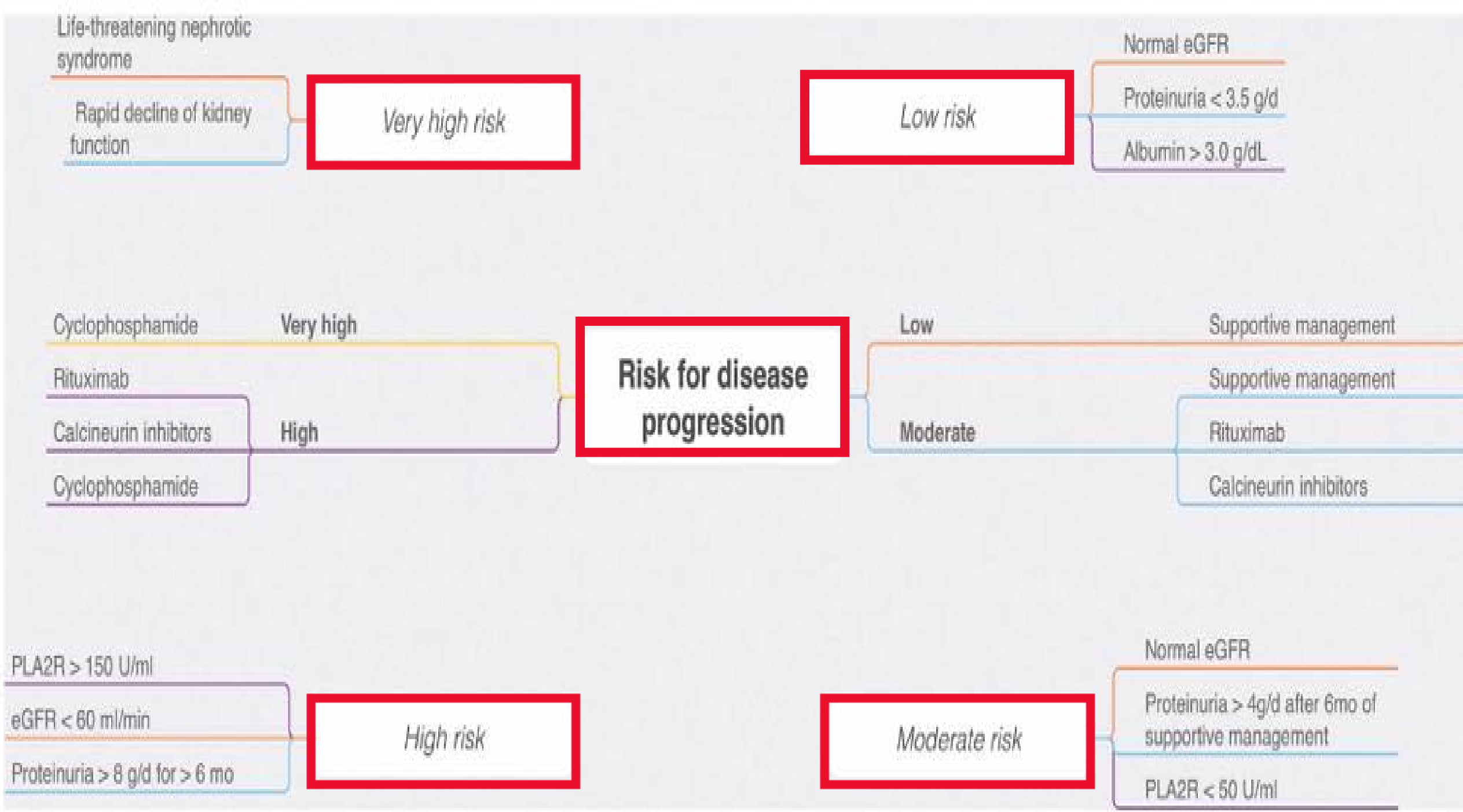
- Serum levels of C3, C4 and CH50 are normal, despite the renal presence of complement components.
- The anti-PLA2R antibody has considerably modified criteria such as clinical and immunological activity or remission, in addition to serving as a prognostic parameter and indication of immunosuppressive treatment.

Management



Algorithm with suggestions to approach according to the risk of progression




Life-threatening nephrotic syndrome
Rapid decline of kidney function
Very high risk
Normal eGFR
Proteinuria < 3.5 g/d
Albumin > 3.0 g/dL
Low risk
Cyclophosphamide
Very high
Rituximab
Calcineurin inhibitors
High
Cyclophosphamide
Risk for disease progression
Low
Supportive management
Moderate
Supportive management
Rituximab
Calcineurin inhibitors
PLA2R > 150 U/ml
eGFR < 60 ml/min
Proteinuria > 8 g/d for > 6 mo
High risk
Normal eGFR
Proteinuria > 4g/d after 6mo of supportive management
PLA2R < 50 U/ml
Moderate risk

Stratifying the risk of kidney disease progression to identify patients who can potentially benefit from immunosuppressive therapy

Following the recommendations of KDIGO

- **low risk** : Up to 30% of patients with MN may experience spontaneous remission of proteinuria, treatment of choice is supportive therapy.
- **moderate risk :** Immunosuppressive treatment can be postponed for 3 to 6 months in because there is a chance of spontaneous remission.
- **In severe cases :** immunosuppression should be instituted soon after diagnosis

supportive measures for all patients

- Blood pressure control
- Reduced sodium intake
- Proteinuria reduction by blocking the renin-angiotensin system
- dyslipidemia control
- Risk assessment for thromboembolic events with decision on prophylactic anticoagulation in nephrotic syndrome with severe hypoalbuminemia

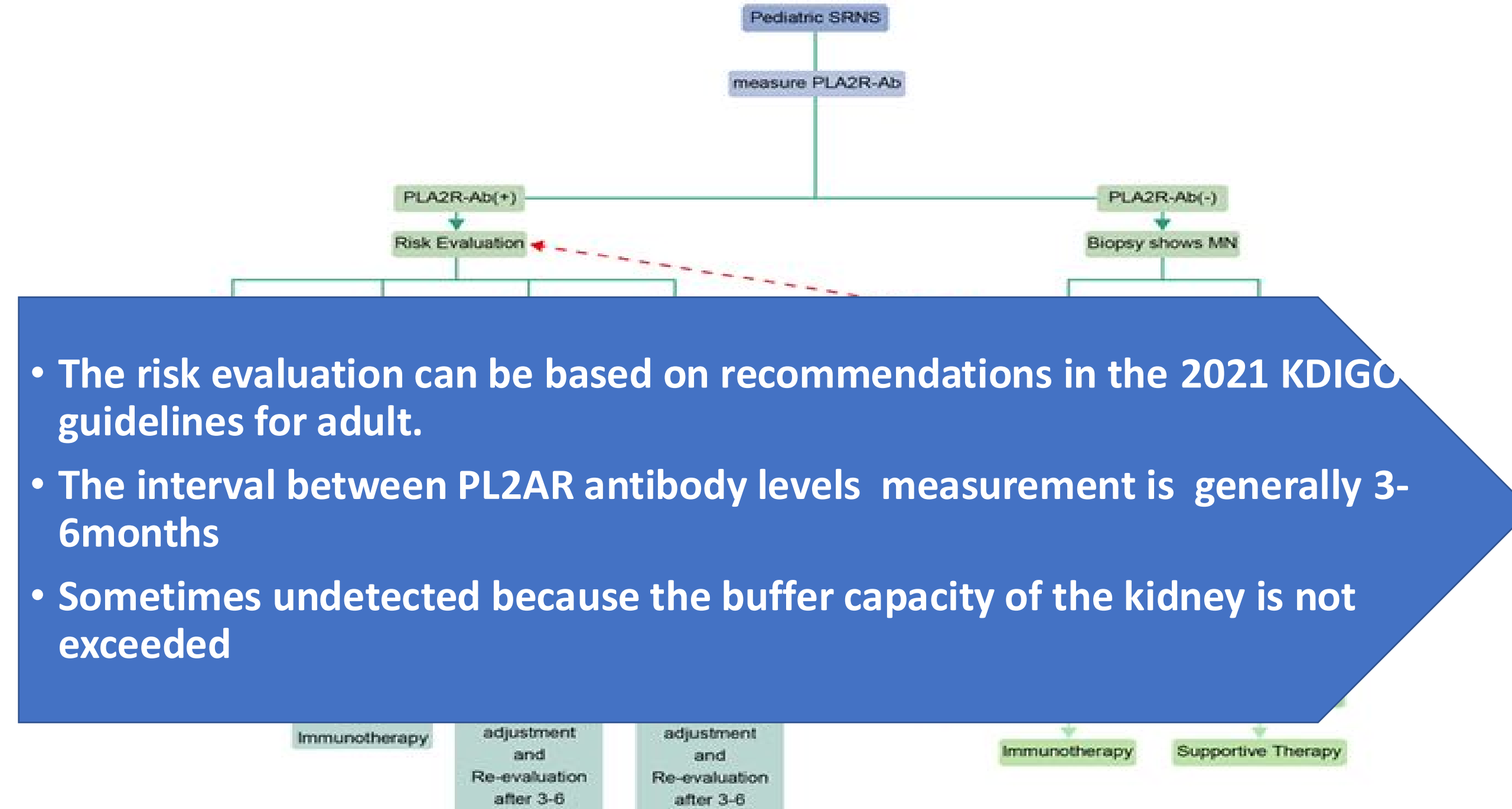
- **In comparison with adults ,**

- ❑ Spontaneous remission is common in pediatric patients
- ❑ Renal function is always normal at presentation
- ❑ Progrssion to ESKD is rare.
- ❑ The most common clinical manifestation is nephrotic-range proteinuria (>50mg/kg) or SRNS.
- ❑ Proteinuria combined with hematuria is more common compared to adults.
- ❑ Some severe cases may also present with impaired renal function.

Supportive treatment

Immunosuppression

Algorithm for the diagnosis and treatment advice in pediatric MN (pediatric SRNS)



- The risk evaluation can be based on recommendations in the 2021 KDIGO guidelines for adult.
- The interval between PL2AR antibody levels measurement is generally 3-6months
- Sometimes undetected because the buffer capacity of the kidney is not exceeded

- Adolescent patients are primarily referred to adult standards, while younger children brings a great challenge to pediatric nephrologists.

- Clinicians have insufficient experience in the treatment of pediatric patients because there are no RCT studies To date.

- There is no consensus on whether immunosuppressive therapy should be used in pediatric patients who have partial response after 4 weeks of steroids use

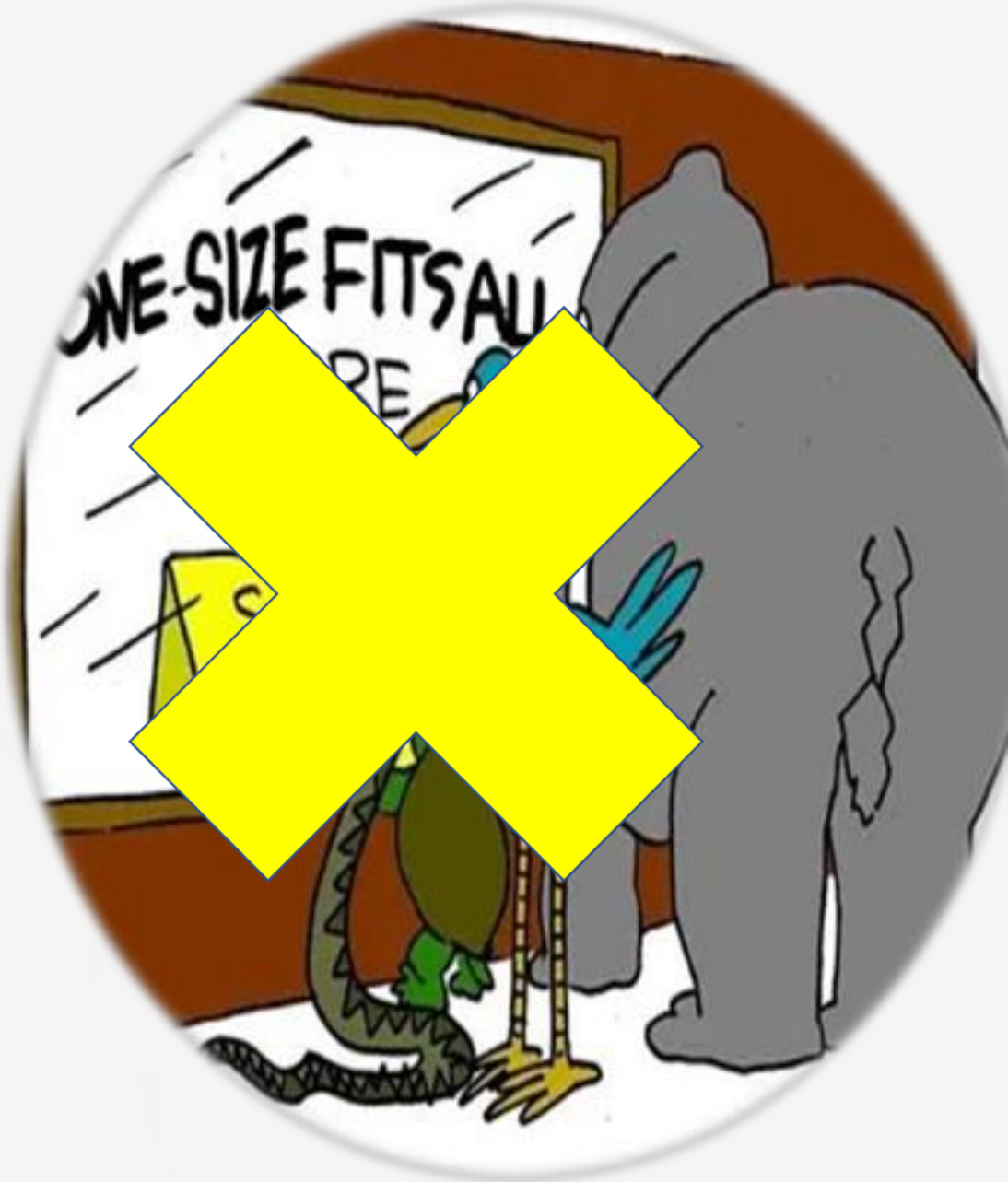
- Management of them should evaluate the risks and benefits of immunosuppressive therapy.

Although there has been no clear recommendation regarding the use o rituximab as a first-line treatment for pediatric patients, the growing number of case series and case reports suggest rituximab is a promising agent to manage pMN.

Although rituximab is effective, the side effects in pediatric patients should be considered

The use of second- and third-generation CD20 antibodies [e.g. ofatumumab, Obinutuzumab, and ocrelizumab could be tried, especially in refractory cases membranous nephropathies.

So children with MN should be managed individually in expert centers in which the adverse effects of immunotherapy are considered



What about complement-directed therapy ????

Therapeutic modulation of the complement system has emerged as a promising treatment strategy in various kidney diseases, and the results in MN are eagerly awaited

TABLE 1 Complement-based therapies currently under trial for MN.

Name of drug	Target	Phase of development
BCX9930	Factor D	Phase II (NCT05162066)
Eculizumab	C5	Aborted
Iptacopan (LNP023)	Factor B	Phase II (NCT04154787)
Narsoplimab (OMS721)	MASP2	Phase II (NCT02682407)
Pegcetacoplan (APL-2)	C3, C3b	Aborted

Prognosis in children

- Chinese researchers first reported the long-term cumulative renal survival rates of ESKD in children with pMN were 95.3% (5-year) and 67.8% (10-year).
- Hypertension and proteinuria ≥ 50 mg/kg/day were associated with renal outcome in those children.
- Because of the rarity of MN in children and its good prognosis with no treatment, no randomized controlled studies have been conducted on MN treatment in pediatric patients.

Conclusion

- Unlike adult patients, renal biopsy is not usually performed in pediatric population with NDNS.
- The degree of pediatric MN responding to steroid monotherapy remains unclear
- Primary forms of MN in adolescents could be treated similarly to adults.

- Literature about immunotherapy management in pediatric patients with MN is rare
- It remains a big challenge for pediatric nephrologists worldwide to choose one immunosuppressant over another preferentially.
- Secondary forms of MN require management of the underlying condition.

Thank you for your Interest