Brigham and Women's Hospital
Founding Member, Mass General Brigham

Membranous Nephropathy

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- Clinical focus: Glomerular diseases
- Research focus: Membranous nephropathy

DISCLOSURES

- Consulting and/or advisory board income from Novartis; Travere Therapeutics; CANbridge Pharmaceuticals; Cerium Pharmaceuticals
- Speaker for Travere Therapeutics
- Author royalties from UpToDate, Inc.
- Patent royalties (“Diagnostics for Membranous Nephropathy”) through Boston University

OBJECTIVES

After completing this seminar, the learner should be able to:

- Recognize clinical and histopathological features of membranous nephropathy (MN)
- Discuss how the expanding number of target antigens in MN challenges a strict binary classification of primary vs secondary disease
- Discuss the use of serology in the diagnosis and monitoring of MN
- Better judge when immunosuppression is indicated to treat MN

Representative case:

A 52-year-old man presents to his PCP complaining of several months of weight gain and worsening lower extremity edema.

BP 148/92 HR 80

Physical examination is notable for clear lungs clear, normal cardiac exam, but 3+ bilateral pitting edema up to his knees.

Initial lab tests: Cr 1.08 mg/dl, Albumin 2.9 g/dl, Cholesterol 386 mg/dl

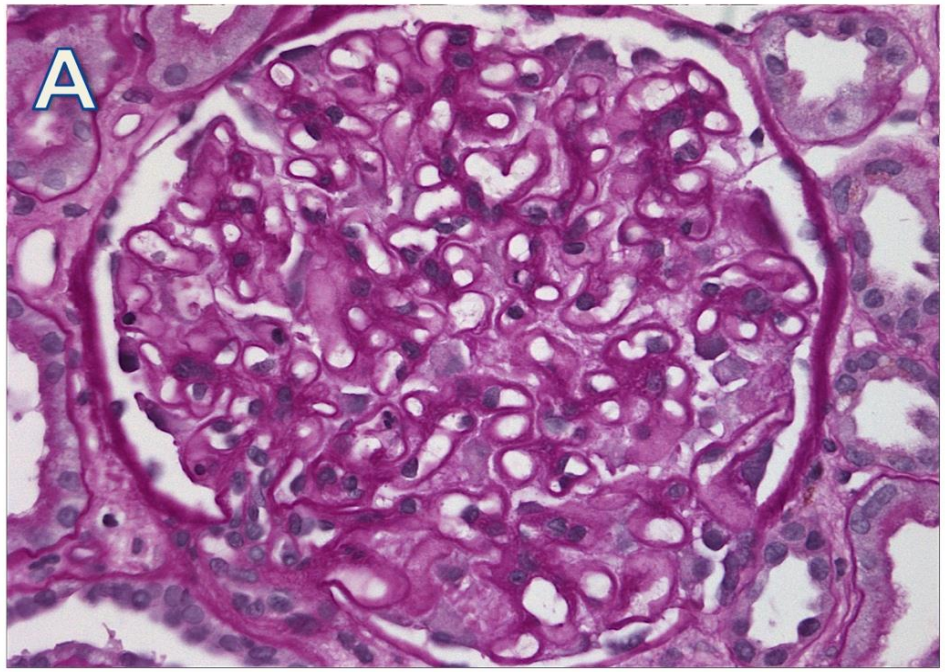
Urine analysis: 4+ protein, trace blood, no leukocyte esterase

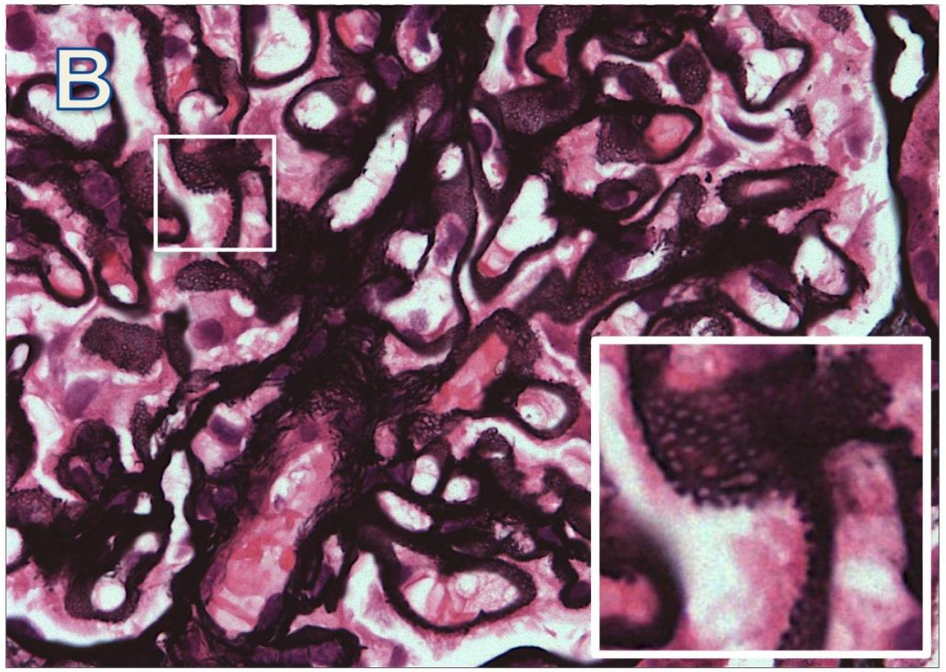
Case, continued

Due to the unexplained nephrotic syndrome and a 24 hr urine proteinuria value of 11.7 g, the patient is referred to a nephrologist, who schedules a kidney biopsy

The biopsy is read as **membranous nephropathy**, with IgG and C3 present as fine granular deposits in a capillary loop pattern

There is minimal glomerular scarring, tubular atrophy, or interstitial fibrosis


A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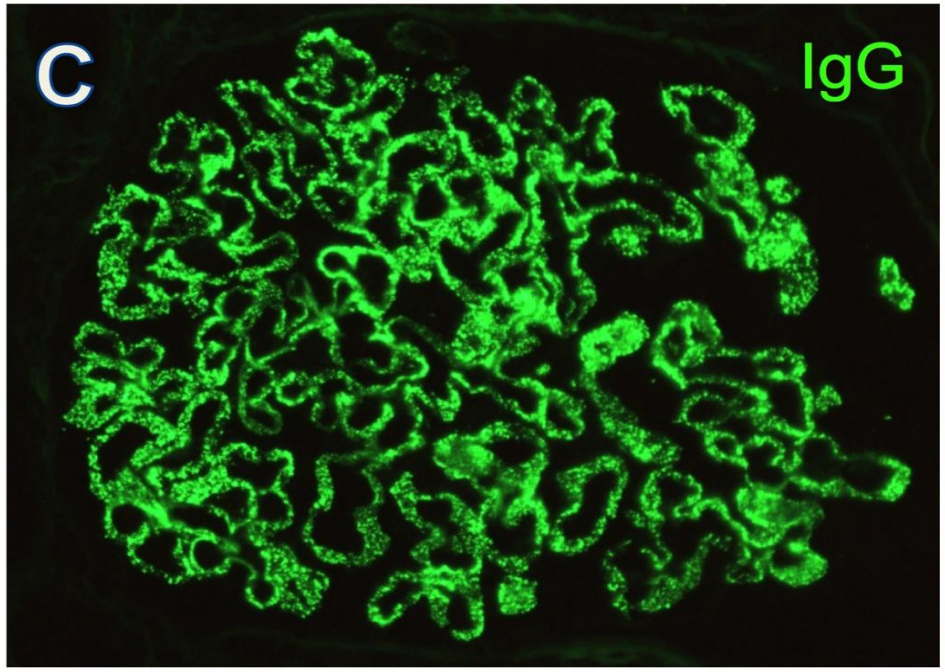
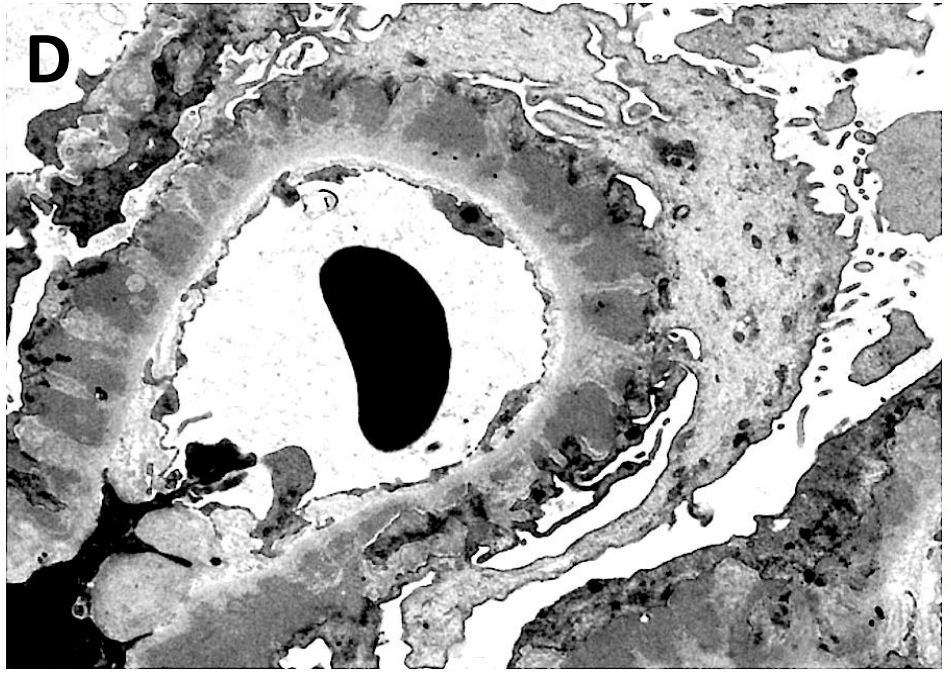

C
IgG


D

Which of the following statements about membranous nephropathy is correct?

a) Nephrotic syndrome can occur rapidly after development of a viral upper respiratory tract infection

b) Prolonged proteinuria greater than 1 g/day is a risk factor for ultimate progression to end-stage kidney disease

c) It is a common cause of nephrotic syndrome in children

d) 30 - 40% of patients may undergo spontaneous remission, given enough time

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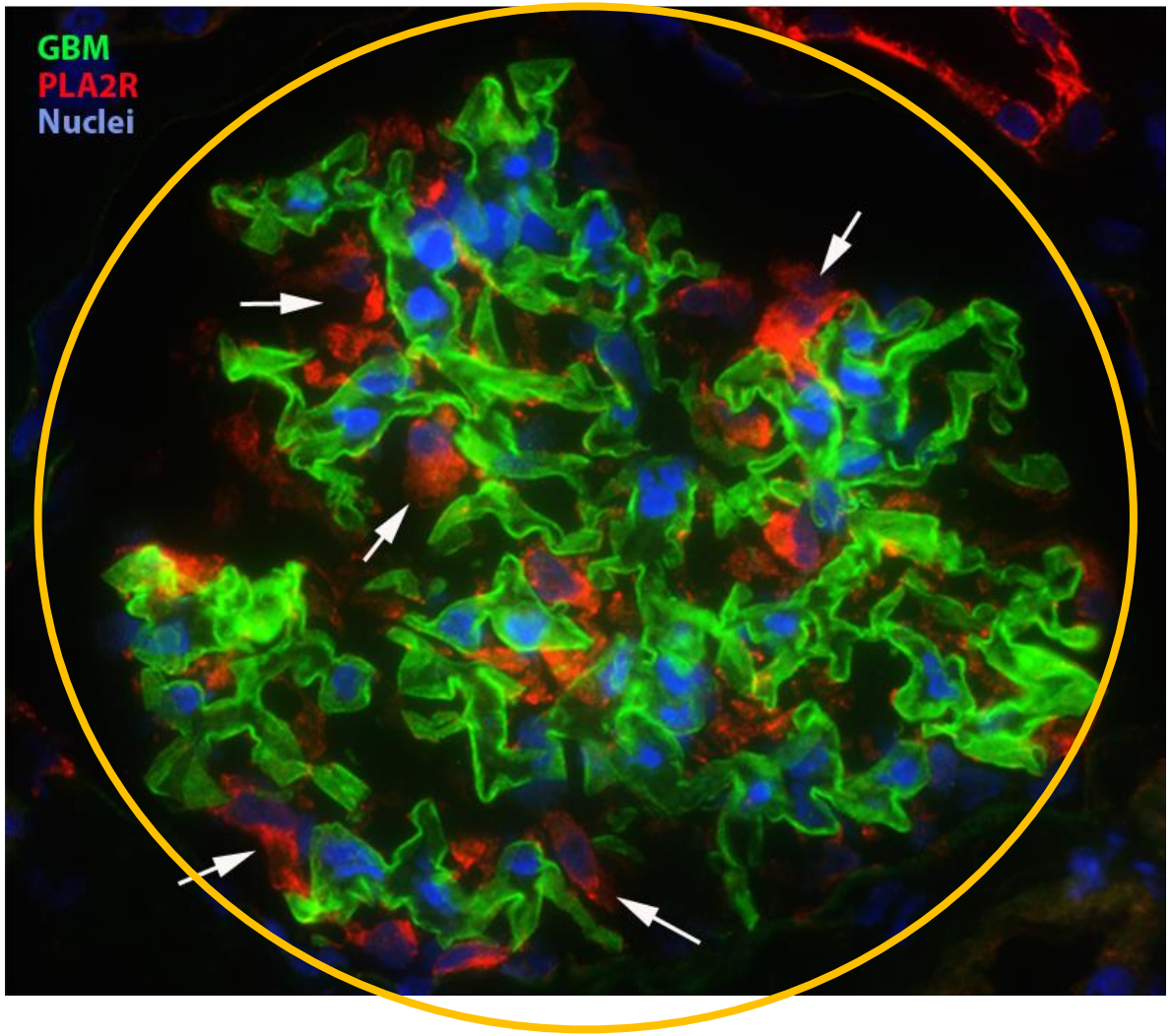
Natural history of MN

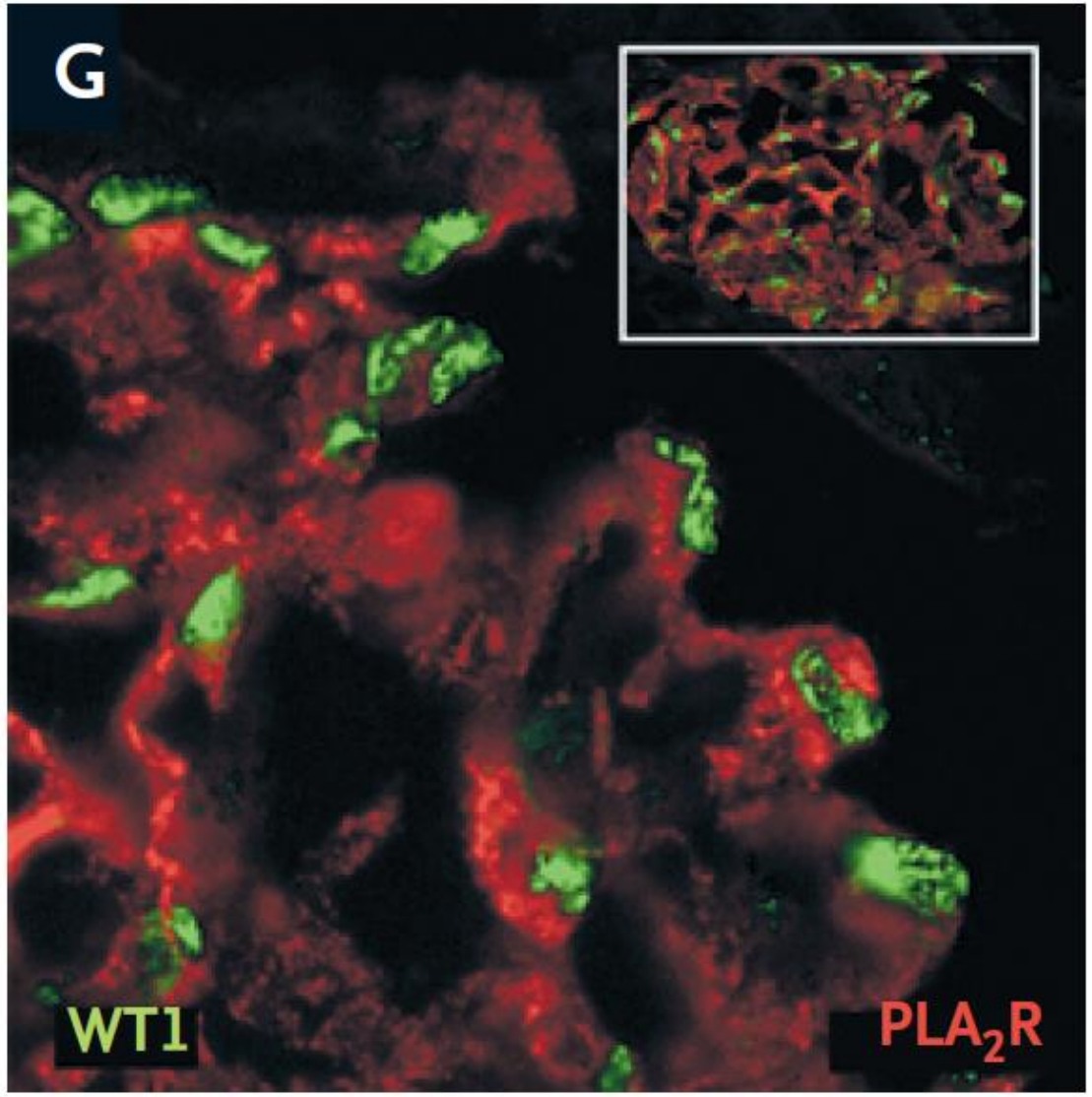
- Insidious onset (compare with MCD or primary FSGS)
- Patients often report weight gain, leg edema that has increased over course of months
- 75% nephrotic at presentation; 25% subnephrotic, but half of these will progress to full nephrotic syndrome
- “Rule of thirds”
  - 1/3 will undergo spontaneous remission
  - 1/3 remain proteinuric with stable renal function
  - 1/3 will progress towards ESKD (esp. with heavy proteinuria)
- Resolution is slow (again, as compared to MCD)
- Relapse can occur in 25-30%

The anti-PLA2R / PLA2R system in MN

- PLA2R is a normal protein in podocytes
- 70-80% prevalence of circulating anti-PLA2R in primary MN
- In disease, the PLA2R antigen co-localizes with IgG within the subepithelial immune deposits
- Genetic association of MN with *PLA2R1* and with class II MHC alleles
- Circulating anti-PLA2R and/or tissue PLA2R is highly specific for MN
- Strong association of anti-PLA2R with clinical disease activity

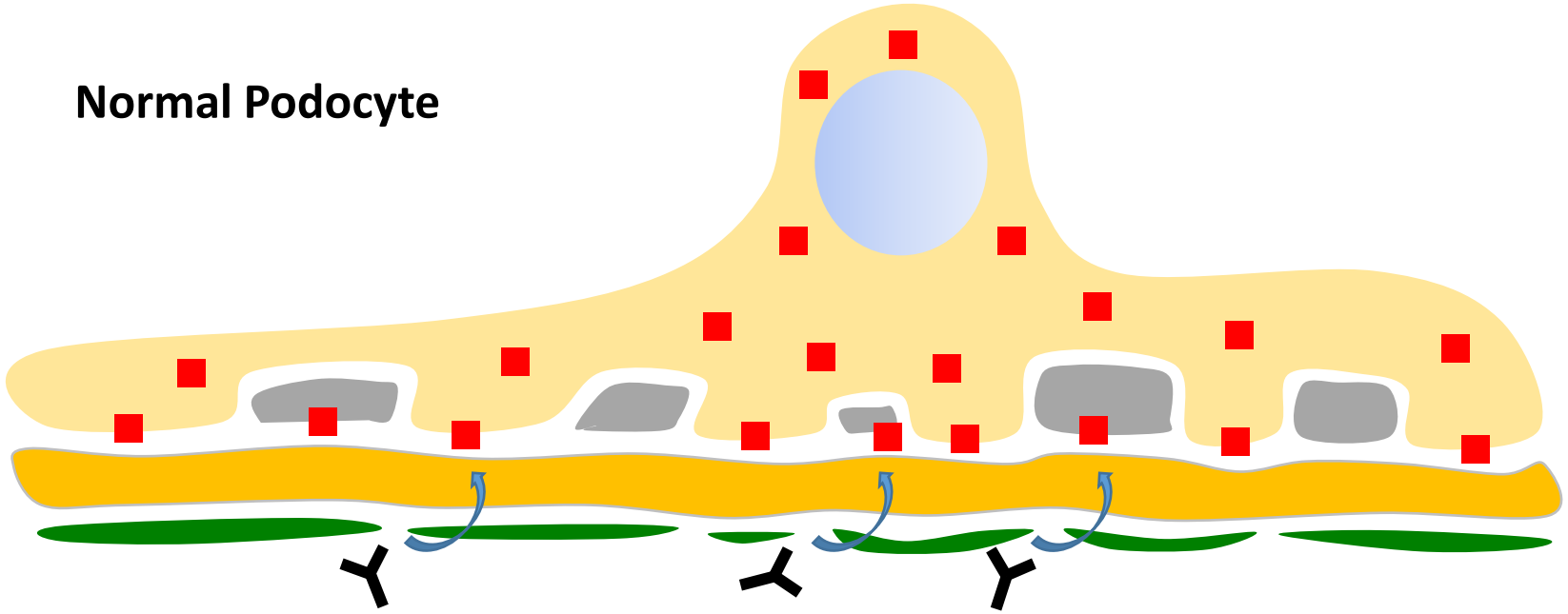
PLA2R is well-expressed by normal human podocytes





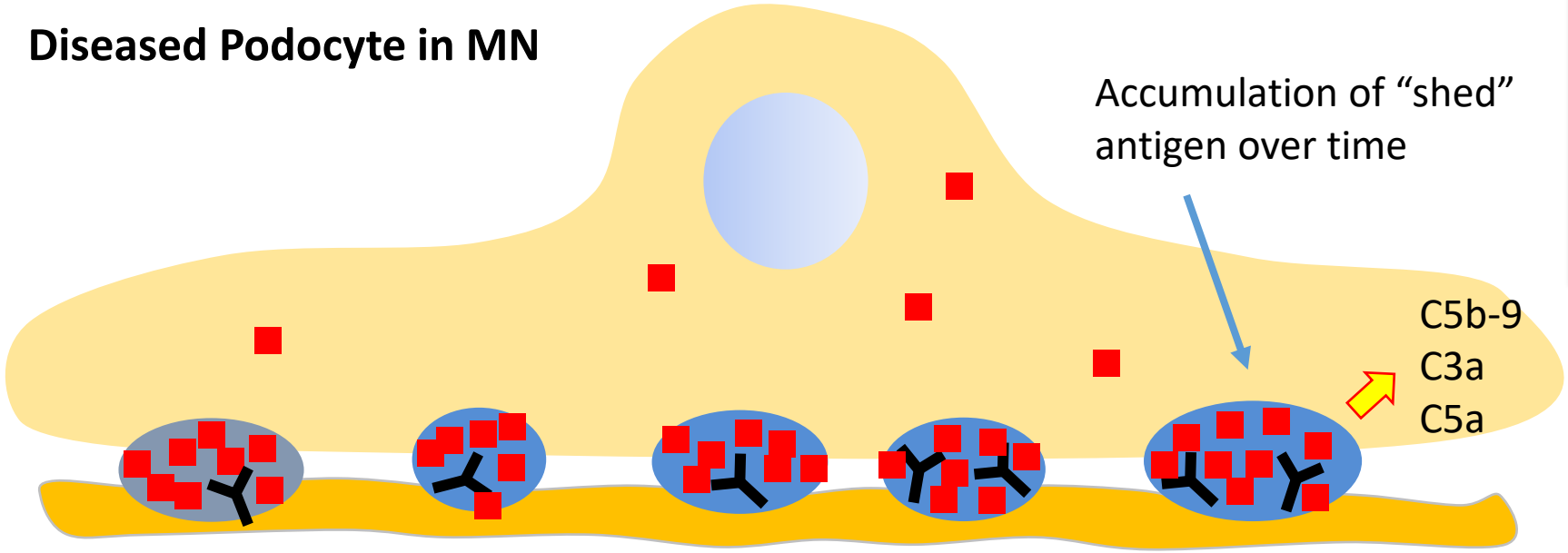
Beck LH Jr et al. (2009) *N Eng J Med* 361: 11-21

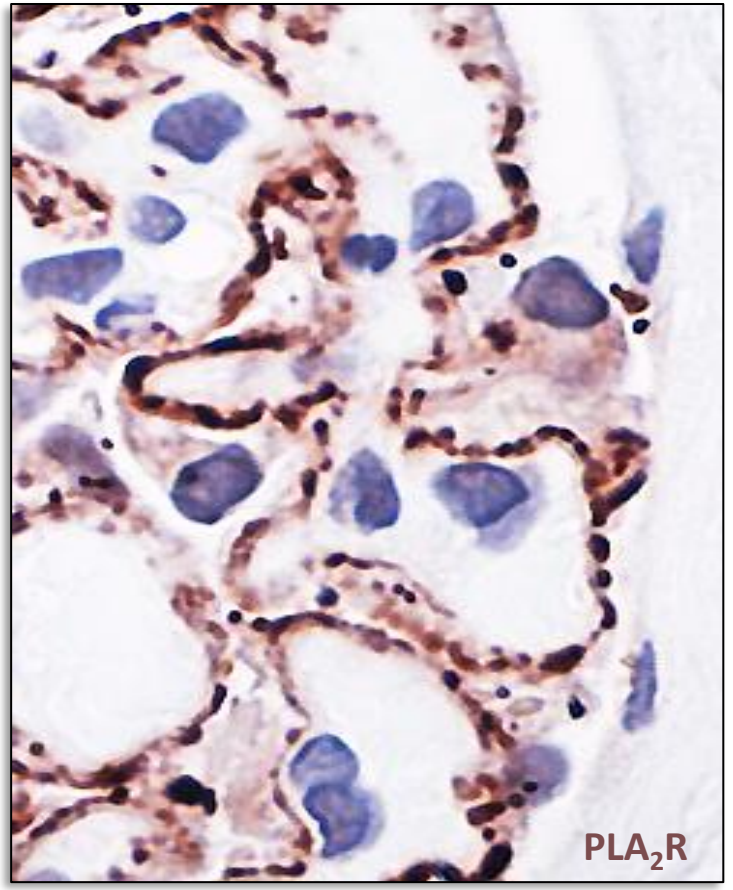
Normal Podocyte



Autoantibodies from circulation target the antigen at the basal side of the podocyte

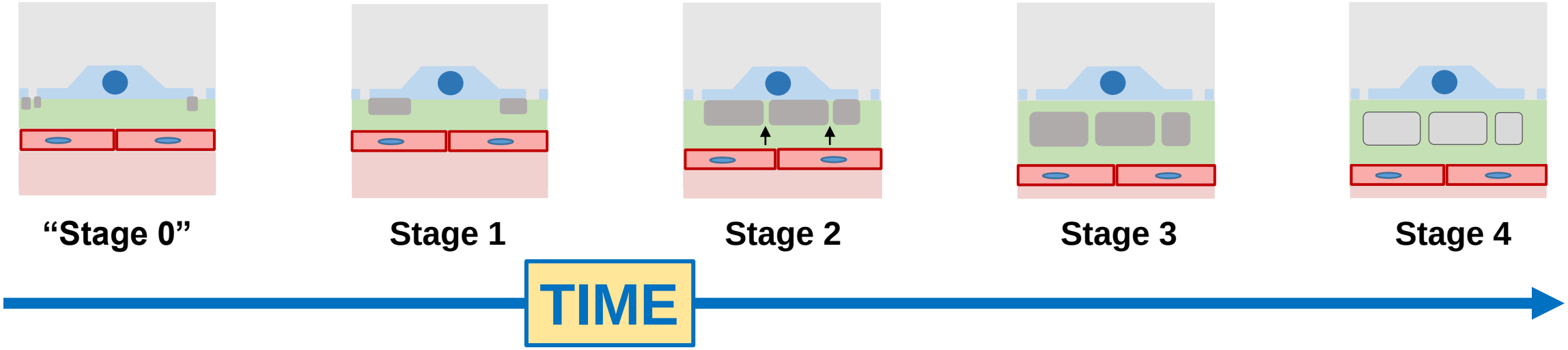
Diseased Podocyte in MN

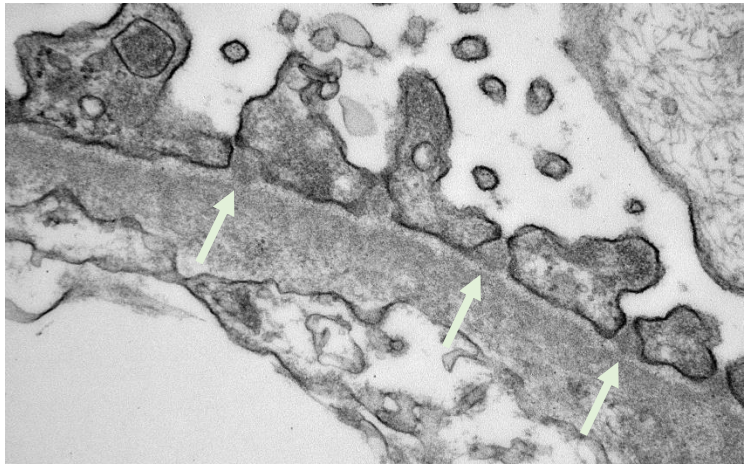




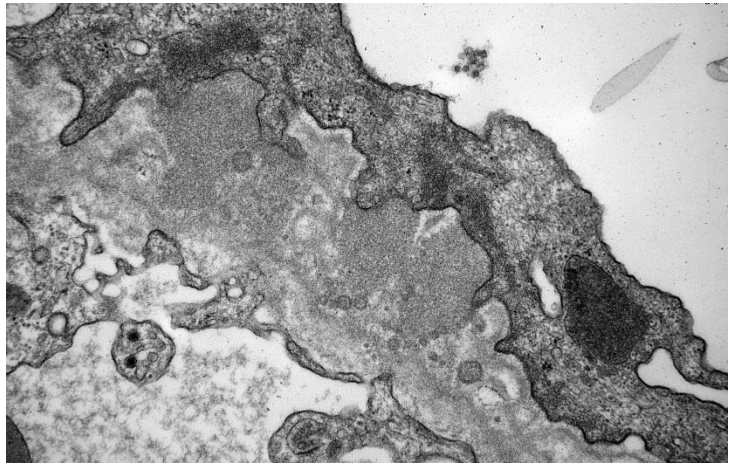
Courtesy of A. Herzenberg, U. Toronto

It takes time for the deposits to form in early disease, and to clear in late disease

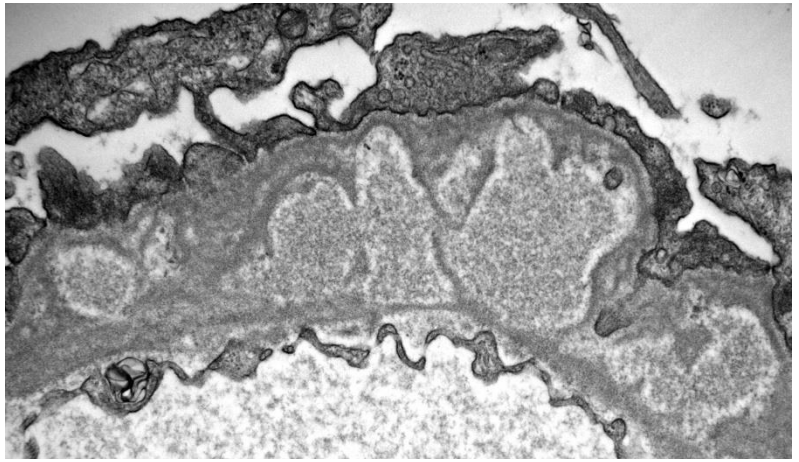




Stage 0-1



Stage 2



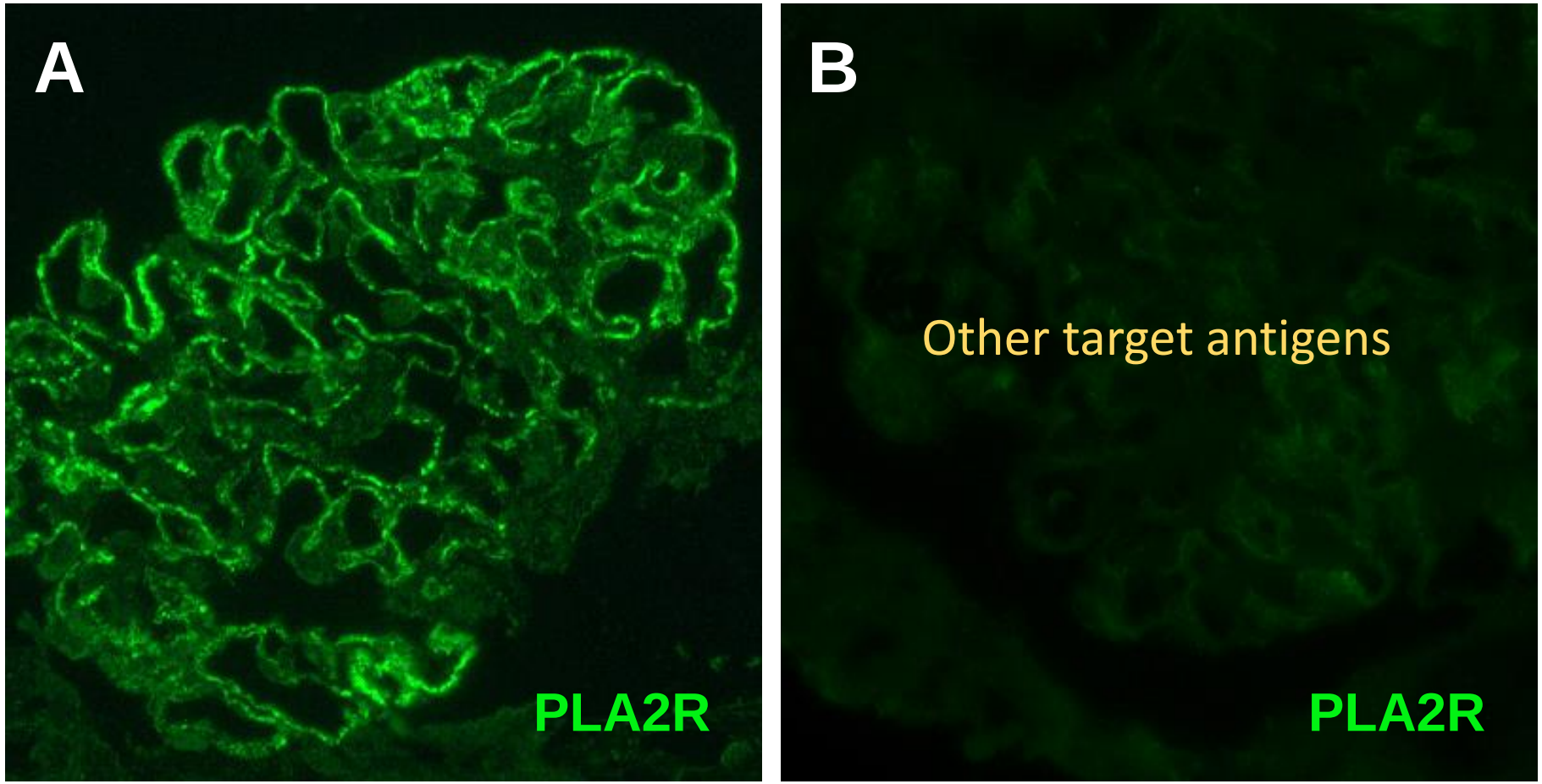
Stage 4

Lerner G et al., *Kidney Int*. 2021

MN can be sub-classified by IF staining of biopsy

PLA2R-associated MN
(55-60% of all MN)

Non-PLA2R-associated MN



The traditional view of MN:

Idiopathic
or **Primary**

Secondary to:
(associated with):

- Lupus
- Infections (HBV)
- Malignancy
- Medications (NSAIDs)

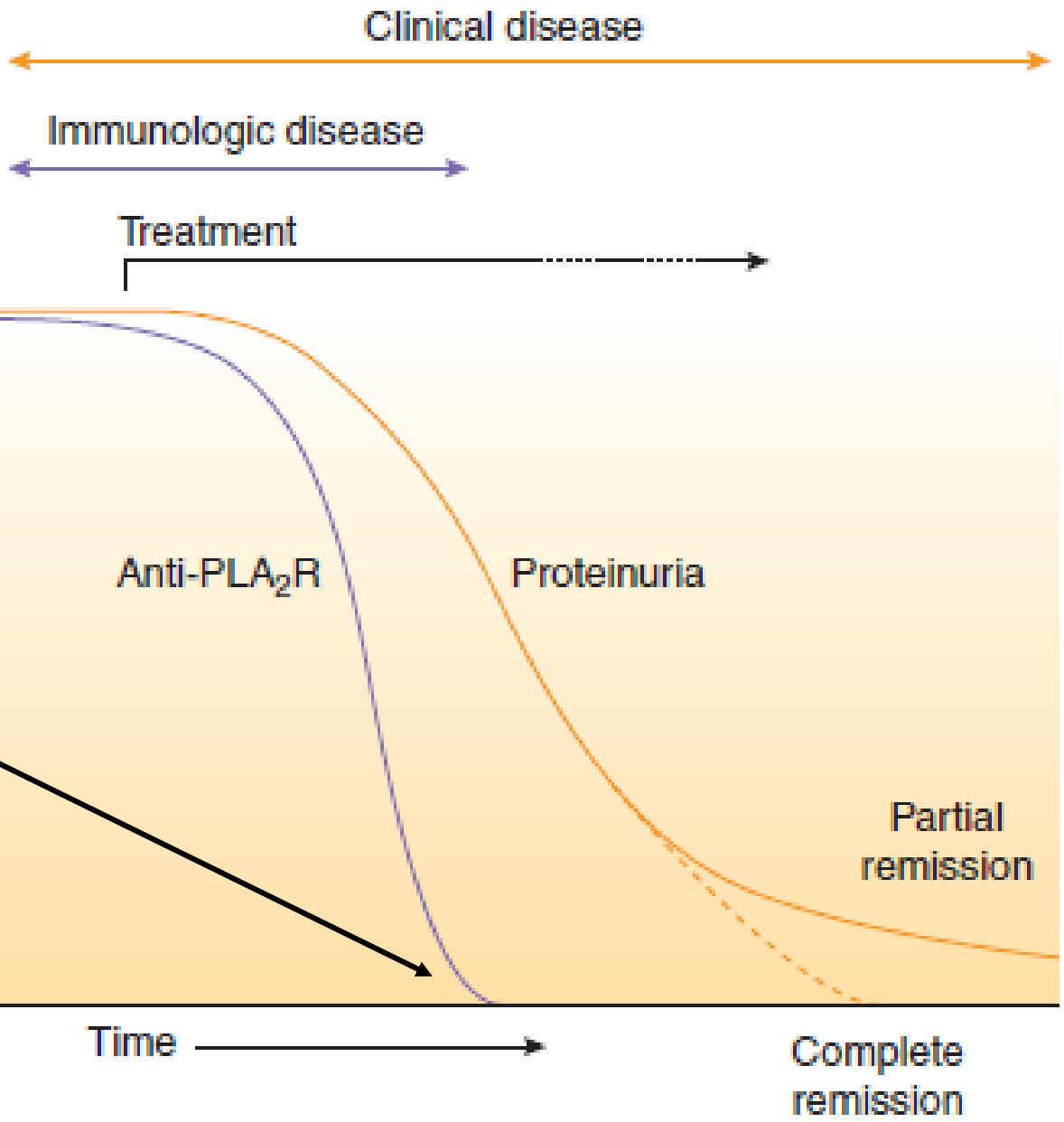
Subepithelial deposits
IgG4 predominant
Ag is a normal podocyte protein

Subepithelial, mesangial, subendothelial
IgG1, IgG2 or IgG3 predominant
Tubuloreticular inclusions

Now, MN is better classified according to **target antigen** (PLA2R, NELL1, etc)

Phospholipase A2 Receptor (PLA2R) is the major target antigen in MN: *Why was this finding so important?*

- Clinicians previously had only proteinuria and serum albumin to follow
- Clinical remissions occur **SLOWLY**
- Now we can additionally follow a serological marker of disease activity
- Serology **precedes and predicts** clinical course
- More rapid treatment decisions!



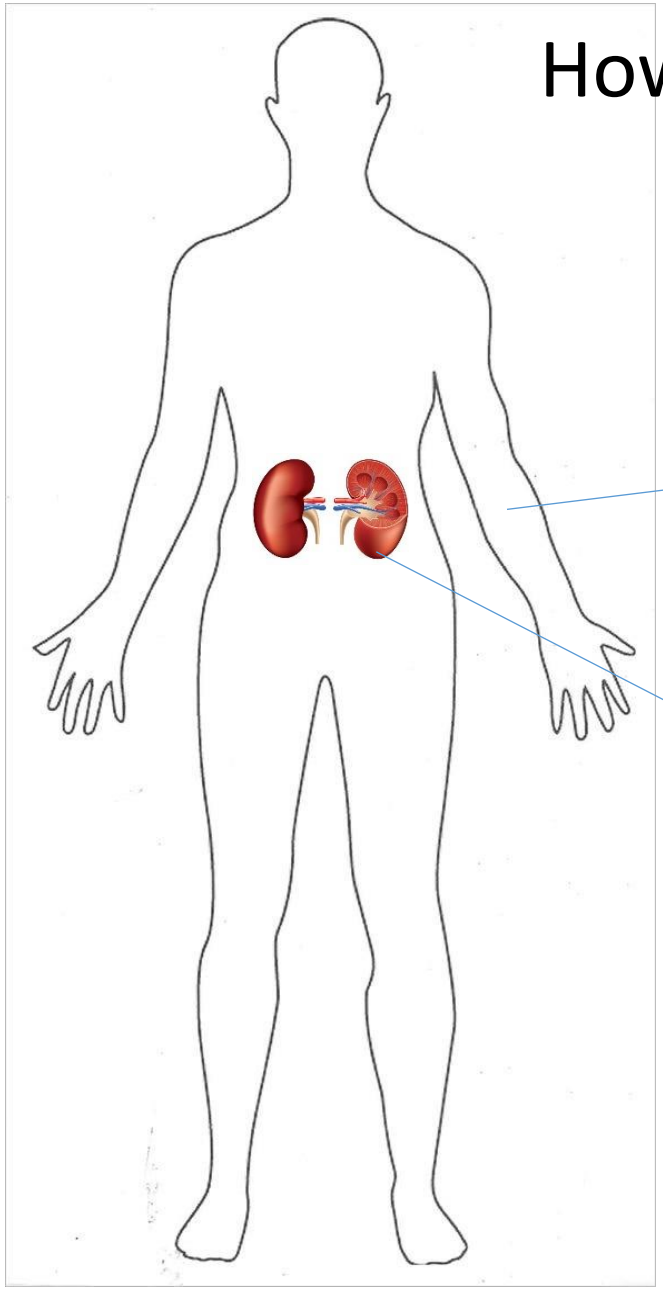
"**Immunological** (or serological) **remission**"

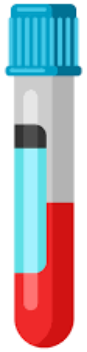
Based on a simple but KEY concept:

There are <u>two</u> disease courses that are separated by a predictable lag time

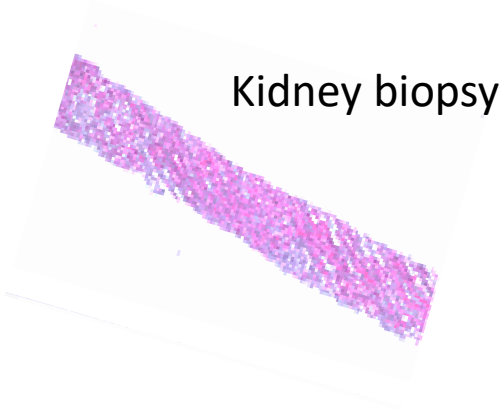
Beck LH Jr and Salant DJ. *Kidney International* (2010) 77: 765-70

How do we diagnose PLA2R-associated MN?



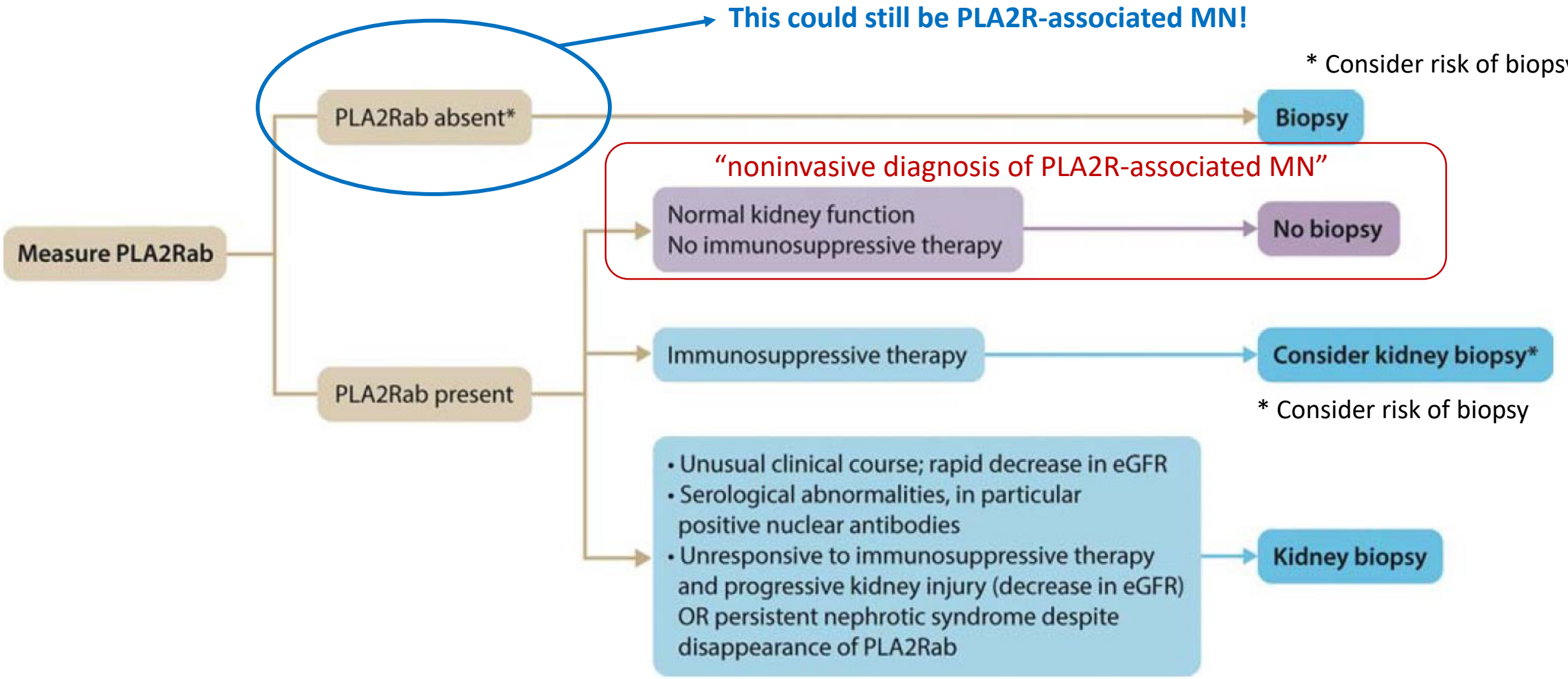


Blood sample for serological testing



Kidney biopsy for pathologic analysis

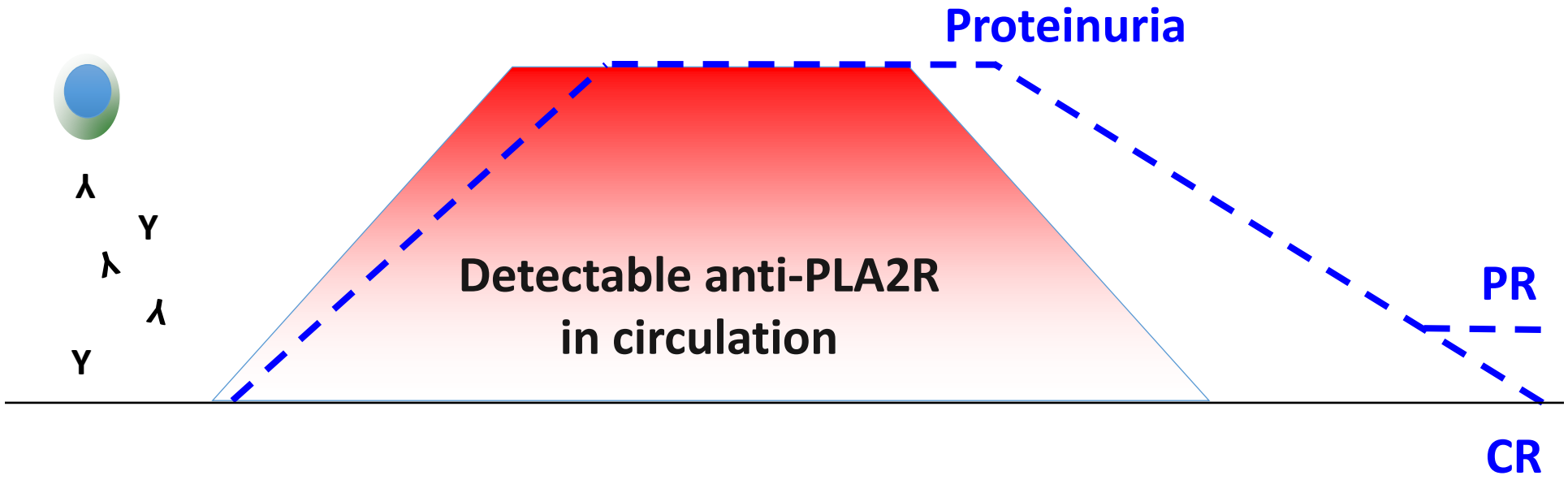
Practice Point 3.1.1: **A kidney biopsy is not required** to confirm the diagnosis of membranous nephropathy (MN) in patients with nephrotic syndrome and a positive anti-PLA2R antibody test.



KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021; 100(4S): S1-S276

Possible test results in PLA2R-associated MN

Clinical manifestations LAG BEHIND the **immunological** course of MN



neg?	Low	High	Anti-PLA2R	High	Low	neg	neg
POS?	POS	POS	Tissue PLA2R	POS	POS	POS	POS

Other target antigens have been discovered

The ones that have been around the longest and/or are most prevalent are:

Target antigen*	% of all MN	Disease association
PLA2R	55%	Usually “primary”
NELL1	10%	Malignancy in 33% Medications
EXT1/EXT2	7%	Lupus
THSD7A	2%	Malignancy (~10%)
SEMA3B	2%	Pediatric MN

* Circulating antibodies to EXT1 or EXT2 have not yet been reported

Practice Point 3.1.2: **Patients with MN should be evaluated for associated conditions**, regardless of whether anti-PLA2R antibodies and/or anti-THSD7A antibodies are present or absent.

Malignancy	Age- and population-appropriate cancer screening
Autoimmune	ANA, Sjögren's, IgG4-RD, thyroiditis, exam, history
Infection	HBV, HCV, HIV, RPR
Medications	NSAIDs, alpha-lipoic acid, mercury-containing products
Other	CXR (hilar adenopathy) or other findings suggestive of sarcoidosis

KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021; 100(4S): S1-S276

Membranous nephropathy and malignancy:

- **One can never discount the possibility that a malignancy may be present**
- The association may be causal or coincidental
- A closer temporal relation between malignancy and diagnosis of MN may be more suggestive of a true secondary process
- Consider searching for malignancy if:
  - no PLA_2R staining within immune deposits; (+)THSD7A or NELL1
  - lack of IgG4 dominance or co-dominance
  - presence of other secondary features on biopsy

Who should be treated with immunosuppression? weighing the risks and benefits:

Short term

- Nephrotic syndrome and associated risks
- Acute adverse effects of treatment

Long term

- Future kidney health
- Late effects of treatment

Which patients with MN should be anticoagulated?

- **Risk of VTE is 10-40% and increases with serum albumin <2.8 g/dL**
- Personalized prophylactic anticoagulation decision analysis based on 539 patients with MN
- Benefit-to-risk ratios were predicted according to bleeding risk and serum albumin:

Low bleeding risk

Ratio increases with worsening hypoalbuminemia

- **4.5 : 1** for albumin < 3 g/dl
- **13.1 : 1** for albumin < 2 g/dl

Intermediate bleeding risk

- **5 : 1** for albumin < 2 g/dl

High bleeding risk

- Unlikely to benefit regardless of albumin level

https://www.med.unc.edu/gntools

Warfarin
Heparin/LMWH

Use of DOACs not well studied

Lee et al. Kidney Int 85: 1412-1420, 2014

All patient should receive optimal supportive therapy:

- RAAS inhibition; SGLT2i
- BP control
- Diuretics + dietary sodium restriction
- Lipid lowering therapy

Immunosuppressive therapy should be restricted to patients considered at risk for progressive kidney injury

Does my patient need immunosuppressive therapy?

Prognosis: Clinical/laboratory criteria to assess 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

KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021; 100(4S): S1-S276

LOW	MODERATE	HIGH	VERY HIGH
Normal eGFR Proteinuria < 3.5 g/d Serum albumin > 3.0 g/dl			Life-threatening nephrotic syndrome, OR Rapid drop in eGFR without other explanation

After 6 months of (optimal) supportive care:

		eGFR < 60 and/or **Proteinuria > 8 g/d**
Normal eGFR Proteinuria **< 3.5 g/d** OR **> 50%** decrease in proteinuria from baseline	Normal eGFR Proteinuria **> 3.5 g/d** AND **< 50%** decrease in proteinuria from baseline	Normal eGFR Proteinuria **> 3.5 g/d** AND **< 50%** decrease in proteinuria from baseline and either: • **PLA2R-ab > 50 RU/ml**, or • **Serum albumin < 2.5 g/dl**

Modified from:
KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int.* 2021; 100(4S): S1-S276

A 36-year-old woman is diagnosed with PLA2R-associated membranous nephropathy by kidney biopsy. Medical history is significant only for regular use of tobacco and marijuana products. She is placed on optimal doses of losartan, torsemide, and atorvastatin with good control of her blood pressure and edema, but proteinuria only declines from 13.5 to 9 grams/day after 6 months of therapy.

What is the most appropriate choice of initial immunosuppression with the goal of achieving sustained remission of her proteinuria?

a) Cyclosporine

b) Alternating months of cyclophosphamide and corticosteroids

c) Rituximab

d) Mycophenolic acid

e) Eculizumab

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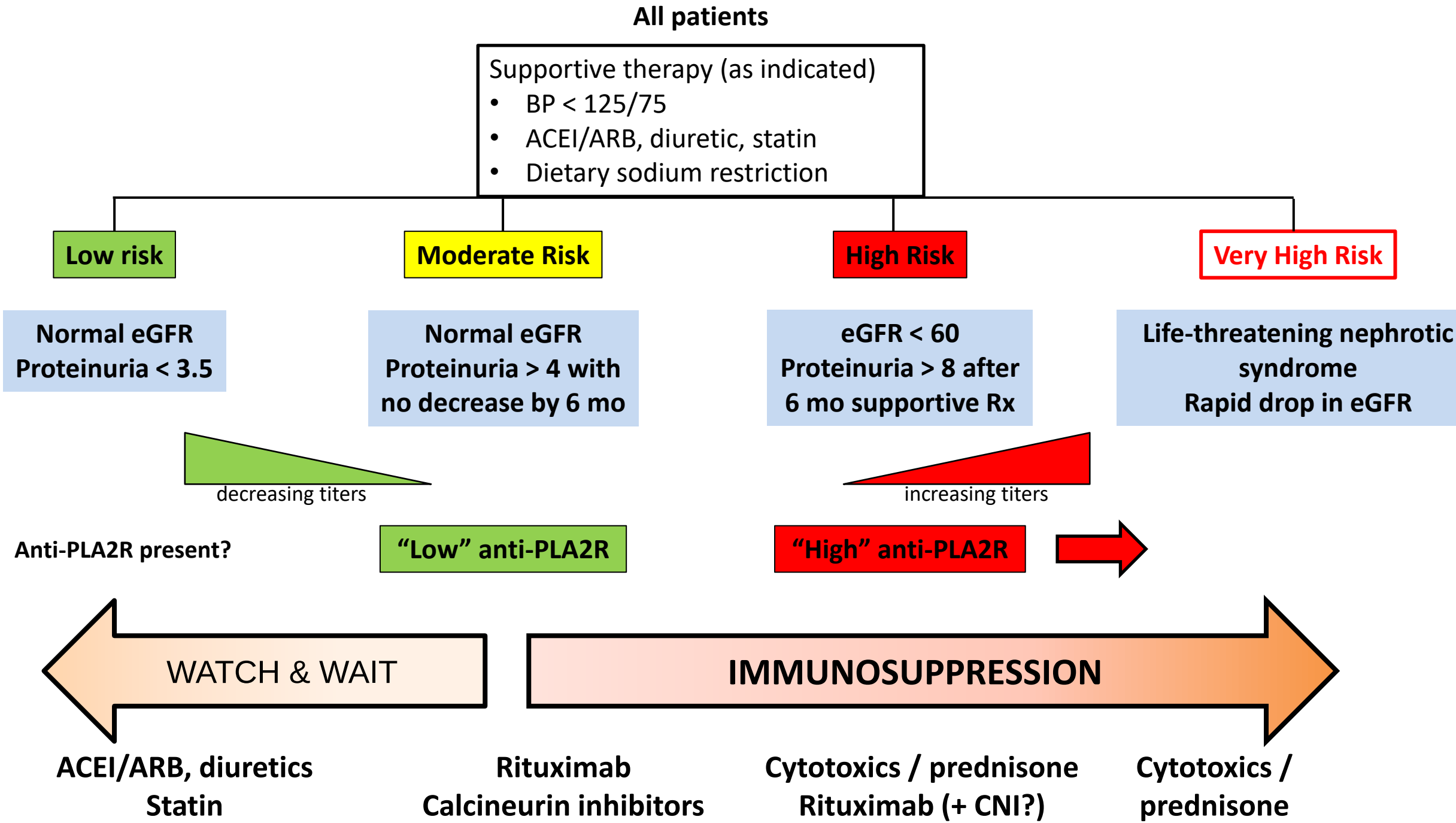
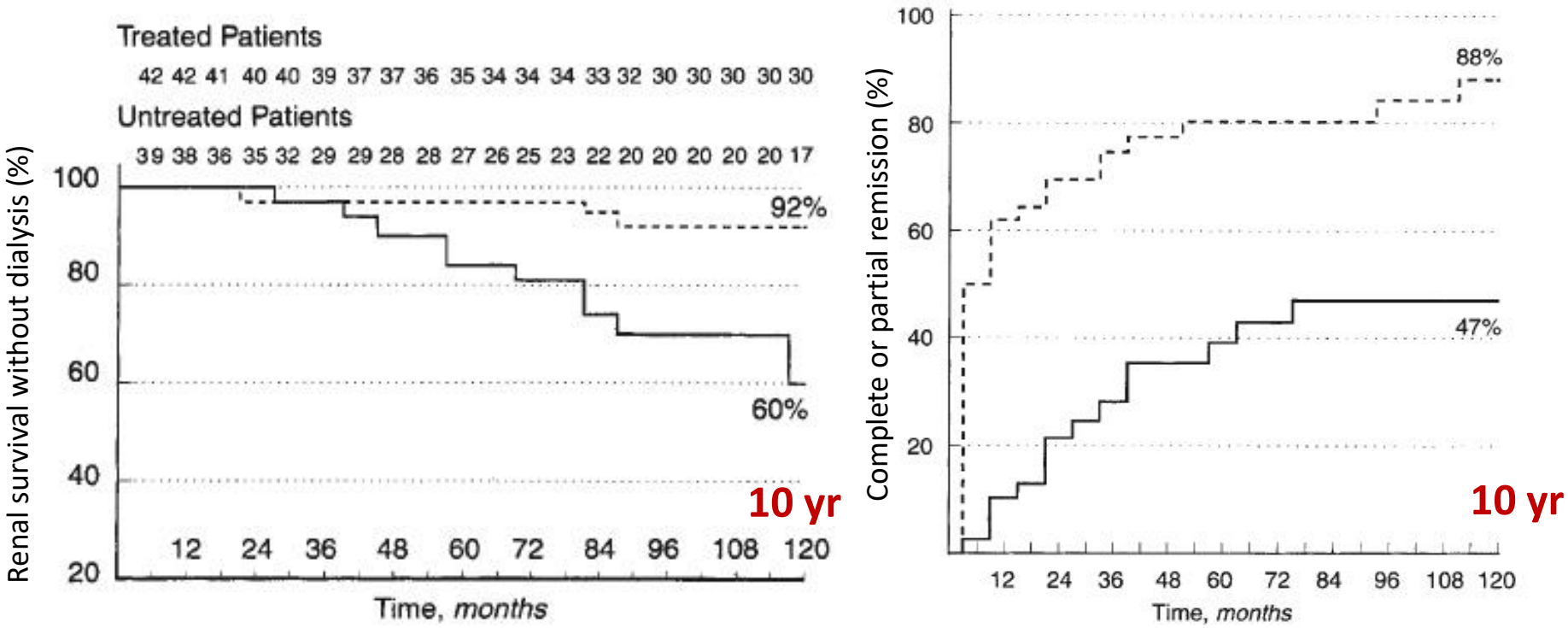

All patients
Supportive therapy (as indicated)
• BP < 125/75
• ACEI/ARB, diuretic, statin
• Dietary sodium restriction
Low risk
Moderate Risk
High Risk
Very High Risk
Normal eGFR
Proteinuria < 3.5
Normal eGFR
Proteinuria > 4 with
no decrease by 6 mo
eGFR < 60
Proteinuria > 8 after
6 mo supportive Rx
Life-threatening nephrotic syndrome
Rapid drop in eGFR
decreasing titers
increasing titers
Anti-PLA2R present?
"Low" anti-PLA2R
"High" anti-PLA2R
WATCH & WAIT
IMMUNOSUPPRESSION
ACEI/ARB, diuretics
Statin
Rituximab
Calcineurin inhibitors
Cytotoxics / prednisone
Rituximab (+ CNI?)
Cytotoxics /
prednisone

The (modified) Ponticelli regimen:

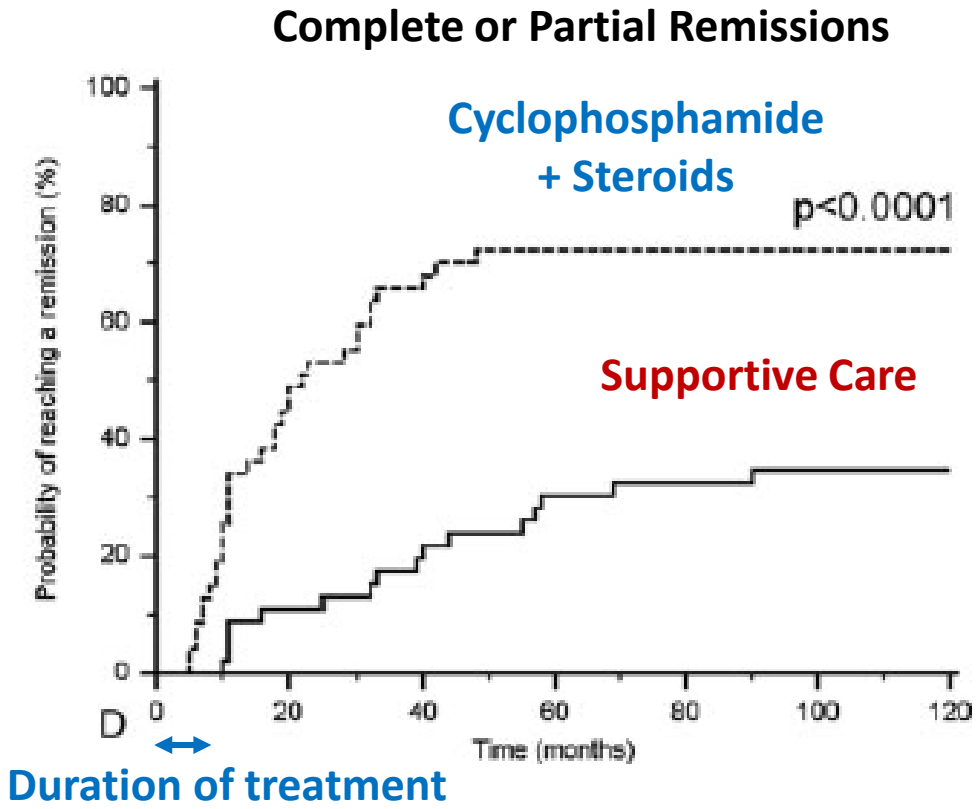
Months 1, 3, 5: 1 g i.v. methylprednisolone daily x 3, then oral methylprednisolone (0.5 mg/kg/d) x 27 days

Months 2, 4, 6: Oral chlorambucil at 0.15-0.2 mg/kg/d (or oral **cyclophosphamide** at 2 mg/kg/d) x 30 days



Ponticelli et al. *Kidney Int* 1995; 48: 1600-4

Remissions occur late following completion of treatment



A second study with 10 yr follow-up data

Jha V et al. *J Am Soc Nephrol* 2007; 18: 1899-1904

ALKYLATING AGENTS remain the only agents proven effective in preventing ESKD or death in MN

- Should be restricted to patients with high risk of progression
- Should be avoided if possible in smokers, patients of child-bearing age

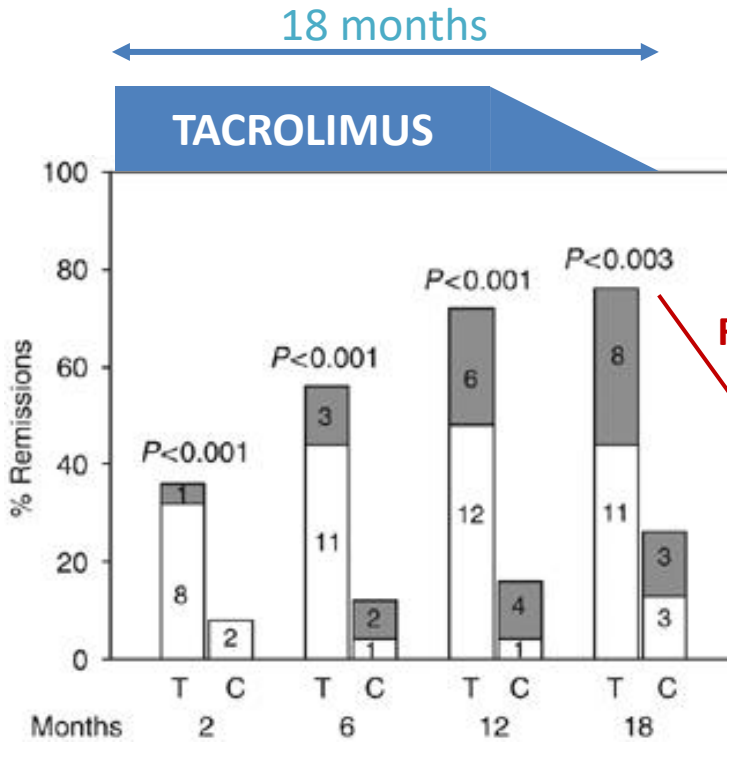
Table 2 | Factors associated with the risk of progressive loss of kidney function in patients with membranous nephropathy

Low risk	High risk
Proteinuria <3.5 g/d	• Serum creatinine >1.5 mg/dl (133 µmol/l) • Decrease in eGFR by ≥ 20% over any time period during the preceding 12 months not explained otherwise[a] • Proteinuria >8 g/d for > 6 mo • Presence of low-molecular-weight proteinuria • Urine IgG > 250 mg/24 h • PLA2R antibody levels and evolution[b]

Floege J *et al*. Management and treatment of GN (part 1): a KDIGO conference report. *Kidney Int*. (2019) **95**, 268-80

Tacrolimus monotherapy in MN: A randomized controlled trial

25 patients received tacrolimus (0.05 mg/kg/day) over 12 months with a 6-month taper; 23 patients were in the control group



Similar findings with cyclosporine, as we will see from the MENTOR study …

Praga M et al. *Kidney Int* 2007; 71: 924-30

Limitations of these therapeutic agents

Calcineurin inhibitors:

- Aggravate severe HTN, impaired GFR and interstitial fibrosis
- Diabetogenic
- Relatively high relapse rate on discontinuation

Alkylating agents and prednisone:

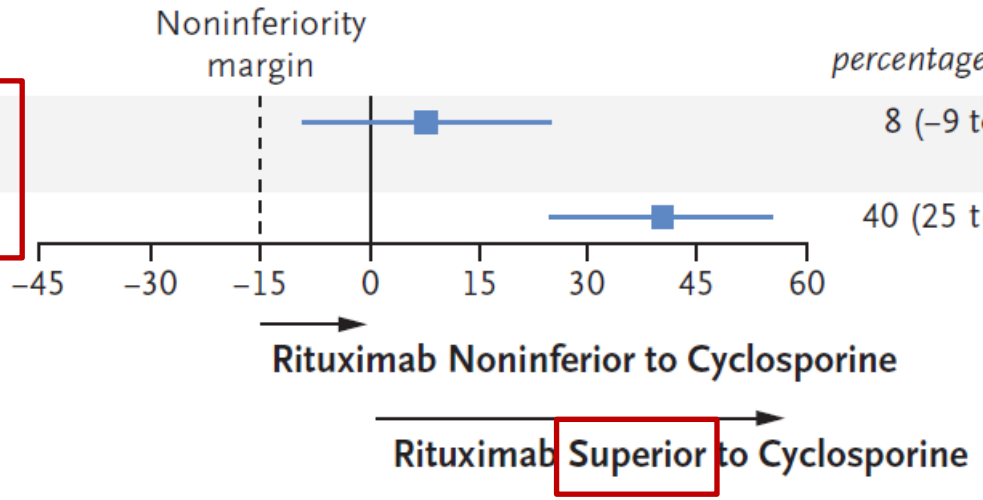
- Cytopenias
- Cancer risk (bladder and lung) in smokers
- Infertility
- Diabetogenic

ORIGINAL ARTICLE

Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy

Fernando C. Fervenza, M.D., Ph.D., Gerald B. Appel, M.D., Sean J. Barbour, M.D., Brad H. Rovin, M.D., Richard A. Lafayette, M.D., Nabeel Aslam, M.D., Jonathan A. Jefferson, M.D., Patrick E. Gipson, M.D., Dana V. Rizk, M.D., John R. Sedor, M.D., James F. Simon, M.D., Ellen T. McCarthy, M.D., et al., for the MENTOR Investigators

Evaluation Time Point	Rituximab (N=65)	Cyclosporine (N=65)	Risk Difference (95% CI)	P Value for Noninferiority	P Value for Superiority
	no. with complete or partial remission (%)		*percentage points*		
End of treatment period at 12 mo	39 (60)	34 (52)	8 (−9 to 25)	0.004	—
End of follow-up at 24 mo	39 (60)	13 (20)	40 (25 to 55)	<0.001	<0.001



Many relapses after cyclosporine was tapered off

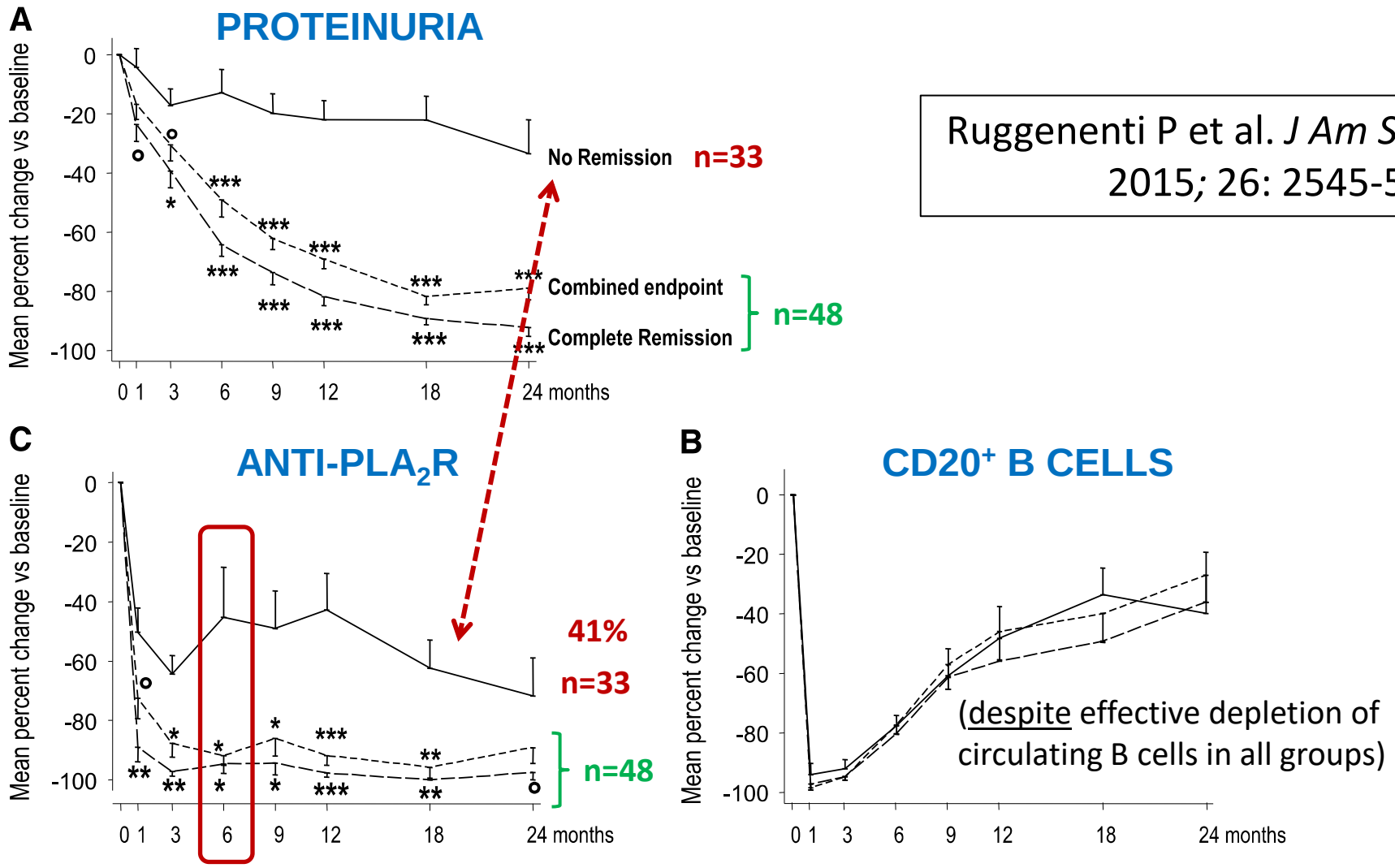
Fervenza FC et al. (2019) *N Engl J Med* 318: 36 - 46

Composite outcome *vs.* complete remission at 6-24 mo.

Time from Randomization	Rituximab	Cyclosporine	Rituximab	Cyclosporine
	Partial or Complete Remission		**Complete Remission**	
6 mo	23/65 (35%)	32/65 (49%)	0/65 (0%)	1/65 (2%)
12 mo	39/65 (60%)	34/65 (52%)	9/65 (**14%**)	3/65 (5%)
18 mo	40/65 (**62%**)	15/65 (23%)	18/65 (**28%**)	1/65 (2%)
24 mo	39/65 (**60%**)	13/65 (20%)	23/65 (**35%**)	0/65 (0%)

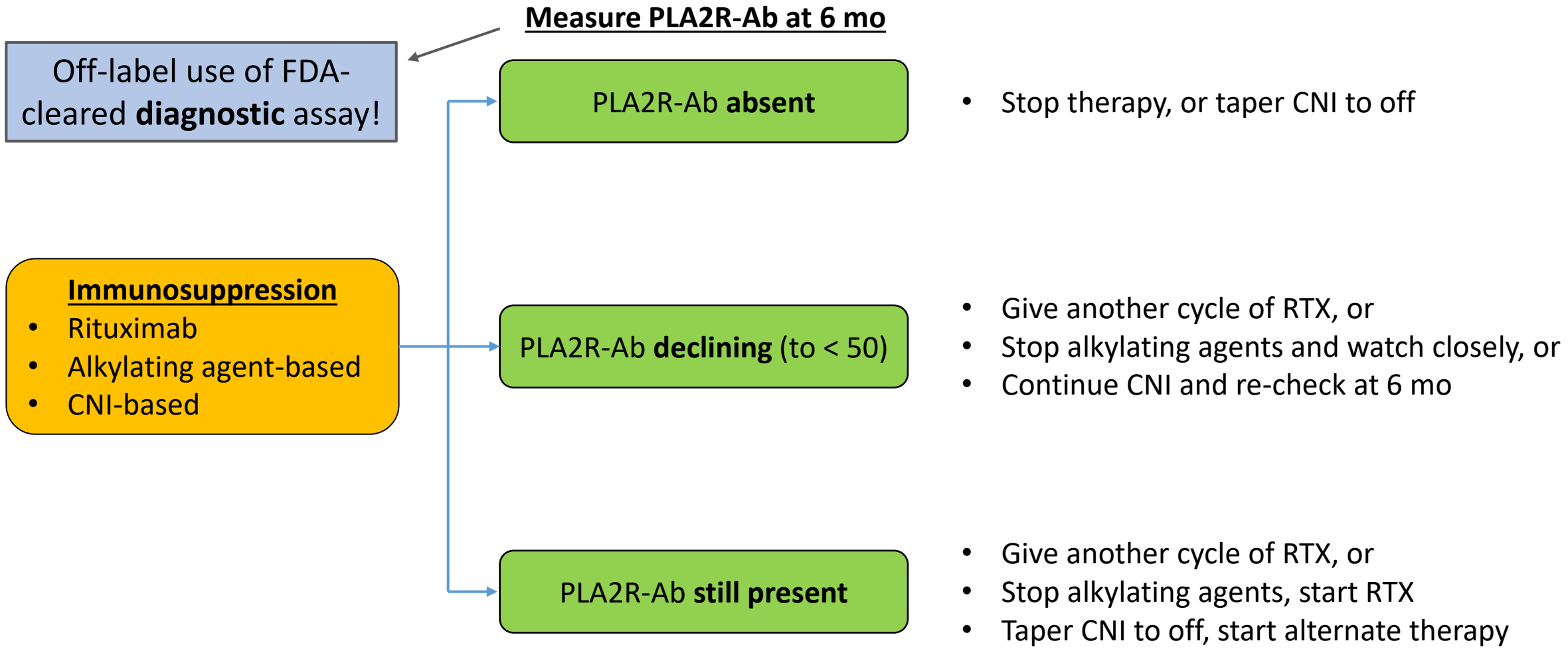
Adapted from Fervenza FC et al. (2019) *N Engl J Med* 318: 36 - 46

Immune surveillance with anti-PLA_2R following treatment with rituximab

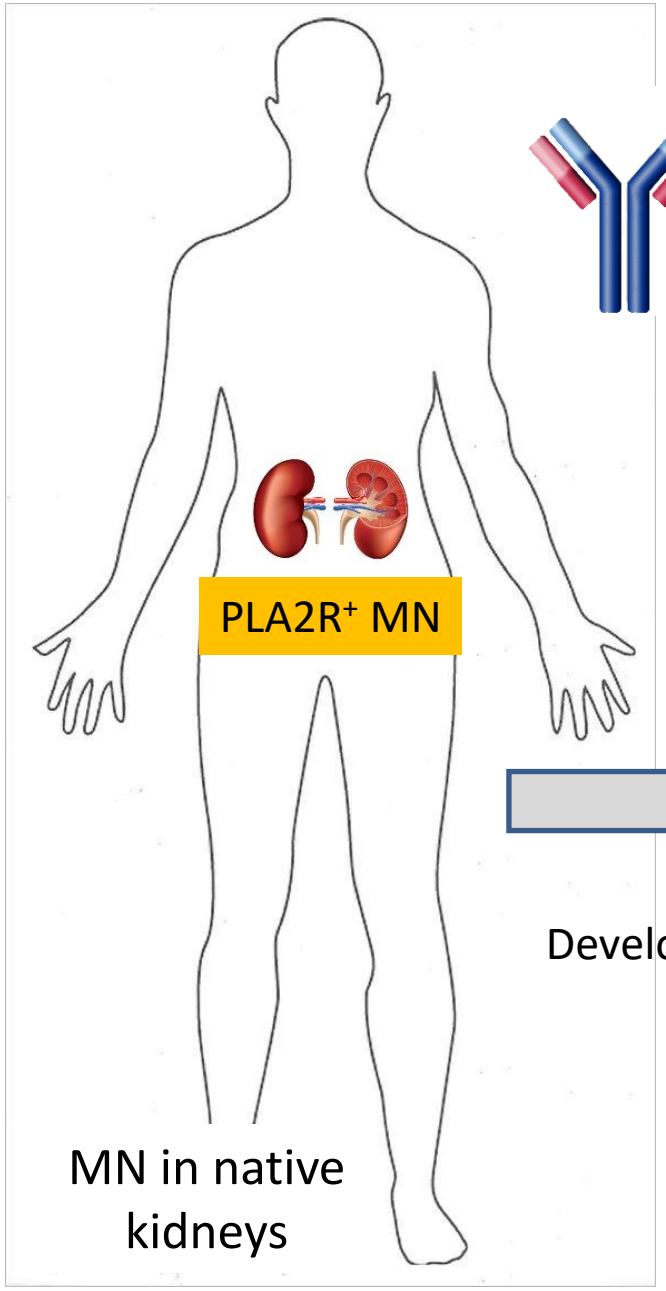


Ruggenenti P et al. *J Am Soc Nephrol* 2015; 26: 2545-58

KDIGO Practice Point 3.3.4: Longitudinal monitoring of anti-PLA2R antibody levels at 6 months after start of therapy may be useful for evaluating treatment response in patients with MN, and can be used to guide adjustments to therapy



KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int* 2021; 100(4S): S1-S276

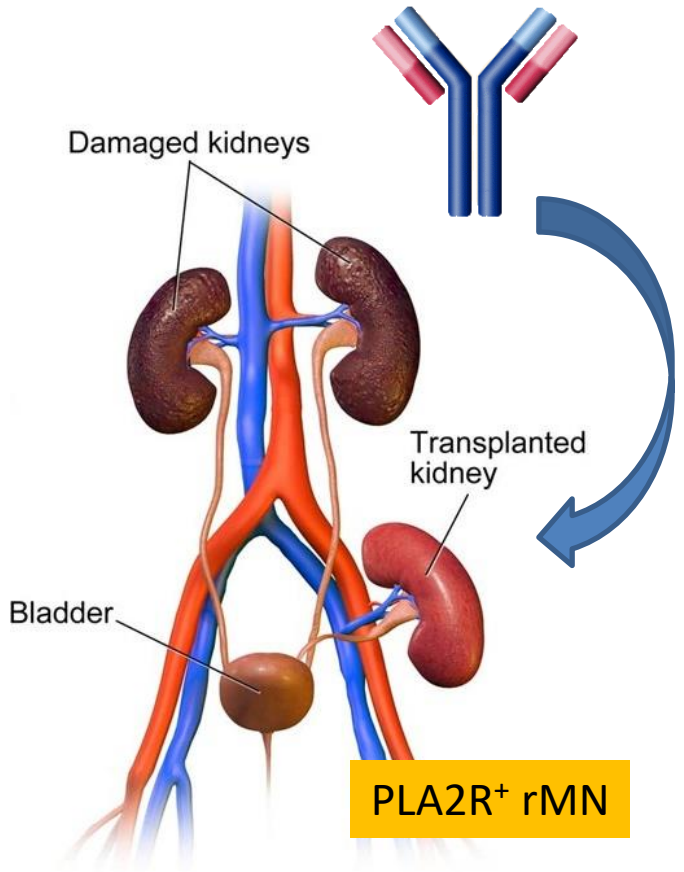


Anti-PLA2R

Development of ESKD

Hemodialysis

Circulating anti-PLA2R at time of transplant



Recurrent Membranous Nephropathy

Assessment of anti-PLA2R pre- and post-transplant can be helpful in guiding management

Recurrent membranous nephropathy

- Incidence of recurrence in allograft: **10 to 45%**
- Centers performing protocol biopsy report higher incidence and earlier recurrence
- The mean time for ***overt*** clinical recurrence is 13-15 months
- Persistent nephrotic range proteinuria increases risk of graft failure
- Anti-PLA2R can be found in association with recurrent (but not *de novo)* MN
- **Positive anti-PLA2R serology at transplantation should not affect decision to transplant**
- Heightened surveillance for proteinuria is warranted if patient is seropositive pre-transplant

TAKE HOME MESSAGES

- ”Membranous nephropathy” is a group of related disorders marked by specific antigens enriched in **subepithelial** (beneath the podocyte) immune deposits
- The major form of MN is associated with autoantibodies that target **PLA2R**, a normal podocyte protein
- Other target antigens* may be suggestive of conditions associated with the MN:
  - **EXT1/EXT2** (lupus)
  - **NELL1** (malignancy, medications)
  - **THSD7A** (malignancy)
- In a patient with nephrotic syndrome, preserved kidney function, and no suggestion of associated conditions, seropositivity for anti-PLA2R is sufficient for the diagnosis of PLA2R-associated MN

TAKE HOME MESSAGES

- A serological approach can be very useful for treatment decisions about starting, stopping, or changing immunosuppression
- Proteinuric patients with autoAb that are declining or have disappeared may never need immunosuppression
- Patients at high risk of progression toward ESKD by virtue of sustained high levels of proteinuria, despite optimal supportive care, warrant immunosuppression
- Anti-CD20 therapy (rituximab) has become a first-line therapeutic agent in MN
- The alkylating agent + corticosteroid regimens are reserved for higher risk patients (especially those with life-threatening manifestations of the nephrotic syndrome or with rapidly worsening kidney function)
- Treatment should be continued until the circulating autoAb is undetectable

CLINICAL TRIALS

Clinical Trial	Change in Management
Ponticelli C, et al. A 10-year follow-up of a randomized study with **methylprednisolone and chlorambucil** in membranous nephropathy. *Kidney Int*. 1995 Nov;48(5):1600-4. doi: 10.1038/ki.1995.453.	• Showed better 10-yr kidney survival (92% v. 60%) and remission from proteinuria with immunosuppressive treatment • Substitution of **cyclophosphamide** as alkylating agent (better safety) became known as the "**modified" Ponticelli regimen**
Jha V, et al. A randomized, controlled trial of **steroids and cyclophosphamide** in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. *J Am Soc Nephrol.* 2007 Jun;18(6):1899-904. doi: 10.1681/ASN.2007020166.	• Confirmed better 10-yr dialysis-free survival with treatment (89% v 65%) • Ultimate remission from proteinuria in 72% v. 35%
Dahan K et al; **GEMRITUX** Study Group. **Rituximab** for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up. *J Am Soc Nephrol*. 2017 Jan;28(1):348-358. doi: 10.1681/ASN.2016040449	• First RCT (vs supportive care) using rituximab • Showed significant reduction of PLA2R-ab at 3 and 6 months with rituximab • In observational phase (following 6 mo primary endpoint), rate of remission was 65% with rituximab vs 34% with supportive care
Fervenza FC, et al; **MENTOR** Investigators. **Rituximab or Cyclosporine** in the Treatment of Membranous Nephropathy. *N Engl J Med.* 2019; 381: 36-46. doi: 10.1056/NEJMoa1814427.	• Rituximab was **non-inferior** to cyclosporine in inducing remission at **12 mo** (60% v. 52%) • Rituximab was **superior** in maintaining proteinuric remission through **24 mo** (60% v. 20%)

MAIN OPTIONS FOR IMMUNOSUPPRESSION IN MN

Alkylating agents (*e.g*. the modified Ponticelli regimen) have the best long-term outcomes for inducing a durable remission and preserving renal function; however side effects are significant

Calcineurin inhibitors are a widely-used alternative agent, but often require a lengthy duration of treatment to fully suppress autoAb levels. Relapse is common with shorter treatments

The anti-B cell agent **rituximab** has emerged as a very effective agent for treating primary MN, as demonstrated in observational trials, GEMRITUX, and most recently, MENTOR

A serological approach (titer, trajectory of autoantibodies) can be very useful for treatment decisions about starting, stopping, or changing immunosuppression

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