Welcome to the ERKNet Webinar

WEBINAR

01/02/22

KDIGO Guideline on Immune GP I – MCD/MN

Speaker: Jack Wetzels (Nijmegen, Netherlands)

Moderator: Marina Vivarelli (Rome, Italy)

ERKNet
The European Rare Kidney Disease Reference Network

Novel emerging treatment guidelines

www.kidney-international.org KDIGO executive conclusions

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

OPEN

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The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Glomerular Diseases is an update to the KDIGO 2012 guideline. The aim is to assist clinicians caring for individuals with glomerulonephritis (GN), both adults and children. The scope includes various glomerular diseases, including IgA nephropathy and IgA vasculitis, membranous nephropathy, nephrotic syndrome, minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), infection-related GN, antineutrophil cytoplasmic antibody (ANCA) vasculitis, lupus nephritis, and anti–glomerular basement membrane antibody GN. In addition, this guideline will be the first to address the subtype of complement-mediated diseases. Each chapter follows the same format providing guidance related to diagnosis, prognosis, treatment, and special situations. The goal of the guideline is to generate a useful resource for clinicians and patients by providing actionable recommendations based on evidence syntheses, with useful infographics incorporating views from experts in the field. Another aim is to propose research recommendations for areas where

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Received 14 March 2021; revised 18 May 2021; accepted 20 May 2021

KDIGO 2021 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF GLOMERULAR DISEASES

Polling question I

Did you study the chapters membranous nephropathy and MCD/FSGS of the 2021 KDIGO guideline?

A: no
B: yes

Polling question II

How many patients with “active” membranous nephropathy or MCD/FSGS are in your care?

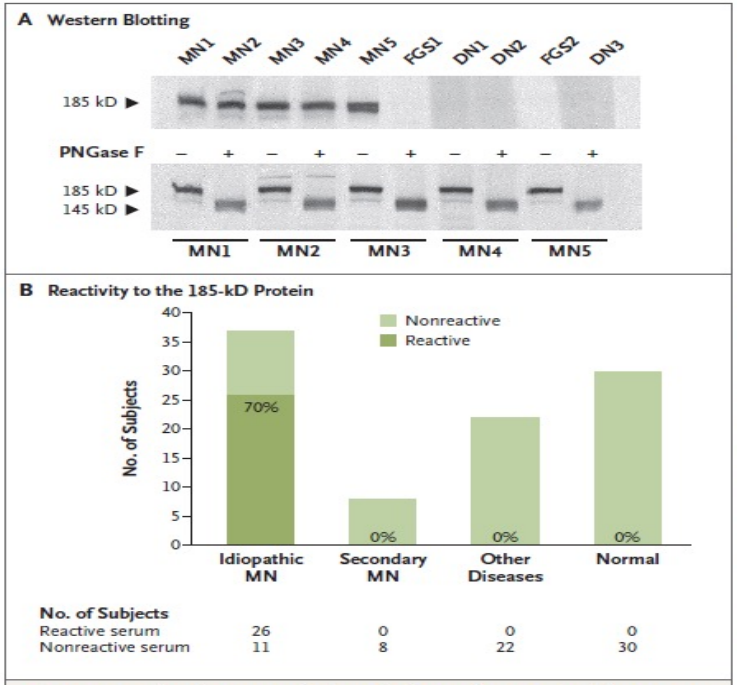
A: < 4
B: 4-10
C: 10 -20
D: > 20

Overview

- membranous nephropathy
- Beyond the guideline: PLA2Rab added value in therapy?
- MCD/FSGS

Note: KDIGO guidelines: few recommendations, many practice points (limited evidence from RTC's; practice point = "old" graded X recommendation)

2009: MN breakthrough: discovery of aPLA2R

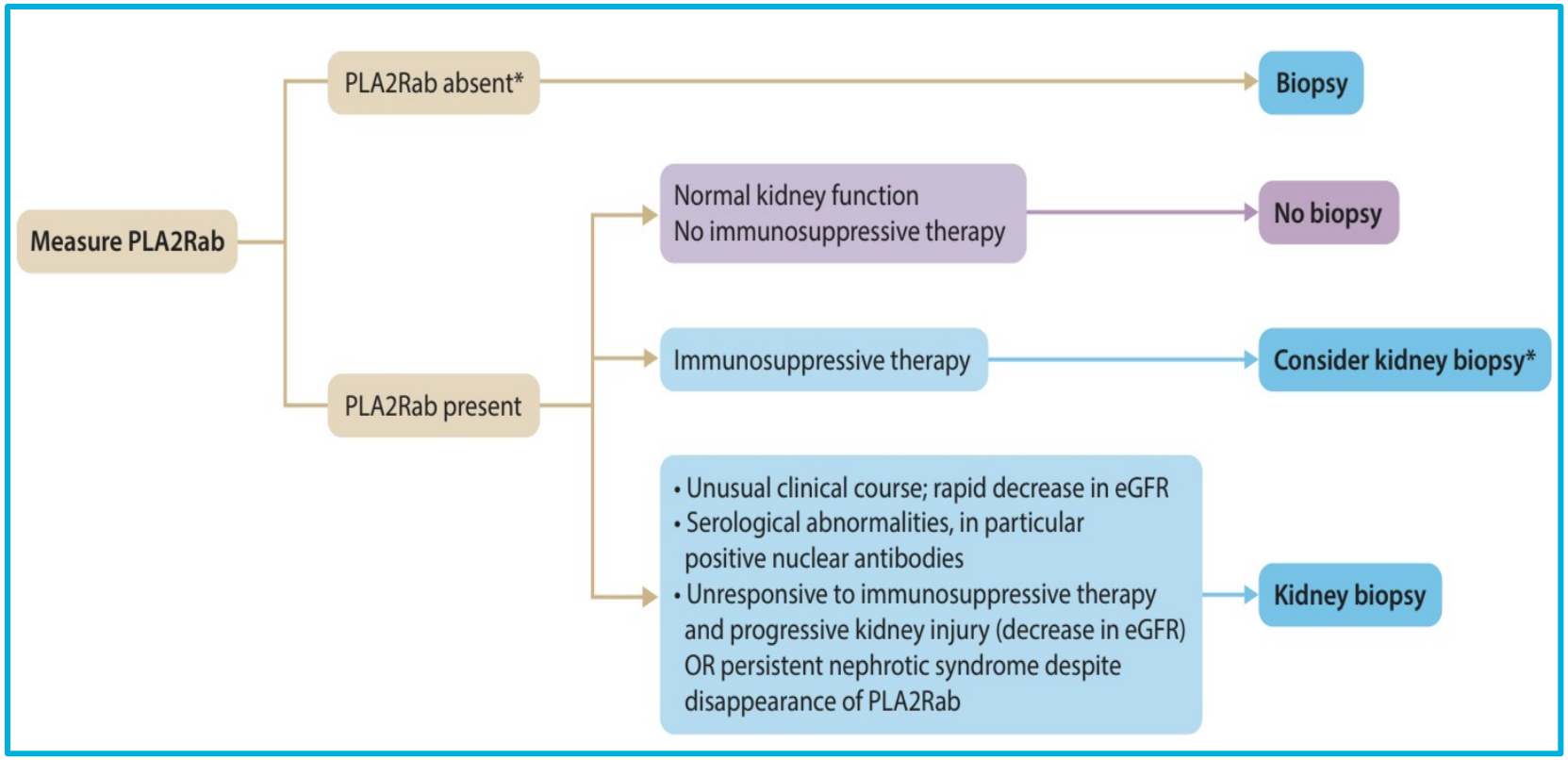


Auto-immune disease: antibodies against M-type **phospholipase A2 receptor** (aPLA2R) in 70% of patients with iMN

Beck et al, NEJM 2009

aPLA2R as biomarker: pathognomonic for MN diagnosis

A biopsy is not needed for diagnosis, can be useful in special conditions



* IFT positive or ELISA > 14 RU/ml; IFT is more sensitive

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membranous nephropathy: treatment

- Supportive therapy in all patients with proteinuria (ACEi or ARB, lipids, smoking, body weight, dietary sodium)

- Non-nephrotic → no immunosuppression, regular follow-up

- Nephrotic:
  - Risk evaluation
    - Arterial and venous thrombosis
    - Kidney disease progression

membranous nephropathy: anticoagulant therapy

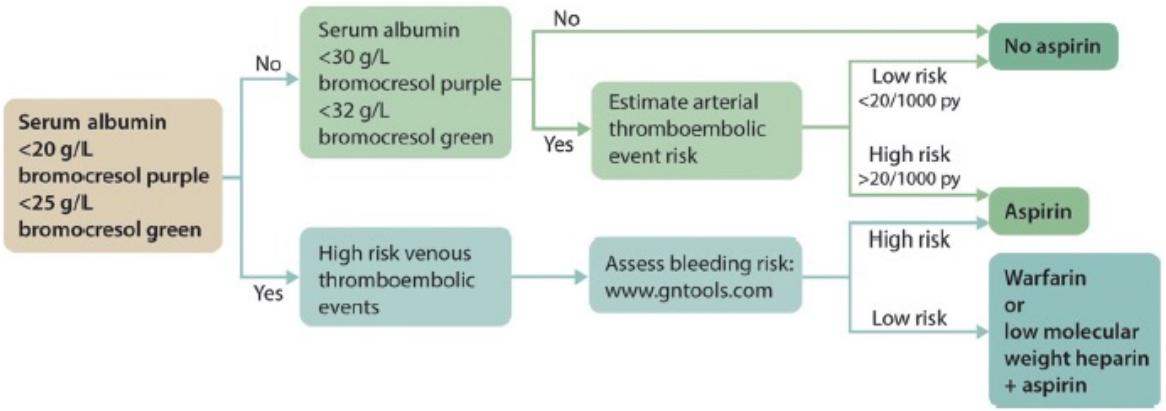

Figure 38| Anticoagulant therapy in patients with MN. Adapted from *Kidney International*, volume 89, issue 5, Hofstra JM, Wetzels JFM. Should aspirin be used for primary prevention of thrombotic events in patients with membranous nephropathy? Pages 89:981–983, Copyright Copyright 2016, with permission from the International Society of Nephrology.[44] Proposed algorithm for anticoagulant therapy in patients with

Serum albumin cut-off values: not validated; differences between assays

Risk of bleeding vs risk of thrombosis

Take into account arterial thrombotic events → aspirin

Warfarin start: → initial higher risk of thrombosis

Steroid pulses: thrombogenic

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Risk prediction:

The usual suspects:

Serum creatinine
Proteinuria
Serum albumin

Additional markers

Duration of proteinuria
Risk score (Toronto)
Urine LMW proteins
PLA2Rab

High risk

- 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[†]
- U a1M >40 µg/min
- U b2M >1 µg/min
- U IgG >250 mg/d
- Selectivity index >0.20[§]

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membranous nephropathy: risk evaluation

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 m²* 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 α1-microglobulin >40 µg/min • Urinary • Urinary >250 mg/d • Selectivity index >0.20§	• Life-threatening nephrotic syndrome OR • Rapid deterioration of kidney function not otherwise explained

• U b2M >1 µg/min
• U IgG >250 mg/d

Clinical course should be considered in risk evaluation

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Membranous Nephropathy: what do the studies tell us?

GEMRITUX: RITUXIMAB + conservative vs conservative

- Rituximab more remission: 65% vs 43%
- 35% failure in RTX
- 43% remission rate in placebo group

MENTOR: RITUXIMAB vs CsA

- Initial response comparable: 60% remission rate
- More persistent remission with Rituximab

MN: what do the studies tell us?

Bergamo RTXcohort/GEMRITUX/MENTOR:

- Rituximab is ineffective in 35% of patients

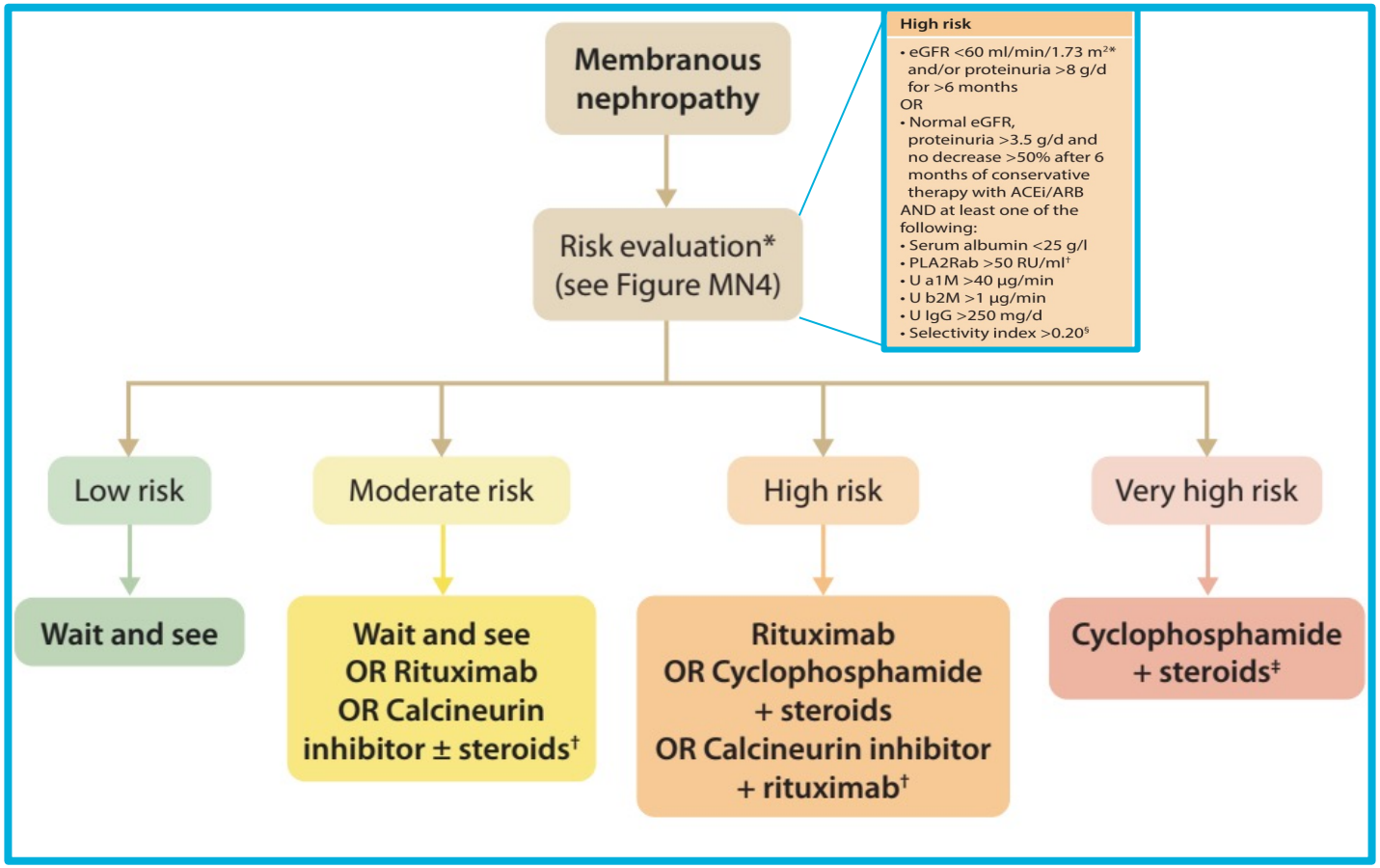
STARMEN: TAC+1g RTX vs cyclophosphamide + steroids

- Cyclophosphamide more remissions than TAC/RTX
- Rituximab prevents relapse after TAC withdrawal

Ri-Ciclo: Rituximab vs cyclophosphamide + steroids

- Rituximab not inferior to cyclophosphamide
- Underpowered study, moderate risk patients, subgroup analysis suggests superiority of cyclophosphamide in high risk patients

Novel emerging treatment guidelines



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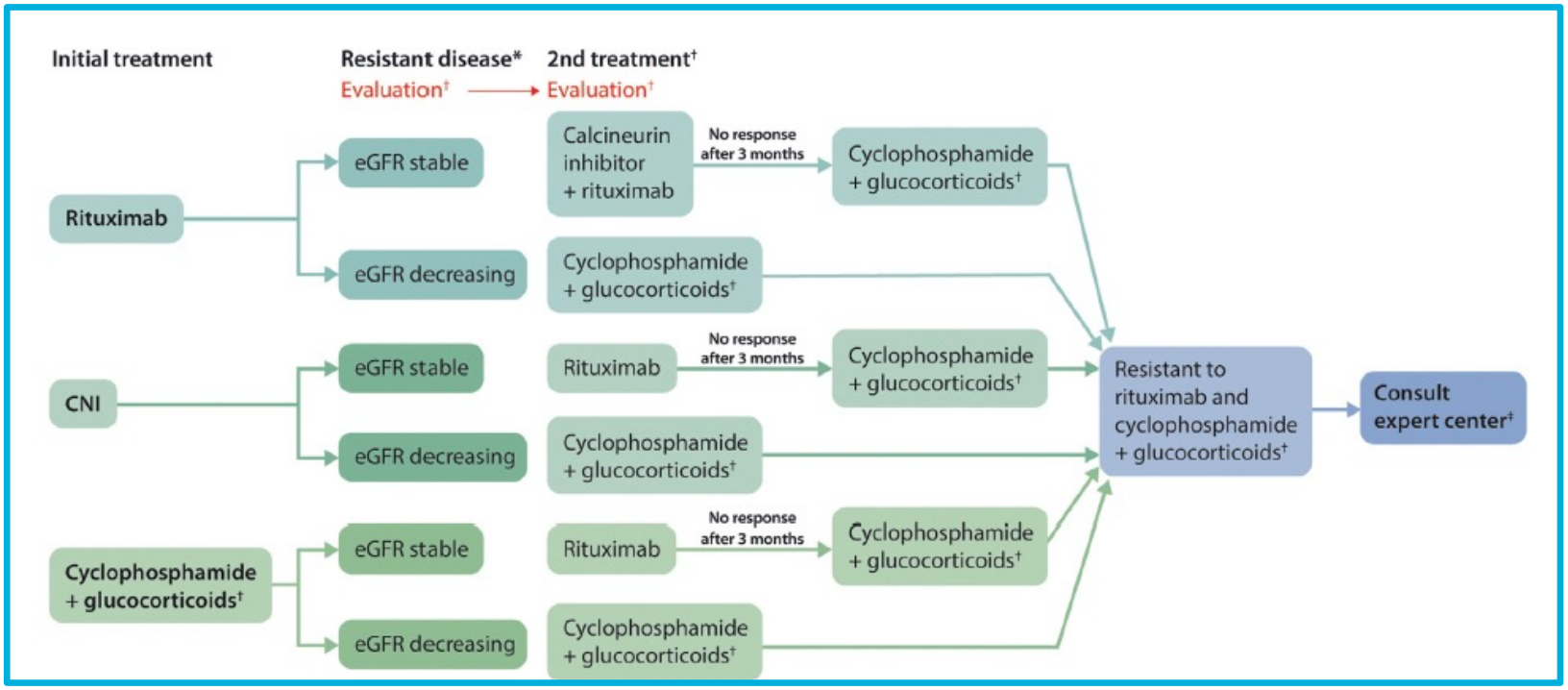
Not all patients respond to current therapies



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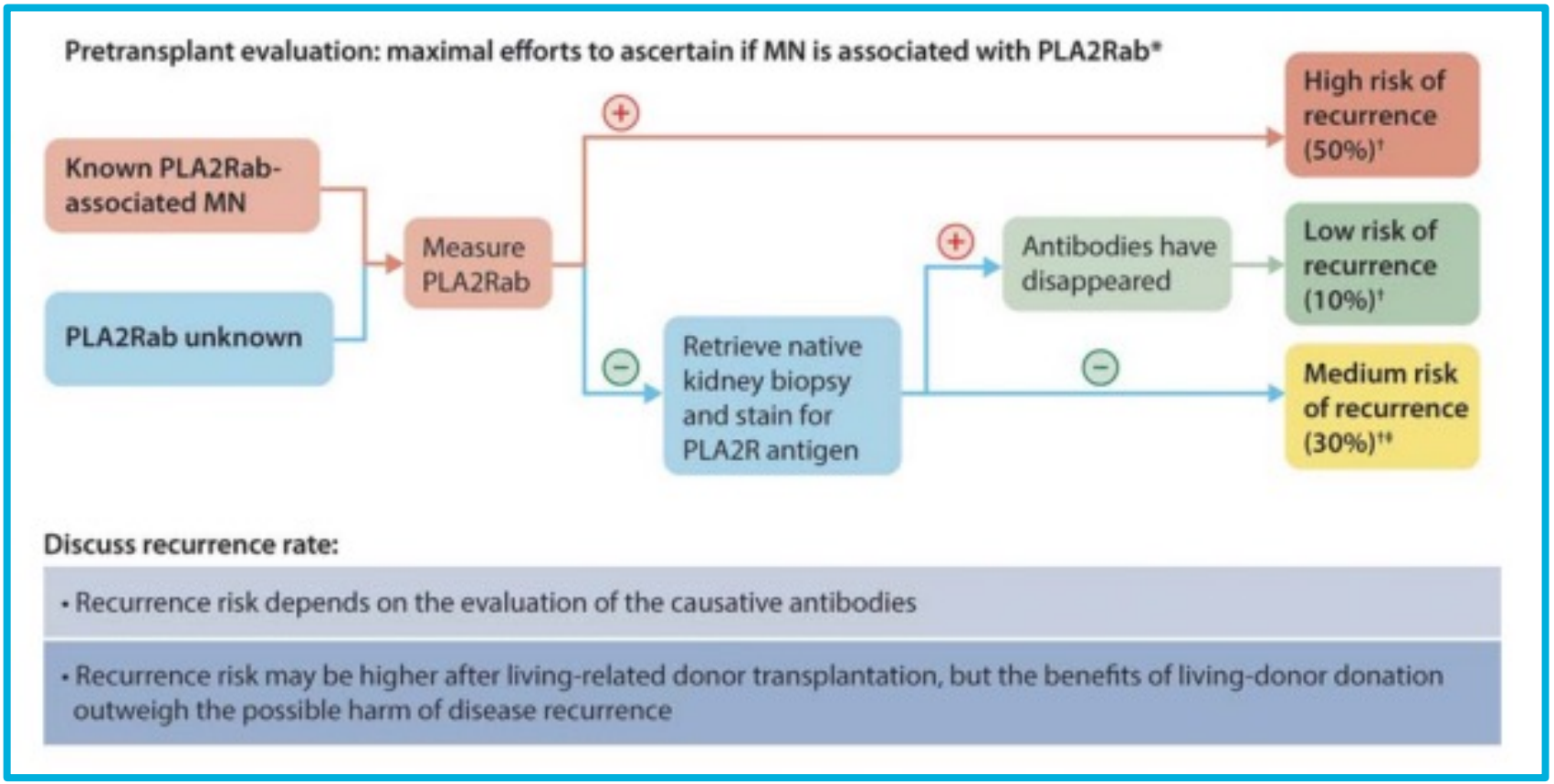
Kidney transplantation in MN



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Beyond the guideline

MN PLA2Rab: what have we learned?

- ❑ We can measure PLA2Rab in serum and detect PLA2Rag in kidney biopsy

- ❑ Sensitivity: biopsy > WB > IFT > ELISA
  - *ELISA provides quantitative levels*

- ❑ PLA2Rab can be absent in PLA2R-associated MN:
  - *"Kidney as a sink" → repeat measurement after 3-6M*
  - *"immunological remission" → precedes proteinuria remission*

- ❑ Weak correlation PLA2Rab levels vs Proteinuria

- ❑ Should we measure IgG4 or total IgG?

MN PLA2Rab: what have we learned?

- ❑ Do we need a kidney biopsy to diagnose membranous nephropathy? → NO
- ❑ Can PLA2Rab levels be used as prognostic biomarker?
- ❑ Can PLA2Rab levels be used as predictive biomarker?
- ❑ Can PLA2Rab levels guide therapy?

MN: useful biomarker? FDA definition

Prognostic Biomarker

Created: December 22, 2016.

Definition

A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.

→ Natural course, untreated

Predictive Biomarker

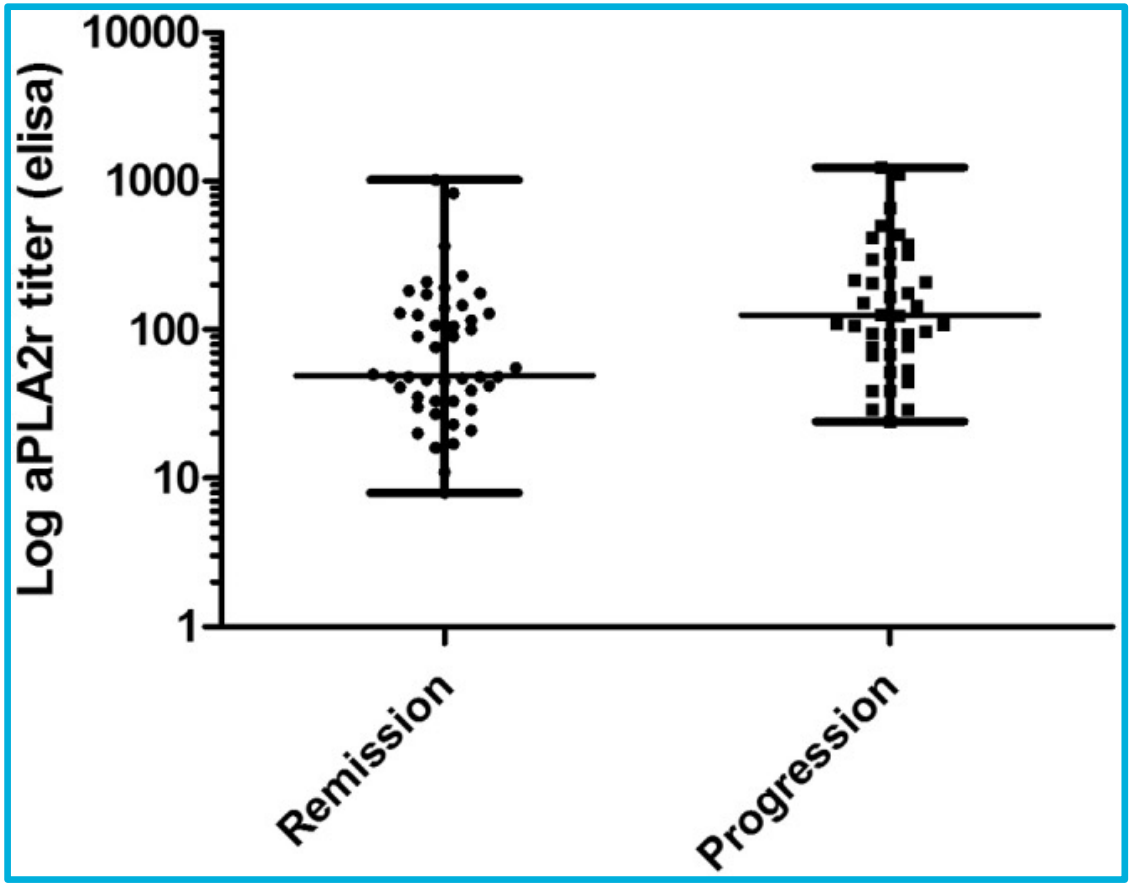
Created: December 22, 2016.

Definition

A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.

→ Response to therapy

PLA2Rab as prognostic biomarker



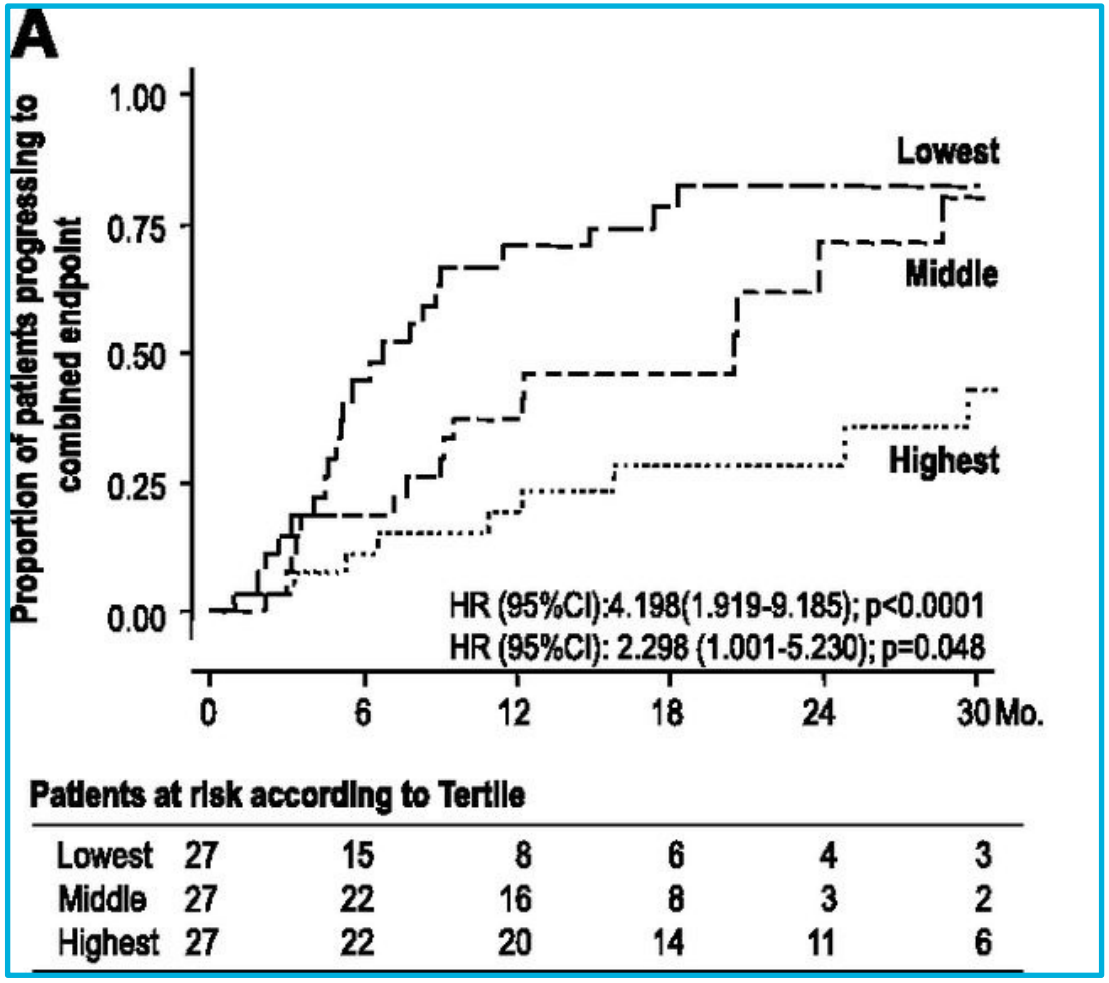
PLA2Rab levels:

Limited prognostic value

aPLA2R1ab levels at baseline of patients with normal serum creatinine with progression (*n* = 39) and or spontaneous remission (*n* = 46).

Logt van de AE, Anti-PLA2R1 Antibodies as Prognostic Biomarker in Membranous Nephropathy. Kidney Int Rep. 2021 Apr 22;6(6):1677-1686.

PLA2R antibodies as predictive biomarker



Predictive =

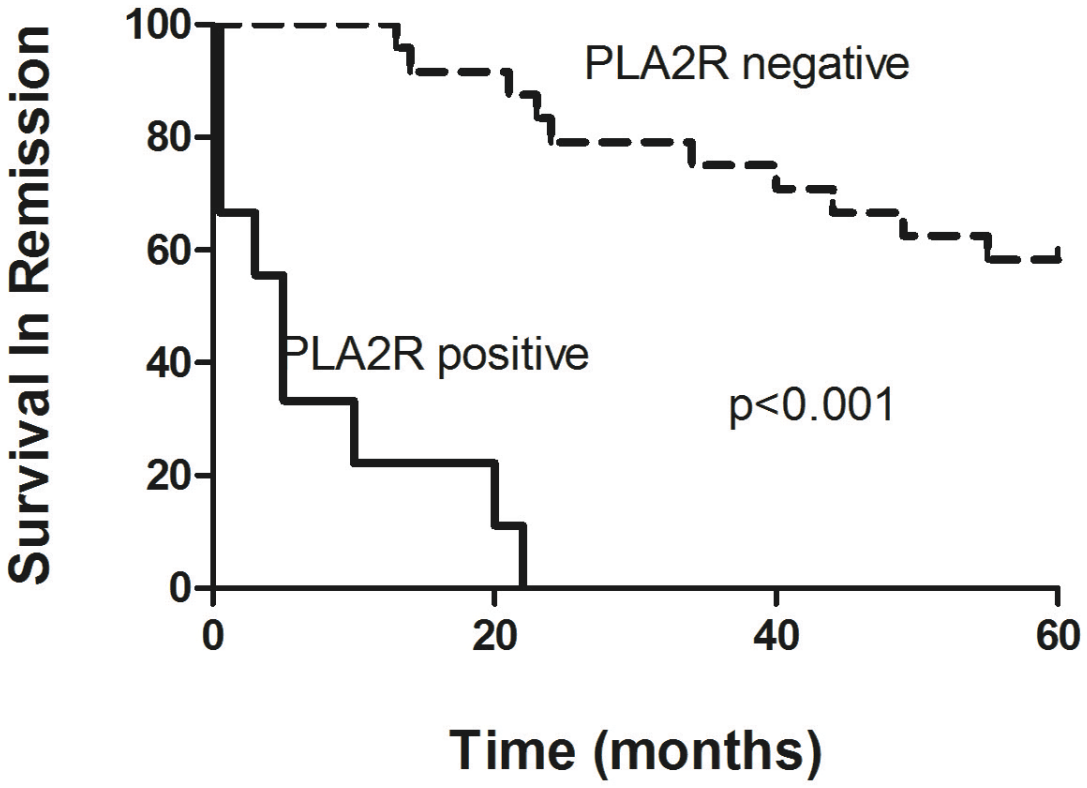
Response to therapy

(Rituximab)

(Confirmed in MENTOR)

Piero Ruggenenti et al. JASN 2015;26:2545-2558

Association of Anti-PLA2R Antibodies with Outcomes after Immuno- suppressive Therapy in iMN.



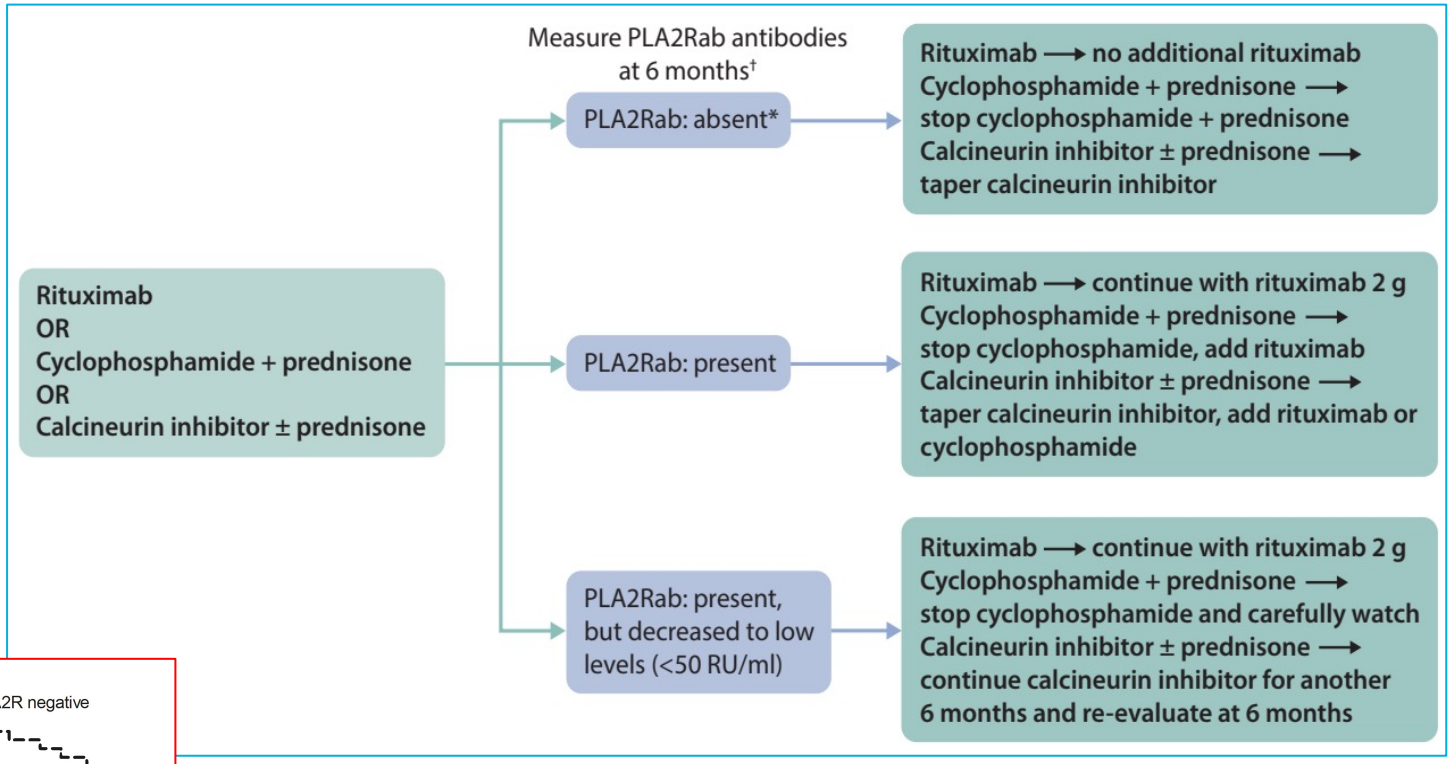
We should aim for immunological remission

Bech et al CJASN 2014

MN PLA2Rab: what have we learned?

- ❑ Do we need a kidney biopsy to diagnose membranous nephropathy?
- ❑ Can PLA2Rab levels be used as prognostic biomarker?
- ❑ Can PLA2Rab levels be used as predictive biomarker?
- ❑ Can PLA2Rab levels guide therapy?

PLA2Rab guidance of therapy



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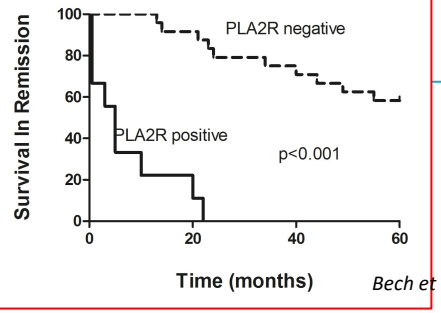


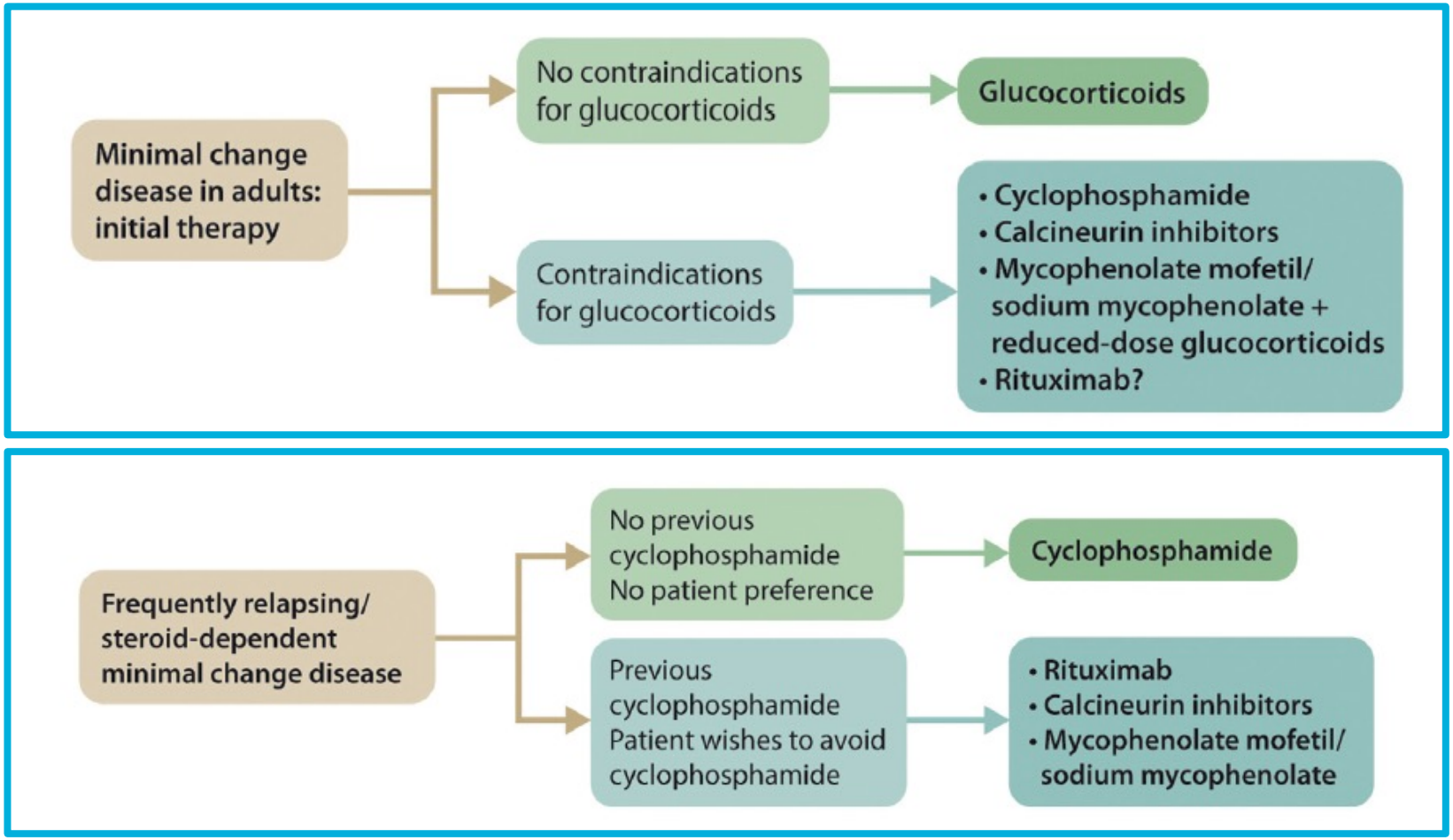
Bech et al CJASN 2014

MN: new antigens

- 2009: PLA_2R: M-type phospholipase A_2 receptor
- 2014: THSD7A:Thrombospondin type 1 Domain 7A
- 2019: EXT1/2: exostosin1/2
- 2020: NELL-1:Neural epidermal growth factor like 1 protein
- 2020: SEMA3B: Semaphorin 3B
- 2021: PCDH7:protocadherin 7
- 2021: HTRA1: high temperature recombinant protein A1
- 2021: NCAM1: neutral cell adhesion molecule1
- 2021: NTNG1: Netrin G1 (abstract ASN2021)
- 2021: CTN1: Contactin 1 (abstract ASN 2021)

Disclosure: validation cohort lacking; clinical data not always available; few patients; many IgG1!; many not present on podocytes! Many associated with underlying disease

Minimal change disease in adults: treatment



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FSGS in adults: diagnosis and definition

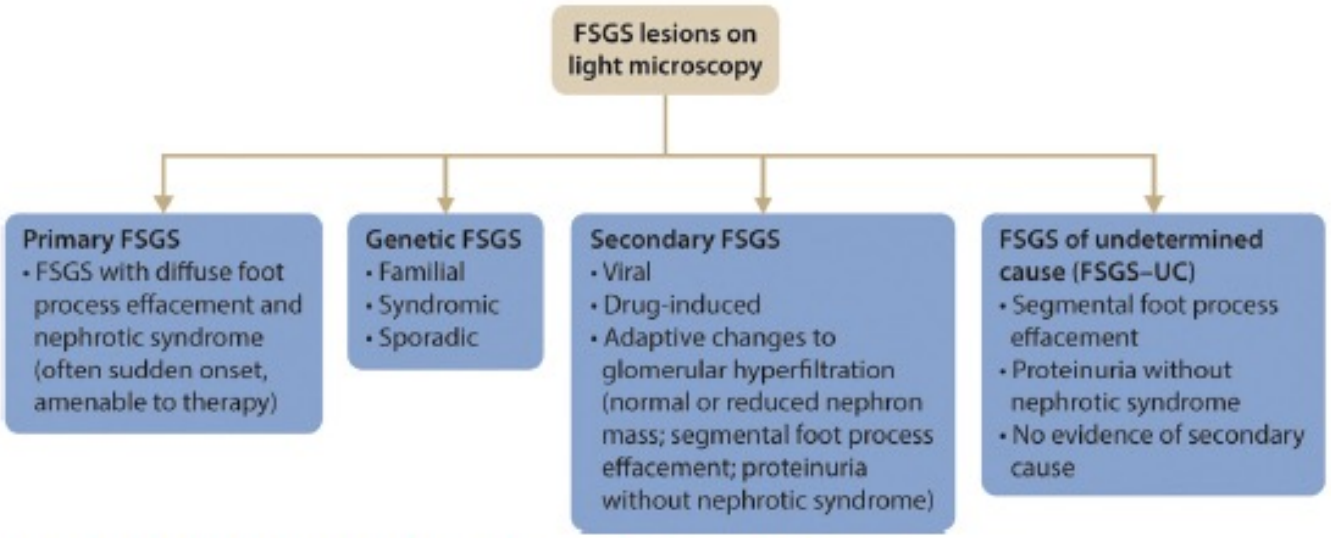

Figure 49 | Proposed classification of FSGS. FSGS, focal segmental glomerulosclerosis.

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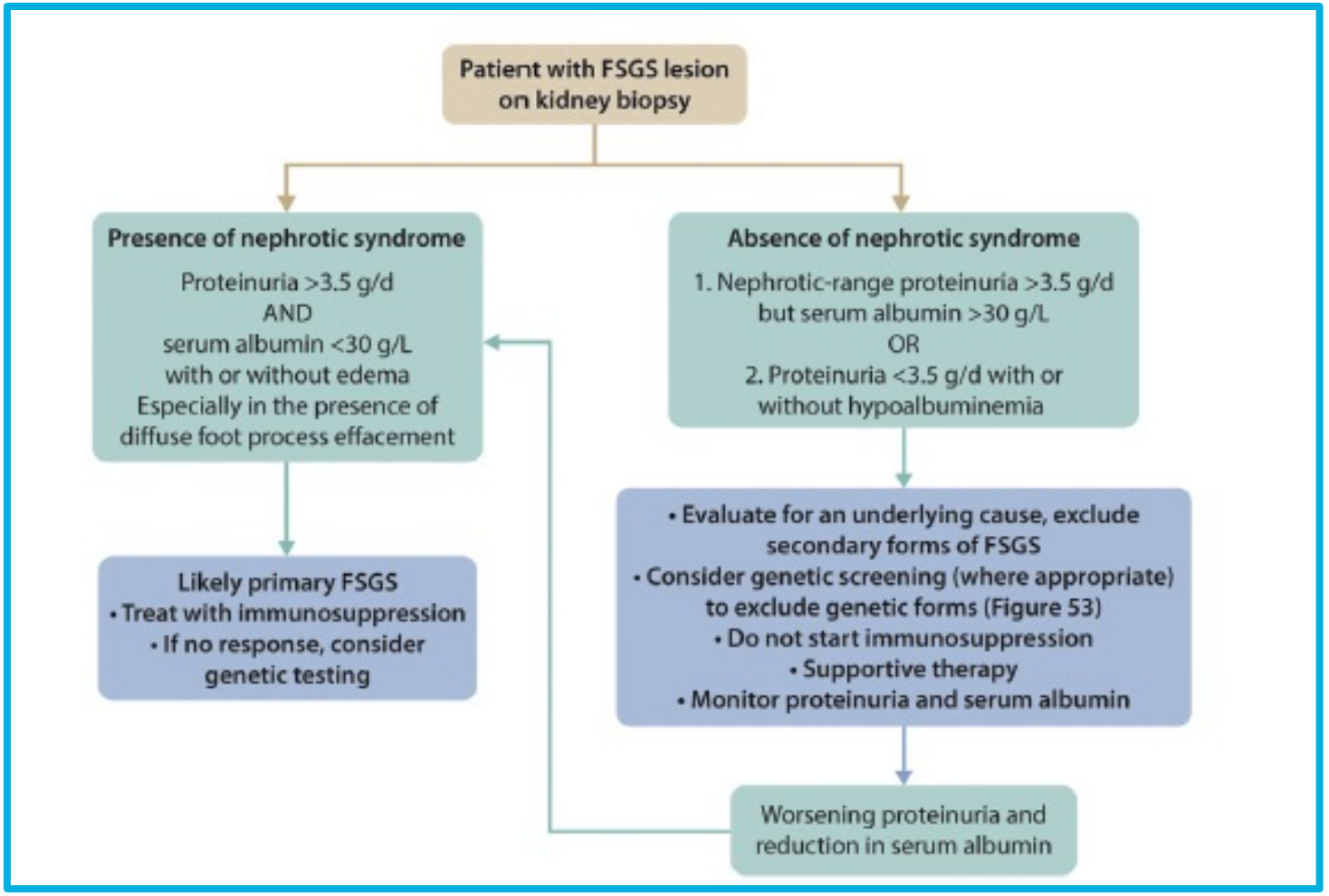
FSGS in adults: management



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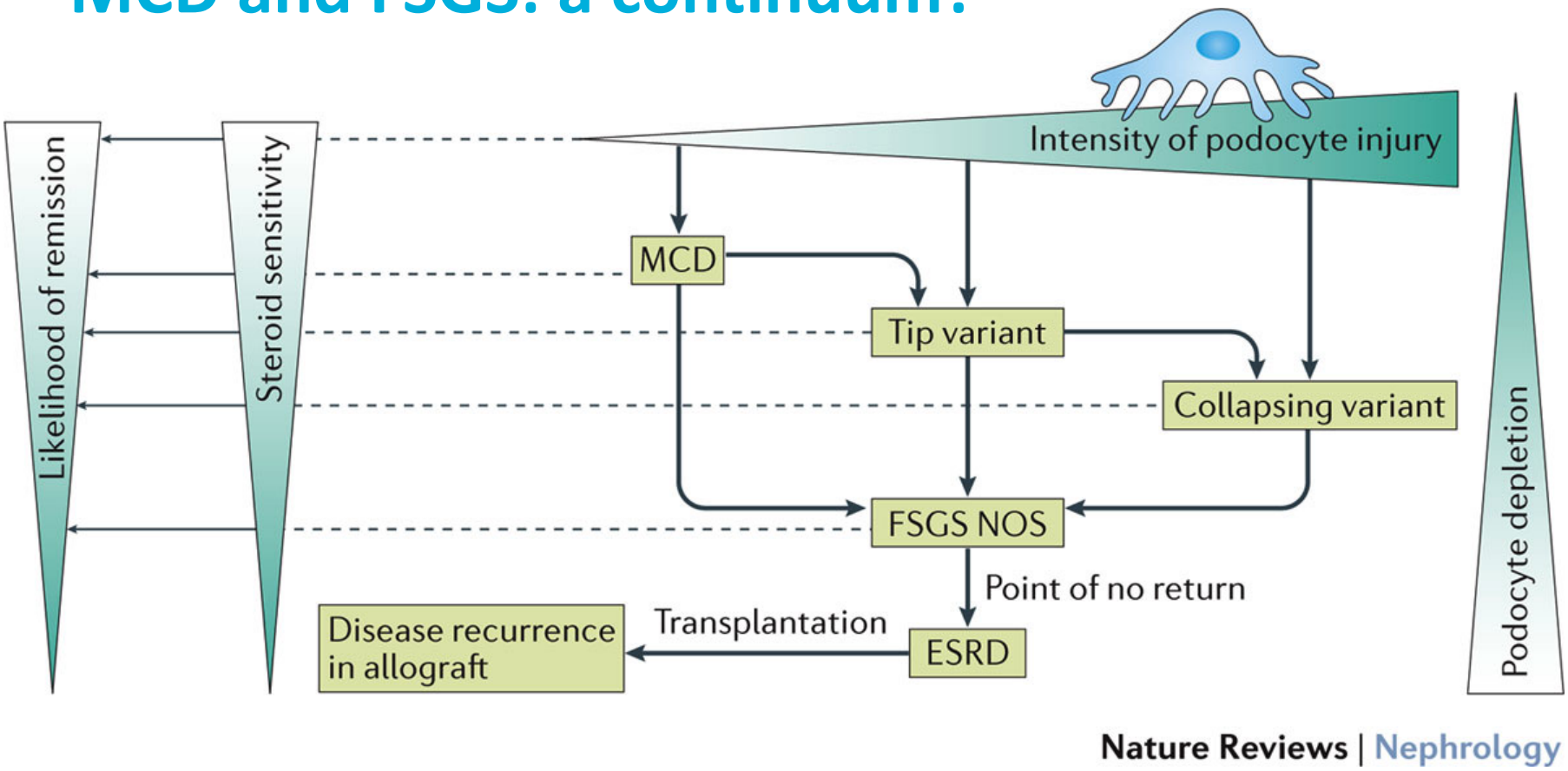
Beyond the guideline

MCD and pFSGS: a disease continuüm?

pFSGS: remissions take time to occur

MCD and FSGS: a continuum?



Maas et al. Nat Rev Nephol 2016

Treatment of FSGS: it takes time

Retrospective study

Patients with pFSGS (clinical)

No CR after 8 weeks

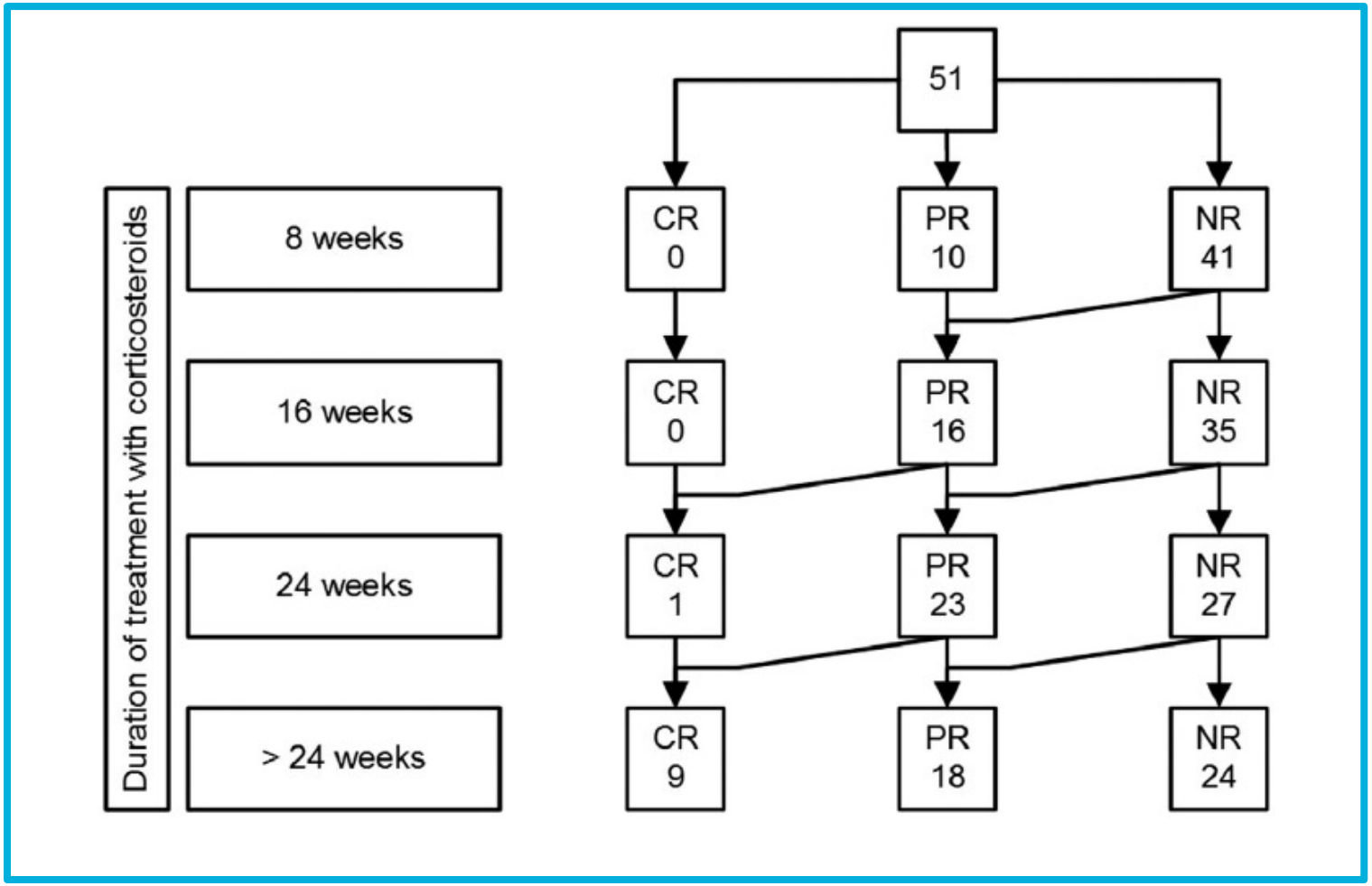
(NB only 2/53 patients treated with prednisone had CR after 8 weeks)

Table 1. Patient characteristics at time of kidney biopsy

Characteristics	Cohort
Total (*n*)	51
Age (yr)	46.7 (31.8–58.3)
Gender (male/female)	31/20
BMI (kg/m^2)	26.0 (24.3–29.5)
Hypertension	47 (94)
AKI	11 (22)
Serum creatinine (μmol/l)	94.0 (77.3–141.0)
Serum creatinine no AKI	89.0 (73.0–102.5)
Serum creatinine AKI	175.5 (106.3–212.3)
eGFR[a] (ml/min per 1.73 m^2)	77 (52–98)
eGFR no AKI	85 (62–101)
eGFR AKI	38 (25–54)
Serum albumin (g/l)	20.9 ± 6.1
Urinary protein excretion (g/24 h or g/10 mmol creatinine)	8.7 (6.3–12.7)
Histologic features	
Interval between onset of symptoms and biopsy (d)	112 (34–144)
Complete podocyte foot process effacement at EM[b]	27 (93)
Pathologic FSGS variant	
NOS	25 (49)
Tip	20 (39)
Collapsing	2 (4)
Cellular	1 (2)
Perihillar	0 (0)
Not defined	3 (6)

Rood I et al. Kidney International Reports 2022;7:87-98

Treatment of FSGS: it takes time



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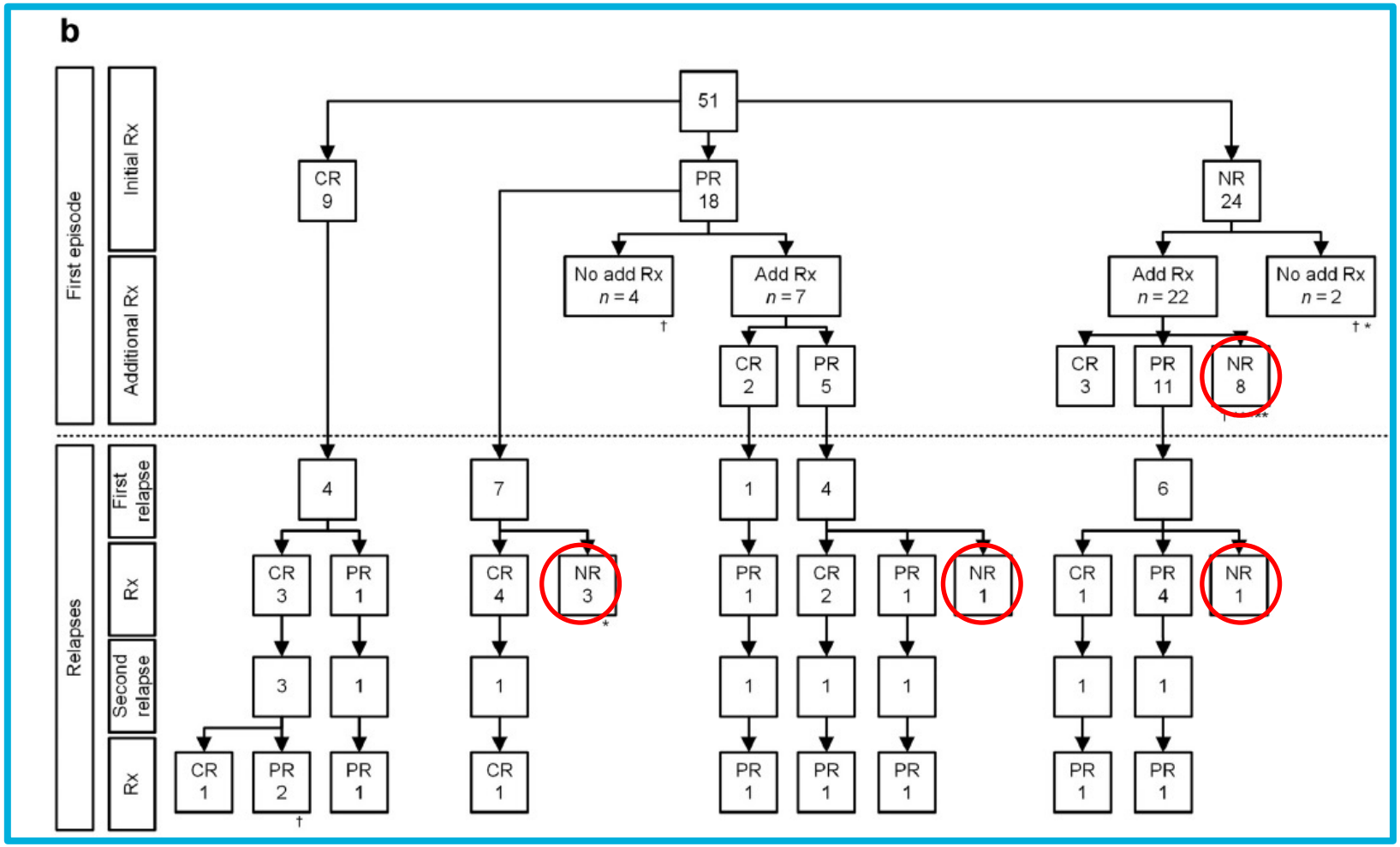
Treatment of FSGS: it takes time



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Treatment of FSGS: define non-responders

Change in proteinuria after 8 weeks may help to identify responders

Note: need validation

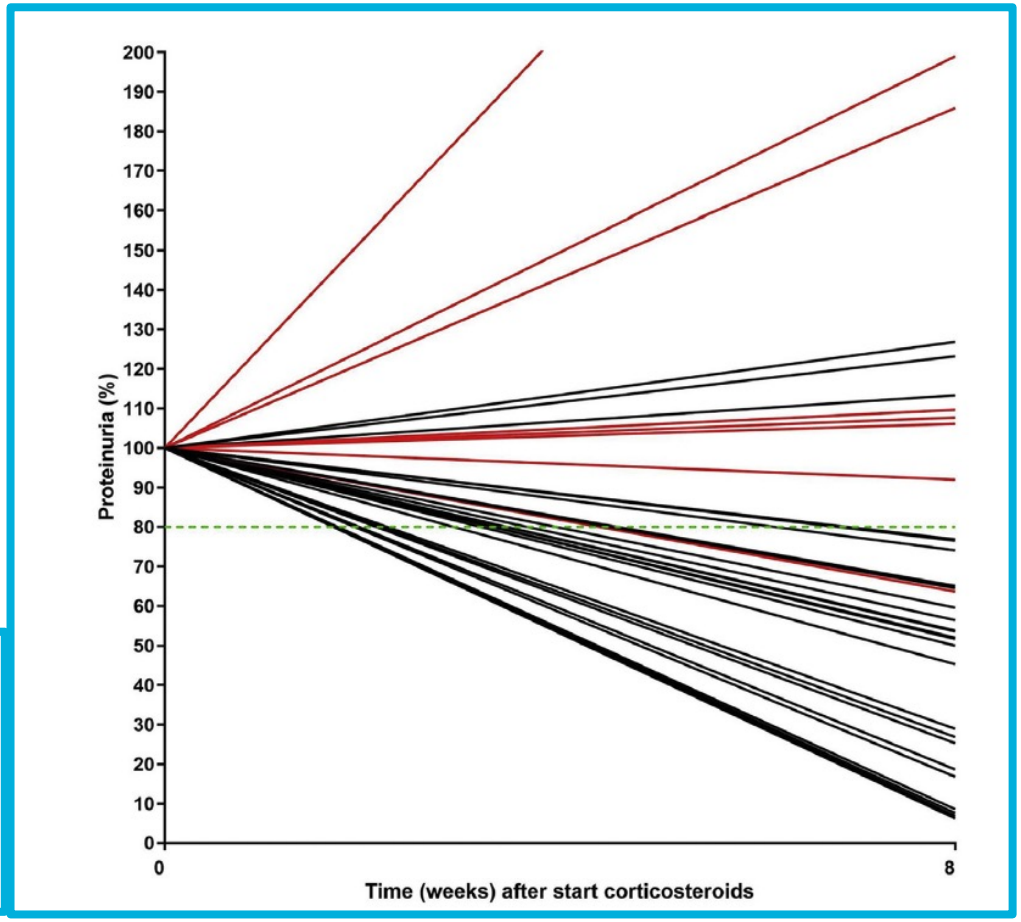
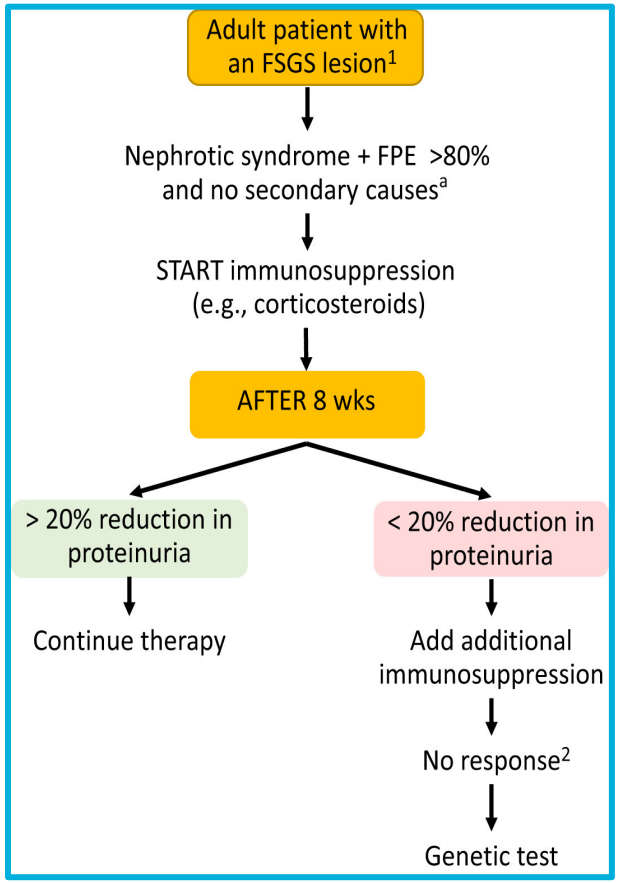


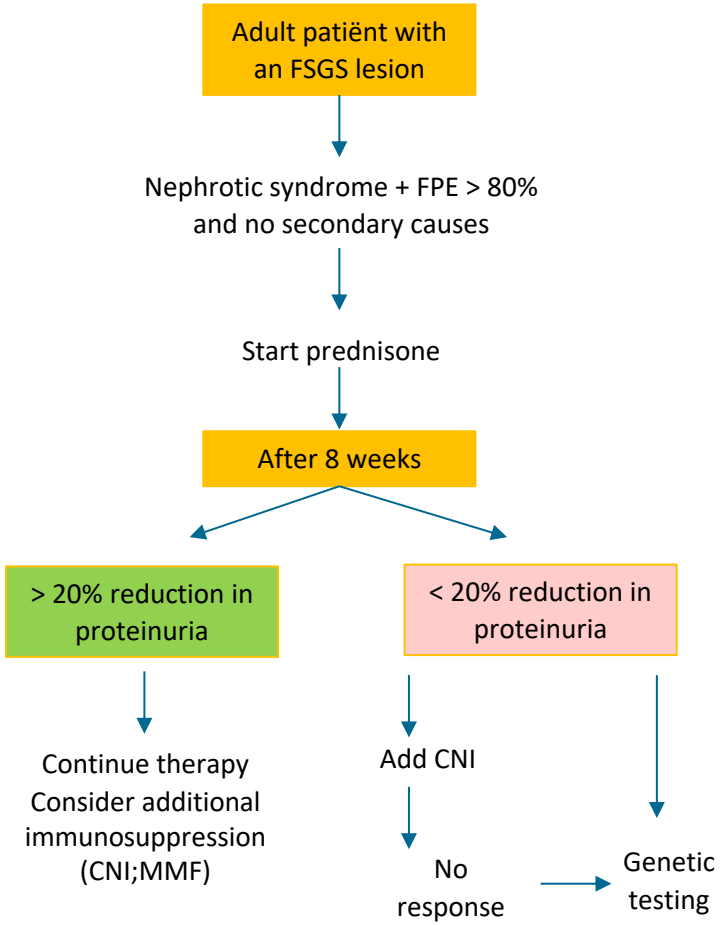
Figure 4. Proteinuria at start of therapy and 8 weeks. Red lines: primary nonresponders; black lines: responders; green line: cutoff of 80%. Missing data: $n = 15$ (no data at start of corticosteroids or at week 8). Patients who were not evaluable ($n = 2$) were excluded.

	Primary nonresponders (*n*)	Responders (*n*)	Total
<20% decrease proteinuria	7	3	10
>20% decrease proteinuria	1	23	24
Total	8	26	34

Rood I et al. Kidney International Reports 2022;7:87-98

Treatment of FSGS: an algorithm?





Glassock and Fervenza. Kidney International Reports 2022;7:9-12

NEXT WEBINARS

15/02/22

KDIGO Guideline on Immune GP II,
Dario Roccatello (Torino, Italy)

22/02/22

The genetics of human renal agenesis and renal dysplasia,
Adrian Woolf (Manchester, GB)

22/03/22

Mendelian and non-mendelian inheritance,
Kálmán Tory (Budapest, Hungary)

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european society for paediatric nephrology

WGIKD Working Group on Inherited Kidney Disorders

IPNA

QUESTIONS

FSGS in adults: secondary and genetic

Secondary to alterations of glomerular epithelial cells	
Viral infections	HIV (established) CMV (probably) Parvovirus B19, EBV, HCV (possibly) Hemophagocytic syndrome (possibly) SARS-COV-2 (with *APOL1* risk genotype)
Drug-induced	Direct-acting antiviral therapy mTOR inhibitors, CNIs Anthracyclines Heroin (adulterants) Lithium Interferon Anabolic steroids NSAIDs
Secondary to adaptive changes with glomerular hypertension	
Reduced nephron number	Reflux nephropathy Renal dysplasia Oligomeganephronia Sickle cell disease Age-related FSGS
Normal nephron number	Obesity-related glomerulopathy Primary glomerular diseases Systemic conditions, e.g. diabetic nephropathy, hypertensive nephrosclerosis

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FSGS in adults: secondary and genetic

Genetic forms of FSGS	
Genetic mutations of podocyte and glomerular basement membrane proteins	• Familial • Sporadic • Syndromic

Considerations for genetic testing in adults with FSGS

- When there is a strong family history and/or clinical features suggestive of a syndromal disease
- Aiding in diagnosis, especially if the clinical features are not representative of a particular disease phenotype
- Limiting immunosuppression exposure, especially in situations where patients appear to be resistant to treatment
- Determining the risk of recurrent disease in kidney transplantation
- Allowing for risk assessment in living-related kidney donor candidate, or where there is a high suspicion for *APOL1* risk variants
- Aiding in prenatal diagnosis

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FSGS in adults: FSGS unknown cause

FSGS of undetermined cause (FSGS–UC)

- Segmental foot process effacement
- Proteinuria without nephrotic syndrome
- No evidence of secondary cause

KDIGO guidelines glomerular disease Kidney Int 2021;100:S1-S276

KDIGO guidelines (and beyond)

membranous nephropathy

MCD/FSGS

Em.prof.dr. Jack F Wetzels, nephrology

Radboudumc