Kumi Kidney

@KumiKidney

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Hello #MedTwitter #nephtwitter

We recently had an interesting case-based discussion in @ASPNeph pathology webinar about #membranousnephropathy @IPNA_pedneph

Let's start with a poll!

Which of these is true about Membranous Nephropathy (MN)?

Correct Answer: D

- MN rare in children <12y (~1-3%)
- Incidence ↑ in adolescents (18-22%)
- Incidence of MN appears to be ↑ worldwide

PMC4074564

Presentation in peds:

- Most common: proteinuria +/- microscopic hematuria
- Nephrotic syndrome: 40-75%
- Hypertension: <10%
- Thromboembolic events: <5%
- Gross hematuria noted in some patients

Differences between pediatric and adult membranous nephropathy (MN)

	Pediatric MN	Adult MN
Disease type/subtype:		
Proportion of primary nephrotic syndrome cases that are MN	< 5% (children) 5–20% (adolescents)	15–30%
MN that is primary ("idiopathic")	Minority	Majority
Proportion of primary MN that is PLA_2R-associated	45% (more common in adolescents)	70–80%
Demographic and clinical features:		
Male predominance	Variable	Yes
Full nephrotic syndrome	40–75%	75%
Microscopic hematuria	70–90% (can be macroscopic)	50%
Hypertension	< 10%	30%
Thromboembolic events	< 5%	10–20%
Spontaneous remission	Common	30%
Progressive renal impairment	< 25%	30–40%
Pathological features:		
Mesangial deposits	Up to 50%	30%
Segmental distribution of deposits	Occasional	Very rare

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Types of MN:

- Primary: Antibody (Ab) to a known podocyte antigen
- Idiopathic: no identified target antigen
- Secondary: due to illness/exposure (75% of peds cases)
- Alloimmune: Ab to foreign antigen

Table 1. Recognized causes of anti-PLA2R/THSD7A–negative secondary membranous nephropathy[a]

Cause	Examples
Infections (1,2,27,56,90)	[b]HBV, HCV, HIV, parasites (filariasis, schistosomiasis, malaria), leprosy, syphilis, hydatid disease, sarcoid
Malignancy (20% in patients >57, 4%<57) (1,2,14–18,55,58,66)	[b]Solid tumors (lung 26%, prostate 15%, hematologic [plasma cell dyscrasias, non-Hodgkin lymphoma, CLL] 14%, colon 11%), mesothelioma, melanoma, pheochromocytoma; some benign tumors
Autoimmune diseases (1,2,4,56–58,91)	[b]SLE (class V), thyroiditis, diabetes, rheumatoid arthritis, Sjogren syndrome, dermatomyositis, mixed connective tissue disease, ankylosing spondylitis, retroperitoneal fibrosis, renal allografts
	Anti-GBM disease, IgAN, ANCA-associated vasculitis
	IgG4 disease
	Membranous-like glomerulopathy with masked IgG κ deposits (90)
Alloimmune diseases (1,4,7,58,82)	Graft versus host disease, autologous stem cell transplants, [b]*de novo* MN in transplants/transplant glomerulopathy
Drugs/toxins (92)	[b]NSAIDs and cyclooxygenase-2 inhibitors, gold, d-penicillamine, bucillamine, captopril, probenecid, sulindac, anti-TNFα, thiola, trimetadione, tiopronin
	Mercury, lithium, hydrocarbons, formaldehyde, [b]environmental air pollution (China)
	Cationic BSA (infants)

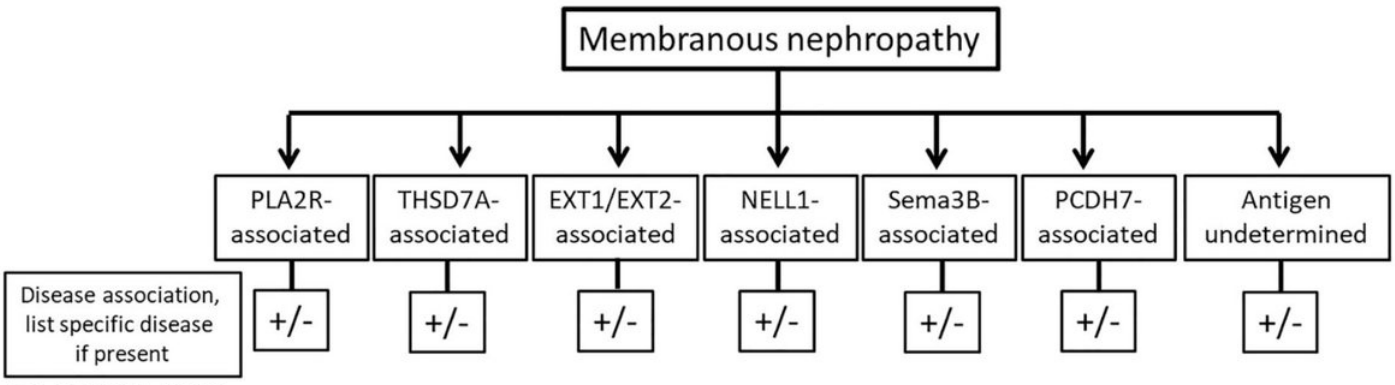
HBV, hepatitis B; HCV, hepatitis C; CLL, chronic lymphocytic leukemia; MN, membranous nephropathy; NSAIDs, non-steroidal anti-inflammatory drugs.
[a]Most of these associations are on the basis of multiple case reports or small series. Causative roles are implied but generally not proven.
[b]Common.

PMC5460716

Which of the following are identified antigens for primary MN?

Correct Answer: D

Although PLA2R was the first antigen discovered in 2009 followed by THSD7A in 2014 (these are the most common antigens), all the above antigens have now been identified with distinct disease entities causing MN



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PLA2R:

- Phospholipase A2 receptor (PLA2R) antibodies bind to antigens on podocytes
- Present in 70% of adults with primary MN
- 45-50% of pediatric patients with primary MN
- Does not seem to be associated with secondary MN

PMC2762083

What is the classic histological pattern seen in MN?

Correct Answer: C

Classic MN Histology:

- LM: thickened GBM (“cheerios” appearance)
- Silver Stain: Spike pattern along GBM
- IF: IgG & C3 staining along GBM
- EM: finely granular electron dense deposits on subepithelial GBM

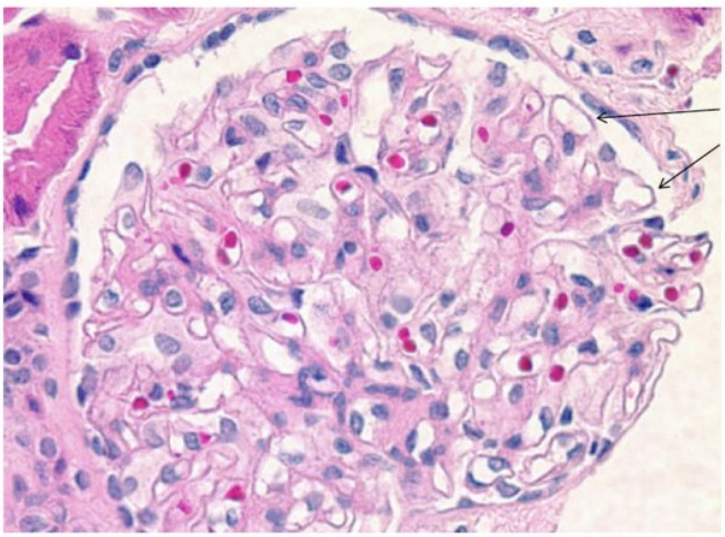

Fig. 1 Primary membranous nephropathy (MN) (hematoxylin and eosin; x200). Glomerular capillary walls are uniform with mild thickening (*arrows*)

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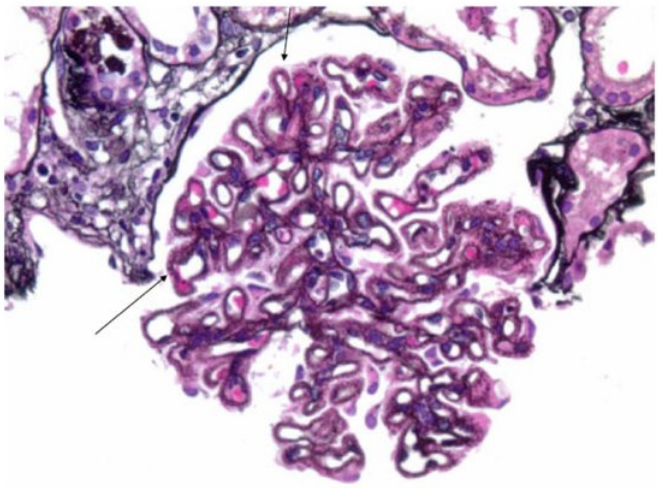

Fig. 2 Primary membranous nephropathy (MN) (periodic acid-methenamine silver-Jones stain; x400). Characteristic spike-like epimembranous projections of basement membrane material on capillary walls (*arrows*)

Natural History:

- No specific peds data
- In adults course is remitting/relapsing and:
  - ~1/3 spontaneously remit without treatment
  - ~1/3 persistent proteinuria with preserved kidney function
  - ~1/3 progress to ESKD

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Management:

Due to rarity of disease and favorable prognosis without treatment, there are no RCTs comparing treatments of MN in children.

Treatment:

- Varies based on severity
- Remission may occur spontaneously
- Can take months/years to achieve

Management cont:

- Asymptomatic subnephrotic proteinuria:
  - Non-immunosuppressants (ACEi or ARBs)
- Nephrotic Syndrome, worsening proteinuria or antibody levels:
  - Immunosuppression (Rituximab, Tacrolimus)

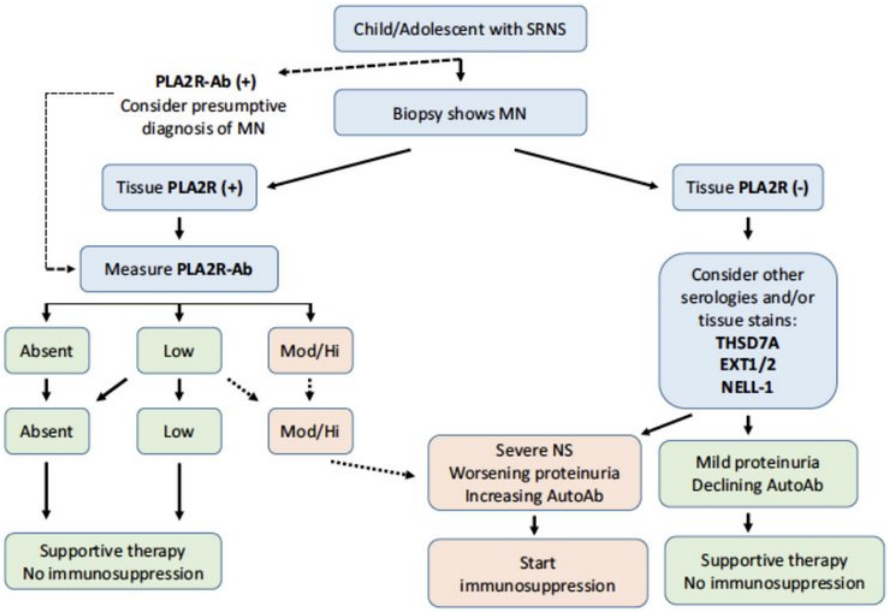

Fig. 2 Algorithm for diagnosis and treatment decisions in pediatric membranous nephropathy. In cases of steroid-resistant nephrotic syndrome (SRNS), a diagnosis of MN may be made either by biopsy (tissue PLA2R) or with serum anti-PLA2R positivity (PLA2R-Ab). If a patient is known to have PLA2R-associated MN by virtue of biopsy staining for PLA2R within the deposits, or by seropositivity, only those nephrotic patients with high or rising antibody titers require immunosuppression; if the antibody titers are decreasing, the patient can be followed with supportive, anti-proteinuric therapy. Patients who are PLA2R-negative on biopsy staining may have other antigen associations, such as THSD7A, exostosin (EXT1/2), or neural epidermal growth factor-like 1 protein (NELL-1) (see [58]). Patients with anti-THSD7A can be monitored as for anti-PLA2R. Treatment decisions in patients with non-PLA2R/THSD7A should be made on clinical grounds.

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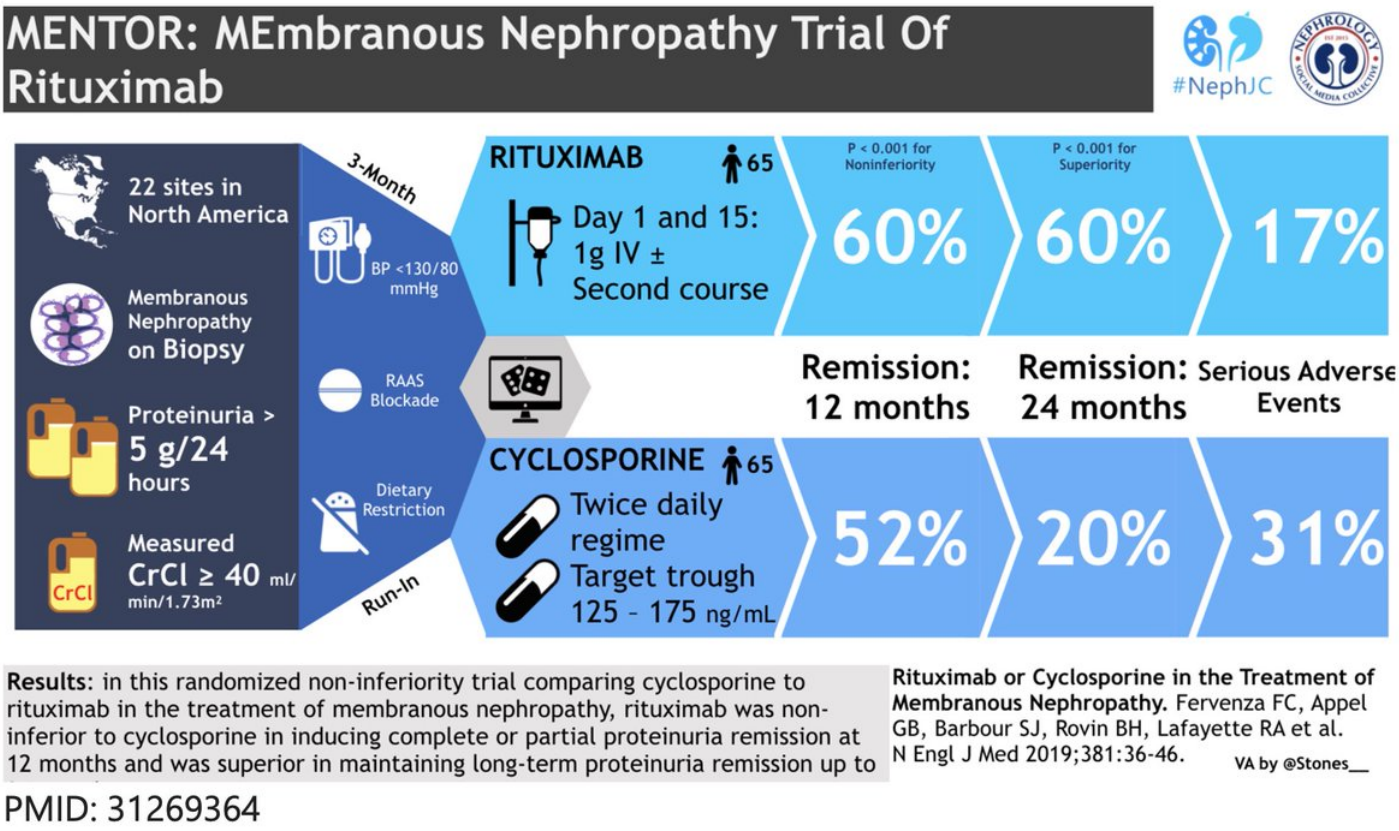
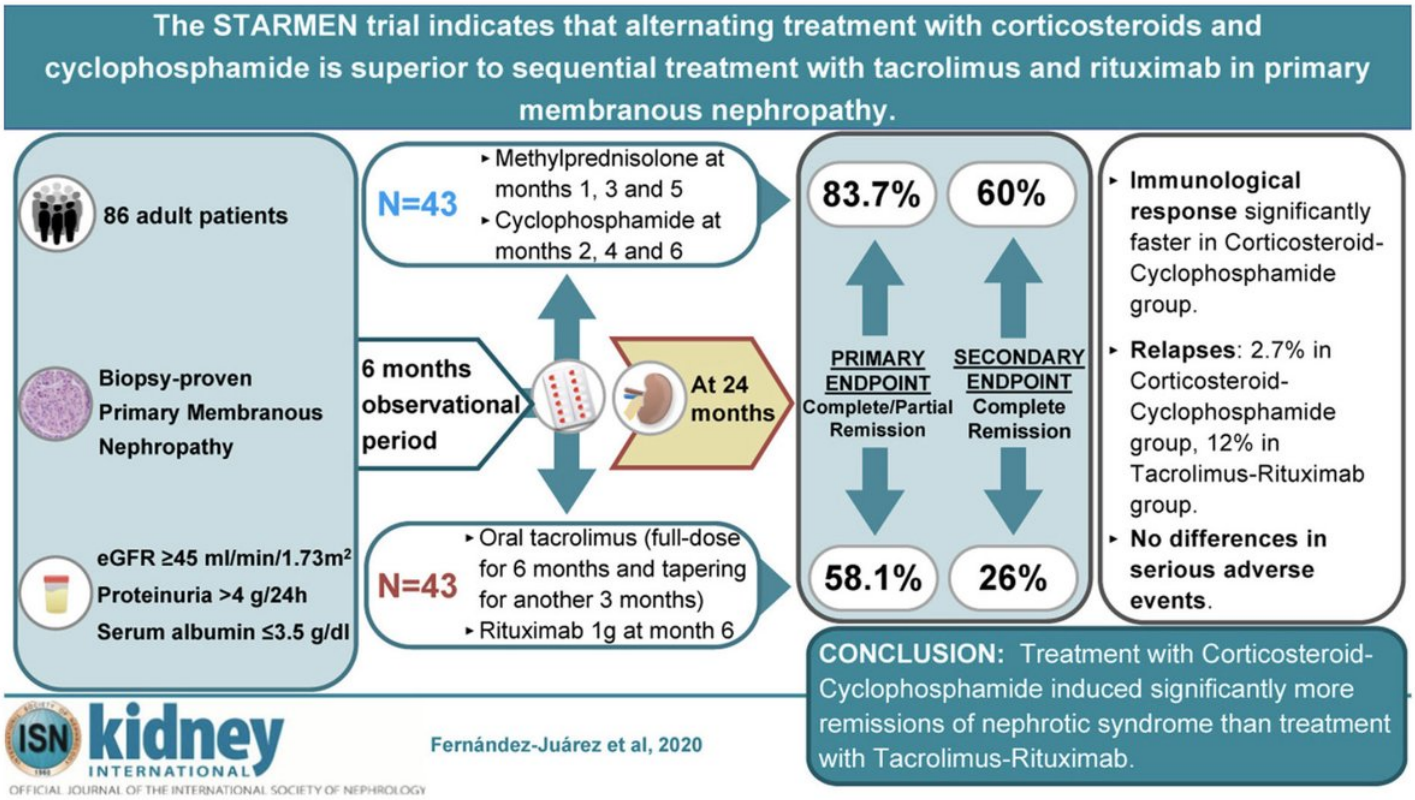
MENTOR Trial:

- Randomized controlled trial
- 130 adult patients with MN and proteinuria > 5g/day
- Rituximab (Ritux) vs. Cyclosporine
- Ritux superior in achieving complete or Partial remission at 2y (60% vs. 20%)



STARMEN Trial:

- Randomized open label controlled trial
- Adults with primary MN and persistent NS x 6months
- Steroid+CYC vs. Tacro+Ritux
- Complete remission higher with Steroid+CYC (60% vs 26%)



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Prognosis:

- Progression to ESKD in childhood is rare
- Spontaneous remission possible
- Younger children have better outcomes
- Primary diagnosis in 0.5 % of children with CKD and 0.4% on dialysis

https://www.naprtcs.org/system/files/2008_Annual_CKD_Report.pdf

Recurrence after transplant:

- Adult rates 7-45%
- anti-PLA2R Ab at the time of transplant ↑ risk
- No peds-specific data

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Now you are mem-BRAINY-ous about membranous nephropathy!

For a case-based clinical discussion with pathology expert login to @ASPNeph website, May webinar. Answer questions to get #MOC2credits #Membereducation #ASPNFOAMgroup

Thanks to @drM_sudha @RoshanPGeorgeMD @priti899

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