Management and treatment of glomerular diseases KDIGO Controversies Conference Part 1

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GENERAL PRINCIPLES IN THE MANAGEMENT OF GLOMERULAR DISEASE

Kidney Biopsy :

Not nessesary for treatment in

- Childhood steroid-sensitive nephrotic syndrome
- Normal kidney function, acute onset of nephrotic syndrome,& positive for anti- PLA2R

In other condition critical for assessing the :

- Degree of histologic activity
- Chronicity
- Identify unexpected features (interstitial nephritis, AKI,crescents)

kidney biopsy

- should be interpreted in the context of ethnicity, age, and hypertension
- variations between individuals in the molecular pathways driving disease progression despite similar histopathology
- need for electron microscopy for every biopsy remains controversial
  - critical for differentiate between immunologically mediated and adaptive FSGS

Assessment of kidney function

Proteinuria

- ACR vs 24 h urine
- Serum Albumin

GFR assessments

- gold standard : inulin or isotopic clearance
- CKD-EPI (not been validated in specific glomerular diseases)
- Errors related to collection and laboratory
- can induce up to 50% of errors in GFR

Assessment of kidney function

Hematuria :

- Disappearance of hematuria, however, associated with complete clinical remission
- Can be important in assessing the activity of diseases such as IgAN & ANCA associated vasculitis

Futility

- Low eGFR, often < 30 ml/min per 1.73 m2
- Biopsy that shows a high degree of irreversible chronic changes
- Rate of change in kidney function vs cross-sectional measurement of eGFR
- Age and overall wellness should be considered
- Patient engagement in trial may become more relevant as low-risk treatments become available

Other determinants of progression of kidney disease

well-established progression factors :

- Persistent proteinuria
- Poorly controlled hypertension
- Diabetes
- Smoking
- Cardiovascular disease

New evidence :

- Birth weight
- sleep hygiene.
- Obesity
- Sex

Table 1 | Established and emerging risk factors for progression of kidney disease

Risk factors for progressive loss of GFR	Emerging risk factors for progressive loss of GFR
• Persistent proteinuria	• Prematurity (low birth weight) and other reasons for low nephron number[29]
• Poorly controlled hypertension	• Low-sleep duration and other related disorders (e.g., restless legs syndrome, sleep apnea)[30]
• Poorly controlled diabetes mellitus	• Obesity[31–33]
• Smoking	• Gender?[34]
• Widespread cardiovascular disease	
• Use of nephrotoxic drugs	

Genetic testing in kidney disease

- Confirming clinical diagnoses
- Establishing inheritance patterns
- Differentiating heterogeneous disorders
- Determining appropriate treatment
- Decisions about family planning
- Determining the cause of unexplained familial kidney disorders
- Identifying new risk factors for susceptibility and progression

Management of complications

Hypertension

- BP target of 125/75 mm Hg in the GN patient with proteinuria >1 g/d

Sodium intake

- lower BP
- Enhance the antiproteinuric effects of renin–RAAS blockers
- Recommends limiting dietary sodium to <1500 mg/d (65 mmol/d)

Management of complications

Proteinuria reduction

- The main approach is through RAS blockade

dual therapy and/or in combination with an aldosterone antagonist

- Hyperkalemia and acute kidney injury outweighed benefits
- Careful monitoring, combination therapy can be safe
- Benefit for dual RAS blockade in GN with high-grade proteinuria is not clear
- Aldosterone blockade reduces cardiovascular mortality in CHF & Reduces albuminuria
- Absolute risk-benefit ratio for aldosterone blockade in GN remains unclear

Management of complications

SGLT2 inhibitors : a new proteinuria reduction strategy

- Recent study, short-term treatment with dapagliflozin
- Did not modify renal hemodynamic function or attenuate proteinuria in nondiabetic humans with FSGS, possiblybecause of downregulation of renal SGLT2 expression in FSGS
- Several large studies are currently investigating SGLT2 inhibitors in nondiabetic CKD

Management of complications

Hyperlipidemia

- Traditionally statins
- Target values may not be achieved, especially in the new era of very low target LDL levels.

Novel powerful agents :

- Proprotein convertase subtilisin/kexin type 9 inhibitors
- evolocumab, alirocumab
- Need to be studied in the GN population
- In contrast to cardiovascular benefits of statins, renal benefits are not well established

Management of complications

Hypercoagulability :

- Decision aids are available online particularly for patients with membranous nephropathy (www.med.unc.edu/gntools)
- Non-vitamin-K antagonist oral anticoagulants can be safely used has only been demonstrated above an eGFR of 30 ml/min per 1.73 m

Prophylactic Anticoagulation in Patients with Membranous Nephropathy

Prophylactic Anticoagulation in Patients with Membranous Nephropathy:

A Decision Analysis

Please enter below the corresponding characteristics of your patient

Age (in Years) [ ]

Sex ○ Male ○ Female

Race ○ African American ○ Non-African American

Serum Creatinine (in mg/dl): [ ]

Serum BUN (in mg/dl): [ ]

Serum Albumin (in g/dl): [ ]

Hemoglobin Level (in g/dl)? [ ]

Any History of Hemorrhage? ○ Yes ○ No

Diagnosis of Hypertension? ○ Yes ○ No

Is your Patient on Dialysis? ○ Yes ○ No

What benefit to risk ratio do you consider acceptable
(number of VTE prevented for 1 major hemorrhage incurred)?
◉ 2:1 ○ 5:1 ○ 10:1

Welcome to GNTools.com

A tool to decide about prophylactic anticoagulation for membranous nephropathy

Our tool is based on a decision analysis weighing the benefits (thrombosis prevention) and risks (major bleed) of prophylactic warfarin anticoagulation.* It is specific for patients with membranous nephropathy with no other risk factors for clot.

*Personalized prophylactic anticoagulation analysis in patients with membranous nephropathy, Kidney International 2013

Management of complications

Risk of infection

- Antimicrobial prophylaxis is needed as per regional practice
- Encapsulated organisms in treatment with the complement inhibitor eculizumab (meningococcal vaccination , multicomponent serogroup B vaccine,at least 2 weeks before treatment)
- Careful evaluation for endemic infections (TB, HBV, and parasites based on geographic origins)

IgA NEPHROPATHY

(1) Mucosal infection primes naive B cells → IgA Ab-secreting cells (ASCs) through (T-cell–dependent &independent [TLR])

(2) IgA ASCs mis-home to the systemic compartment

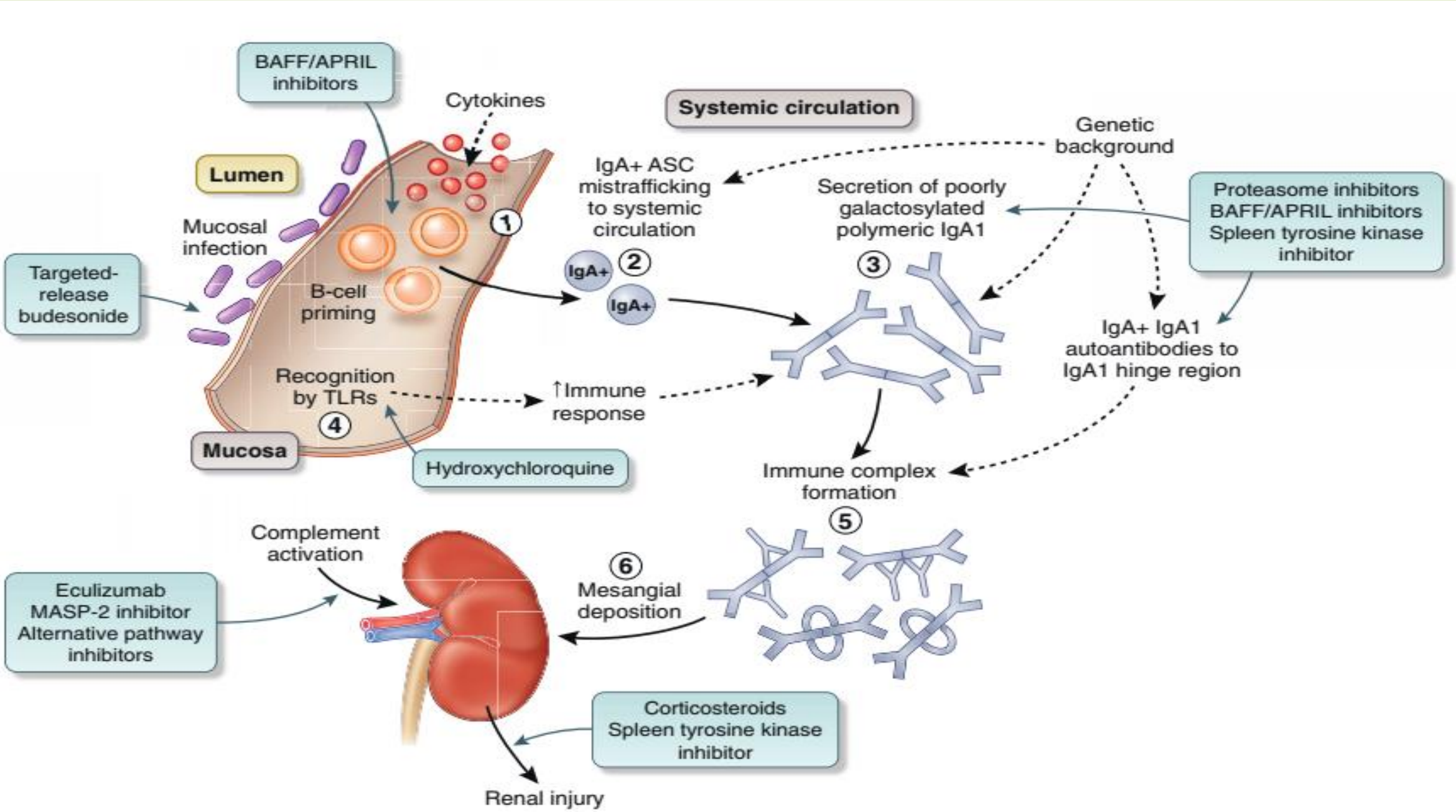
(3) Displaced in systemic sites and secrete normal "mucosal-type" (poorly galactosylated) IgA1 into the systemic circulation

(4) IgA1 secretion is augmented by TLR ligation from mucosal-derived pathogen-associated molecular patterns

(5) IgA1 immune complexes form in the systemic circulation (with IgG and IgA autoantibodies)

(6) IgA1 immune complexes deposit in the masangium . triggers downstream pathways, complement activation (mannose-binding lectin & other pathways → glomerular injury and tubulointerstitial scarring.

IgA NEPHROPATHY



Biomarkers and prediction of prognosis

1-MEST-C score

- Mesangial (M), endocapillary (E) hypercellularity, segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T), crescents (C)

  crescents in >25% were associated with poor renal outcome

2-proteinuria

3-BP

4-eGFR

5-Time-averaged microhematuria >5 RBC/hpf

6-Time-averaged proteinuria

Treatment

Controversy : Supportive Versus Immunosuppressive

Progressive IgA Nephropathy

- Steroids alone,or + sequential cyclophosphamide & azathioprine
- Immunosuppression transiently reduced proteinuria over 3 years but no impact on eGFR & only resulted in significant,infectious adverse events
- benefit of steroids similar in eGFR > or <50 ml/min/1.73 m2
- MMF in IgA nephropathy (New trials)
- Tonsillectomy → controversial

higher proteinuria reduction, no impact on eGFR over 12 m

Future studies

Trials of rituximab and tacrolimus → yielded negative results.

Current trials

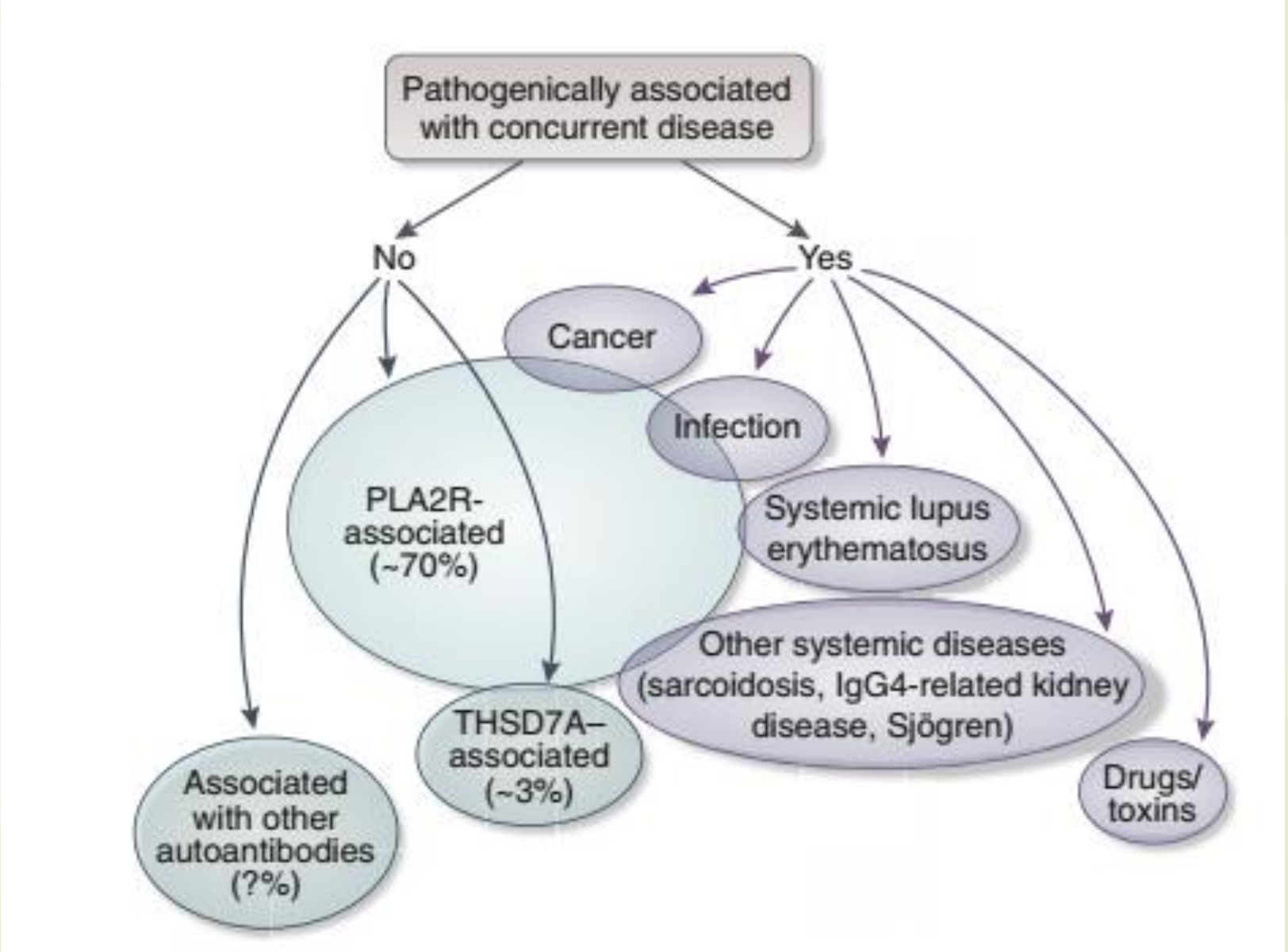
- spleen tyrosine kinase inhibitor fostamatinib
- B-cell activating factor
- B-cell proliferation inducing ligand blocker atacicept
- pilot study of the proteasome inhibitor bortezomib

MEMBRANOUS NEPHROPATHY

- Subepithelial glomerular immune complexes
- The discovery of podocyte antigens has been a major breakthrough
- Ab against PLA2R and thrombospondin-like domain 7A [THSD7A]
- presence of anti PLA2R does not rule out the concurrence of infection, malignancy, or other disease processes

- Categorization of MN based on the
  - Detectable auto Ab
  - Nephropathy not associated with either antibody (infections, systemic lupus erythematosus ,sarcoidosis , malignancies)

MEMBRANOUS NEPHROPATHY

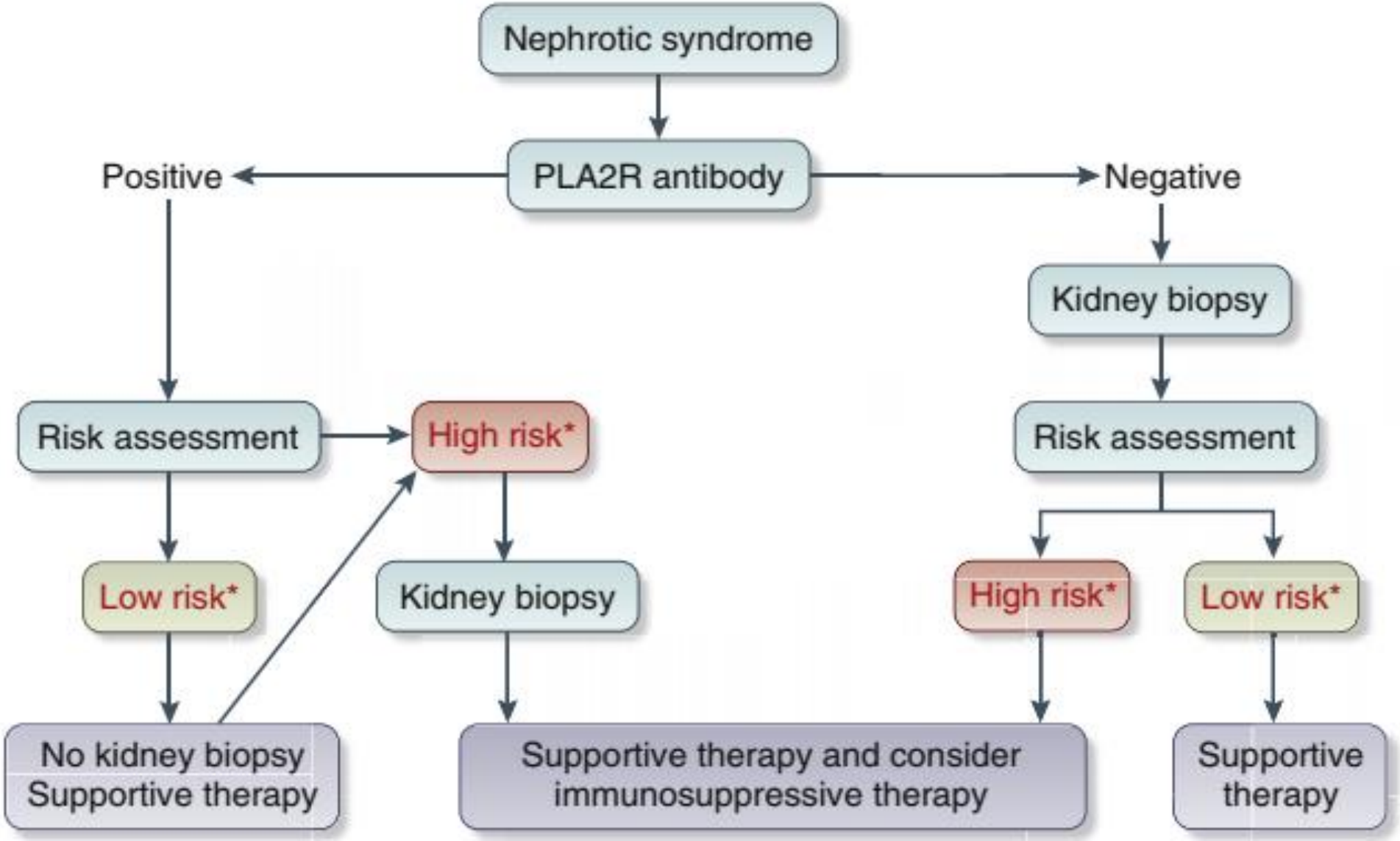


MEMBRANOUS NEPHROPATHY

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]

MEMBRANOUS NEPHROPATHY



MEMBRANOUS NEPHROPATHY

Kidney biopsy

- In cases of nephrotic syndrome and AKI , it may identify cases of membranous nephropathy with crescentic GN (anti–glomerular basement membrane or ANCA–associated) even in cases that are positive for anti-PLA2R
- look at IgG subclasses in the biopsy, with IgG1-dominant staining suggestive of secondary causes
- The specificity of THSD7A antibodies is not well established

MEMBRANOUS NEPHROPATHY

Risk-stratification

- Subnephrotic proteinuria : excellent long-term renal survival and do not need immunosuppression
- Nephrotic range proteinuria :
  severity& prognosis varies (spontaneous remission to severe nephrotic syndrome and ESKD)
- The risks of immunosuppression should not exceed the short-term risks of nephrotic syndrome
- The current risk stratification of patients who need treatment (>6 months of nuria >4 g/d)
  Lacks specificity, as a substantial proportion of such patients may still develop spontaneous remission

MEMBRANOUS NEPHROPATHY

Treatment :

Patients with minimal symptoms and preserved kidney function

- Delaying immunotherapy while maximizing treatment of proteinuria, hypertension, and hyperlipidemia for up to 3 years may be acceptable
- Less toxic immunomodulators : earlier initiation of immunotherapy to rapid disappearance of symptoms of nephrotic syndrome.
- Apart from small kidney size there is no other threshold for which treatment is deemed futile(even patients with eGFR <30 ml/min per 1.73 m2)

MEMBRANOUS NEPHROPATHY

Treatment with immunosuppressive agents

- First screening for infections &age-appropriate malignancies
- Alkylating agents :only proven effective in preventing ESKD or death (Risk of bladder & lung cancer in smoker &Infertility)
- Cyclical and accompanied by pulses of i.v. methylprednisolone
- In clinical practice: daily cyclophosphamide and omission of pulses of steroid
- CNI induced remissions:similar frequency as cyclophosphamide but with higher relapse rate

MEMBRANOUS NEPHROPATHY

Treatment with immunosuppressive agents

- Chlorambucil, but not cyclosporine, reduced eGFR loss in MN with renal insufficiency
- Rituximab : In Idiopathic MN (GEMRITUX) study
  - More effective than placebo in inducing remissions after 17m
  - The nonresponse :approximately 35%
  - lower partial remission versus cyclophosphamide.
- Measurement of PLA2R antibodies might aid in predicting treatment response

MEMBRANOUS NEPHROPATHY

Disease remission

- Complete remission :(proteinuria <0.3 g/d combined with stable GFR)
- Partial remission (50% reduction of proteinuria to a level <3.5 g/d)

Thanks

Part 2

MCD AND FSGS