Membranous Nephropathy- Full Clinical Guideline (For the use of nephrology team only)

Reference no.: CG-REN/4183/23

1. Introduction

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in non-diabetic adults. Majority of MN presents with nephrotic syndrome, while others present with sub-nephrotic proteinuria, with or without associated eGFR reduction.

It is an immune complex disease caused by subepithelial deposits. Approximately 70% of primary MN cases were reported to be caused by autoantibodies to phospholipase A2 receptor (PLA2R). There are increasing number of other circulating autoantibodies implicated in MN in the recent years (i.e.: THSD7A, NELL-1, etc).

Secondary causes of MN include malignancy, autoimmune disease (especially SLE), infections (HBV, HCV, HIV), sarcoidosis and drugs (NSAIDs, gold, penicillamine, anti-TNF, etc).

2. Aim and Purpose

This guideline is for the use of renal department to guide diagnosis and management of membranous nephropathy.

3. Definitions, Keywords

Anti-TNF: anti-tumour necrosis factor
ELISA: enzyme-linked immunosorbent assay
GBM: glomerular basement membrane
HBC: Hepatitis C virus
HBV: Hepatitis B virus
HIV: Human immunodeficiency virus
KDIGO: Kidney Disease Improving Global Outcome
MDT: multi-disciplinary team
MN: membranous nephropathy
NELL-1: NEL-like protein 1
NSAIDs: non-steroid anti-inflammatory drugs
PLA2R: anti-phospholipase A2 receptor
SLE: systematic lupus erythematosus
THSD7A: thrombospondin type 1 domain containing 7A

4. Main body of Guidelines

Diagnosis

- Serum PLA2R antibodies (indirect immunofluorescence and ELISA).
    - Renal biopsy might not be required to confirm the diagnosis of MN in nephrotic patients with positive PLA2R antibodies, preserved renal function and no other serological abnormalities.
- Renal biopsy:
    - Light microscopy: diffuse thickening of glomerular basement membrane (GBM). Segmental sclerosis and tubulointerstitial fibrosis may be present with progressive advanced disease.
    - Silver stain: spikes/holes appearance resulting from projections of GBM between the deposits.
    - Immunofluorescence: granular deposit of IgG (often IgG4 in primary MN) with variable C3. Corresponding PLA2R positive staining in some cases.
    - Electron microscopy: extensive podocyte foot process effacement. Subepithelial deposits.
- Patients with MN should be evaluated for associated conditions (secondary causes, see above), regardless of the presence of PLA2R antibodies.

Prognosis

- The natural course of MN is variable. Spontaneous complete remission was reported to occur in 5-30% in 5 years [1, 2]. End-stage renal failure occurs in approximately 14% of untreated patients with nephrotic syndrome in 5 years [1, 3].
- It is important to weigh up the risk of loss of kidney function against the adverse effects of immunosuppressants when considering treatment options.
- KDIGO advises using clinical and laboratory criteria to assess the risk of progressive loss of kidney function (see Table MN1)

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‡	• Life-threatening nephrotic syndrome OR • Rapid deterioration of kidney function not otherwise explained

Table MN1: Clinical criteria for assessing risk of progressive loss of kidney function (KDIGO GN guidelines 2021) [4]
* Patients with high level of proteinuria or anti-PLA2R levels should be re-evaluated earlier than 6 months after starting on maximal anti-proteinuric therapy.

Treatment

- **All patients with primary MN and proteinuria should receive optimal supportive care with RAAS inhibitor, statin, optimisation of blood pressure control and anticoagulation** (if indicated, see below).
- Consider treatment options based on risk of progressive loss of kidney function (Table MN1, Figure MN1).
- It is reasonable to wait 6 months for spontaneous remission while using maximal antiproteinuric therapy, especially for low and moderate risk patients.
- Patients with high level of proteinuria or anti-PLA2R levels **should be re-evaluated with respect to additional therapies earlier than 6 months** after starting on maximal anti-proteinuric therapy.
- Patient with very high risk of progression or severe unresponsive nephrotic syndrome should be considered for immediate immunosuppressive therapy.
- **Discuss patients at the Glomerulonephritis MDT meeting** when considering immunosuppressive therapy (bimonthly meeting, Tuesday 1-2pm, seminar room. Email Dr Khai Ping Ng: khaiping.ng@nhs.net).

Anticoagulation in MN

- Nephrotic syndrome is associated with increased risk of venous and arterial thrombo-embolism, which is related to the level of serum albumin. Patients with MN have the greatest risk.
- Anticoagulation with warfarin should be started for patients with serum albumin < 20 g/L and refer to anticoagulation clinic for monitoring.

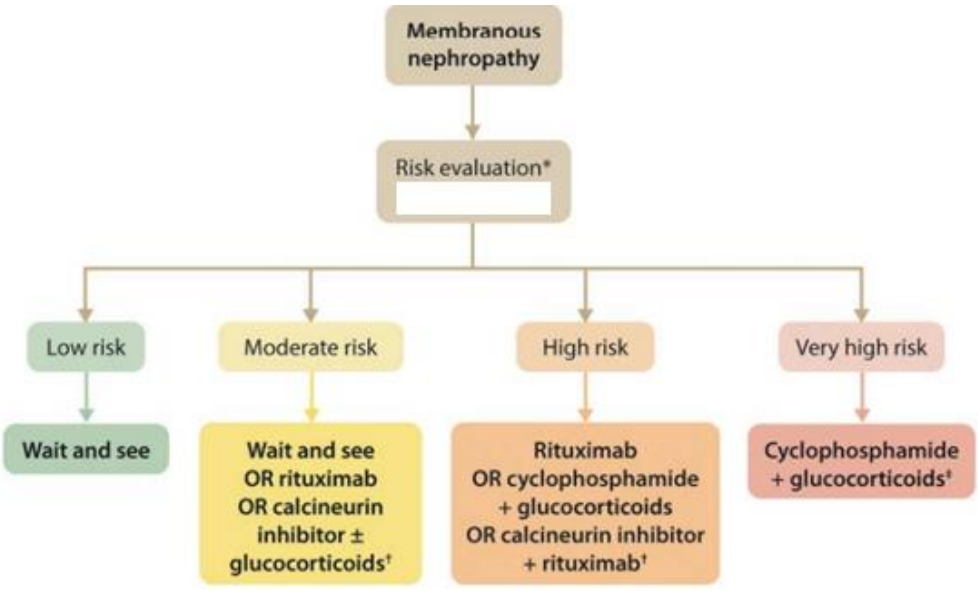

Figure MN1: Risk-based treatment for MN (from KDIGO GN guidelines 2021)

Cyclophosphamide and Prednisolone	• Prednisolone* 50mg OD for 4 weeks, 25mg OD for 4 weeks, then taper off 5mg every fortnight and stop.
	• Oral cyclophosphamide** 3 months
	  ○ Refer to Table MN3 for dosing
	  ○ Check FBC weekly for the 1st month, fortnightly for 2nd and 3rd months. Halve the dose if ANC falls below 2.0 X10^9 and pause if ANC drops below 1.5 x10^9

Rituximab	• Rituximab** 1g IV administered twice within 2 weeks Consider repeating after 6 months in patients with persistent nephrotic syndrome, stable eGFR, especially if anti-PLA2R antibodies remained positive
Tacrolimus	• Tacrolimus 0.05-0.1 mg/kg/d, target trough level 3-8 ng/ml, duration 12 months
Cyclosporine	• Cyclosporine 3.5 mg/kg/d, target trough level 125-225 ng/ml

Table MN2: Treatment regimens for patients with MN
*Please ensure prescription of gastric and bone protection with the course of Prednisolone
** Please ensure prescription of PCP prophylaxis (co-trimoxazole) and provide contraceptive counselling (for female patients).

Age (years)	**eGFR (ml/min/1.73m^2)**	
	>30	**< 30**
<60	2	1.5
60-70	1.5	1.25
>70	1.25	1

Table MN3: Oral cyclophosphamide dosing mg/kg body weight

Monitoring for PLA2R positive MN

- Longitudinal monitoring may be useful for PLA2R positive MN at 3- 6 months after start of therapy.
  - PLA2R ab level should be used in combination with clinical and laboratory parameters for evaluating treatment response and can be used to guide adjustments to therapy.
  - If measured by ELISA, a cut-off value of 2RU/ml should be used to define complete immunologic remission.
- In addition to ongoing care, we suggest that an evaluation approximately six months after initial diagnosis with PLA2R Abs, clinical information, eGFR and uACR will be useful to review response to initial management, including discussion at the Glomerulonephritis MDT meeting when appropriate (e.g. when immunosuppressive treatment changes are being considered).

5. References

[1] Jha V, Ganguli A, Saha TK, 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;18(6):1899-904.

[2] Ponticelli C, Zucchelli P, Passerini P, et al. A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. Kidney Int. 1995;48(5):1600.

[3] Hogan SL, Muller KE, Jennette JC, Falk RJ. A review of therapeutic studies of idiopathic membranous glomerulopathy. Am J Kidney Dis. 1995;25(6):862.

[4] Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guidelines for the management of glomerular diseases. Practice Guidelines; vol 100(4): Supplement S1-S276. DOI: https://doi.org/10.1016/j.kint.2021.05.021

6. Documentation Controls

Reference Number CG-REN/4183/23	**Version:** 1		**Status** Final	
Version / Amendment History	Version	Date	Author	Reason
	1	May 2023	Dr Khai Ng	New Guideline
Intended Recipients: Clinical Staff working in Nephrology.				
Training and Dissemination: Induction				
Development of Guideline: Dr Khai Ng **Job Title:** Consultant Nephrologist				
Consultation with: UHDB Consultant Nephrologists				
Linked Documents: Rituximab for Renal Patients				
Keywords: Membranous nephropathy				
Business Unit Sign Off	**Group:SMBU2** **Date:21/7/23**			
Divisional Sign Off	**Group:Medicine Division** **Date:June 2023**			
Date of Upload	July 2023			
Review Date	July 2026			
Contact for Review	Dr Khai Ng			