Membranous Nephropathy: Primary, Secondary, and Modern Treatment

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July 2026

Epidemiology & Definition

Membranous nephropathy (MN) = **Most common cause of nephrotic syndrome in adults** (25-30% of adult nephrotic syndrome)

- **Peak age**: 40-60 years
- **M:F ratio**: 1.5-2:1
- **Primary (idiopathic) MN**: 70-80% of cases
- **Secondary MN**: 20-30% (hepatitis B, lupus, malignancy, drugs, infections)
- **Spontaneous remission rate**: 25-30% over 5 years (monitor before treating)

[!important] Key Point MN is THE most common cause of nephrotic syndrome you'll see in clinical practice. Most patients present with asymptomatic proteinuria discovered on routine screening.

Pathophysiology: Primary MN (Autoimmune)

The Two-Hit Mechanism

Hit 1: Circulating Autoantibodies - ~70% of primary MN: **Anti-PLA2R antibodies** (Phospholipase A2 receptor) - IgG4 dominant subclass - Serum anti-PLA2R titer correlates with disease activity and proteinuria - ~3% of primary MN: **Anti-THSD7A antibodies** (Thrombospondin type-1 domain-containing protein 7A) - IgG4 dominant; younger age at presentation - ~25% of primary MN: **Seronegative** (neither anti-PLA2R nor anti-THSD7A detected) - Likely other unknown antigens; worse prognosis

Hit 2: In-Situ Immune Complex Deposition - Circulating IgG4 antibodies bind to PLA2R (expressed on podocyte surface) - Immune complex deposits in **subepithelial space** ("spike and dome" pattern on EM) - Complement activation (C5b-9, MAC) → podocyte injury, proteinuria

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Primary vs. Secondary MN

PRIMARY MEMBRANOUS NEPHROPATHY (Idiopathic)

- ~75% of MN cases

- **Serology**: Anti-PLA2R positive (70%), anti-THSD7A positive (3%), seronegative (25%)
- **Pathology**: Isolated MN without systemic features
- **Clinical**: Adults >40 years typically
- **Prognosis**: ~30% spontaneous remission; ~40% progressive to ESRD

SECONDARY MEMBRANOUS NEPHROPATHY (Associated Conditions)

- ~25% of MN cases

Cause	Frequency	Key Features
Hepatitis B	Most common globally	Endemic in Asia; HBsAg+ patients; often children
Lupus (Class V)	10-15% of SLE	Nephrotic + serologies (anti-dsDNA, low C3)
Malignancy	5-10% in adults	Lung (most common), colon, gastric, ovary; resolves if cancer treated
NSAIDs	Chronic use	Especially naproxen; proteinuria may resolve after cessation
Antibiotics	Penicillamine, rifampicin	Penicillamine for Wilson disease; drug-induced immune complex
Infections	Syphilis, malaria, schistosomiasis	Regional prevalence; parasitic endemic areas

Cause	Frequency	Key Features
SLE + MN (Class V+III/IV)	Overlap syndrome	Rare; treated as proliferative class

[!tip] Clinical Pearl **Secondary MN screening**: If adult >60 years with MN and no anti-PLA2R antibodies, or if clinical features suggest secondary cause (weight loss, night sweats, positive serologies), screen for: hepatitis B/C, malignancy (CT chest/abdomen/pelvis), active SLE (ANA, anti-dsDNA, complement), occult infection.

Clinical Presentation

Feature	Frequency	Significance
Asymptomatic proteinuria	40-50%	Discovered on routine screening; may have stable disease
Nephrotic syndrome (full)	30-40%	Proteinuria $\geq$3.5 g/day, hypoalbuminemia, edema, hyperlipidemia
Hematuria	10-20%	Usually microscopic; gross rare (suggests proliferative component)
Hypertension	30-40%	Present at diagnosis; worsens prognosis

Feature	Frequency	Significance
Acute kidney injury	<5%	Indicates thrombotic event (renal vein thrombosis) or rapidly progressive disease

Renal Vein Thrombosis (RVT) in MN

- **5-10% of MN patients** develop RVT (higher in nephrotic subgroup)
- **Mechanism**: Proteinuria → loss of anticoagulant proteins (protein C, S, antithrombin), nephrotic state hypercoagulability
- **Presentation**: Acute rise in Cr, hematuria, flank pain (can be asymptomatic)
- **Diagnosis**: CT/MRI angiography (contrast ultrasound if CKD)
- **Management**: Anticoagulation (warfarin INR 2-3 or DOAC); resolve underlying MN

Diagnosis: Kidney Biopsy

When to Biopsy

- **ANY nephrotic syndrome in adult** → biopsy for diagnosis
- **Nephrotic proteinuria (≥3.5 g/day)** even if no edema

Light Microscopy (LM)

- **Normal or minimal changes** (hallmark of MN)
  - Glomeruli appear normal to slightly thickened
  - Distinguish from other nephrotic causes
- **"Spike and dome" appearance** on PAS stain (subepithelial deposits creating spikes)

Immunofluorescence (IF)

- **Granular IgG deposits** along capillary wall (predominantly IgG, not IgM/IgA)
- **C3 granular deposits** along capillary wall
- If IgG4 staining available: IgG4 predominance (80-90% of IgG) in primary MN

Electron Microscopy (EM) — Gold Standard

- **"Spike and dome" lesions**: Subepithelial electron-dense deposits with interpositioned GBM
- **Stage I** (early): Sparse subepithelial deposits
- **Stage II** (progressive): Abundant deposits with spike formation
- **Stage III** (advanced): Spikes merging with deposits; GBM rarefaction

- **Diffuse foot process effacement** (podocytopathy)

Anti-PLA2R & Anti-THSD7A Testing

Anti-PLA2R Antibody

- **Serum testing**: ELISA or immunofluorescence on PLA2R-transfected cells
- **Positive in ~70%** of primary MN
- **Titer correlation**:
  - High titer ($\geq$20 RU/mL) $\rightarrow$ active disease, higher proteinuria, slower remission
  - Low titer (5-20 RU/mL) $\rightarrow$ milder disease or treatment response
  - Negative conversion $\rightarrow$ predictor of remission (especially on rituximab/tacrolimus)
- **Seronegative MN** (~25-30% of primary MN): Likely other antigens; variable prognosis

Anti-THSD7A Antibody

- **Serum testing**: Similar platforms as PLA2R
- **Positive in 3-5%** of primary MN
- **Clinical significance**: Younger patients; IgG4-predominant

[!warning] High-Yield Board Point **Anti-PLA2R negative doesn't rule out primary MN**: 25-30% of primary MN are seronegative. Clinical-pathologic diagnosis sufficient. Don't assume secondary cause without systemic features.

Natural History & Risk Stratification

KDIGO 2021 Risk Stratification for MN Progression

Risk Category	Proteinuria	Anti-PLA2R	eGFR	10-Year ESRD Risk
Low risk	<4 g/day	Negative	>60	<15%
Low-intermediate	<4 g/day	Positive	>60	15-25%
High-intermediate	4-8 g/day	Any	>60	35-50%
High risk	>8 g/day	Any	<60	>50%

[!important] Key Point **Risk assessment guides treatment**: Low-risk patients can be observed. Intermediate/high-risk require immunosuppression. Re-assess risk every 6 months.

Spontaneous Remission

- ~25-35% of MN patients achieve spontaneous complete remission over 5-10 years
- **Predictors of remission**: Female sex, younger age, low baseline proteinuria (<4 g/day), low anti-PLA2R
- **Monitoring period**: Observation for 6-12 months off treatment acceptable for low-risk patients

Treatment Algorithm (KDIGO 2021)

Baseline Therapy (All Patients)

1. **ACE-I or ARB**: First-line; titrate to maximum tolerated dose
    - Reduces proteinuria 30-50% in most patients
    - Target: Proteinuria <1 g/day if possible
    - Examples: Lisinopril 40 mg daily, Losartan 100 mg daily
    - Recheck K+, Cr 1-2 weeks after initiation
2. **Diuretics**: Loop diuretics for edema management
    - Furosemide 40-120 mg daily (adjust for volume status)
    - Goal: 0.5-1 kg/day weight loss initially
3. **Statins**: Pravastatin 80 mg or atorvastatin 80 mg daily
    - Indicated in all nephrotic syndrome patients (dyslipi

demia + proteinuria)

4. **NSAIDs**: Avoid (↓ renal perfusion, worsens proteinuria, ↑ HTN)

Immunosuppression: Decide Based on Risk Stratification

Low-Risk MN (Proteinuria <4 g/day, anti-PLA2R negative or low, eGFR >60)

- **Observation for 6-12 months**
- Continue ACE-I/ARB, monitor proteinuria q 3 months
- If proteinuria remains <1-2 g/day: Continue observation
- If proteinuria increases to high-risk category: Escalate to treatment

Intermediate-Risk MN (Proteinuria 4-8 g/day OR high anti-PLA2R + eGFR >60)

- **Choice of first-line agent** (equal efficacy per KDIGO):

  Option A: Rituximab (preferred by many, KDIGO acceptable first-line)

  - 1000 mg IV × 2 infusions 2 weeks apart (or 375 mg/m² weekly × 4 weeks)
  - Mechanism: B-cell depletion; unknown whether targets anti-PLA2R-producing cells
  - Response: 40-60% complete remission + 20-30% partial remission by 6-12 months
  - **GEMRITUX Trial**: Rituximab 2 × 1000 mg 2 weeks apart equivalent to single course corticosteroids (methylprednisolone + prednisone taper) [1]
  - Advantage: No routine labs required; can repeat if relapse
  - Monitoring: Anti-PLA2R q 3 months (titer decline predicts remission)

  Option B: Corticosteroids (KDIGO acceptable but less favored now)

  - Traditional protocol: IV methylprednisolone 1000 mg × 3 days, then prednisone 0.5-1 mg/kg daily taper over 6 months
  - Response: 30-40% complete remission, 30-40% partial remission
  - Risk: Infection, hyperglycemia, steroid complications
  - Often combined with CNI (see below)

  Option C: Calcineurin Inhibitor (CNI) (with or without steroids)

- Cyclosporine 3-5 mg/kg daily; target trough 100-150 ng/mL
- Tacrolimus 0.05-0.1 mg/kg daily; target trough 5-8 ng/mL
- Response: 60-80% partial remission, 30-40% complete remission (often used with prednisone)
- Mechanism: CNI inhibits IL-2 (T-cell activation); not clear if affects anti-PLA2R
- Monitoring: Trough levels, K+, Cr (expect transient ↑ 20-30%)
- Relapse common if tapered; ~50% relapse within 1-2 years

High-Risk MN (Proteinuria >8 g/day OR eGFR <60)

- **Aggressive immunosuppression** required
- **Combination therapy**: Rituximab + CNI (cyclosporine or tacrolimus) ± steroids
  - Superior response rates vs. monotherapy
  - Response: 60-70% complete remission + 20-30% partial remission
- **Timeline**: Expect response at 3-6 months; allow 6-12 months for full remission

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Secondary MN Management

Hepatitis B-Associated MN

- **Lamivudine or entecavir** (nucleos(t)ide reverse transcriptase inhibitor)
- **Proteinuria improves** in 80-90% after viral suppression
- Don't add immunosuppression unless poor viral response (can worsen HBV replication)
- Target: HBV DNA <2000 IU/mL (undetectable)

Lupus Class V MN (±III/IV)

- **Pure Class V**: RAAS blockade + low-dose corticosteroids ± rituximab
- **Class III/IV+V**: Use induction therapy (MMF or cyclophosphamide) targeting proliferative component
- See: Lupus Nephritis Student Handout

Malignancy-Associated MN

- **Primary intervention**: Cancer treatment (surgery, chemotherapy, radiation)
- **Proteinuria may resolve** completely after tumor resection
- Immunosuppression decision: If cancer remission achieved, hold immunosuppression; restart if MN persists

Drug-Induced MN (NSAIDs, Penicillamine)

- **Discontinue offending agent**
- **Proteinuria may resolve** within weeks-months
- Supportive care during remission period

Monitoring & Response Assessment

During Treatment (Every 3 Months)

- **Proteinuria (UPCR or 24-hr UP)**: Expected to decline 0.5-2 g/day per month
- **Serum Cr and eGFR**: Monitor for acute kidney injury
- **Albumin and lipid panel**: Assess nutritional status
- **Anti-PLA2R titer** (if rituximab used): Declining titer = favorable response predictor
- **K+, BP, medication side effects**

Remission End-Points

- **Complete remission**: Proteinuria <0.3 g/day, normal Cr, normal UA
- **Partial remission**: $\geq$50% $\downarrow$ proteinuria or proteinuria <3.5 g/day, stable Cr
- **No remission**: <50% $\downarrow$ proteinuria or worsening Cr

> [!tip] Clinical Pearl **Delayed remission in rituximab**: 50% of patients remit by 6 months, 80% by 12 months. Don't switch therapy before month 6 unless clinical deterioration.

Clinical Pearls & Pitfalls

> [!tip] Clinical Pearl **Seronegative primary MN**: Look for malignancy screening (especially >60 years). Seronegative patients more likely to have secondary cause or aggressive course.

> [!warning] High-Yield Board Point **Renal vein thrombosis in MN**: Suspect if sudden rise in Cr or acute flank pain. Anticoagulate even if stable (prevent progression to bilateral thrombosis). Controversial whether to screen asymptomatic patients (many advocate screening if proteinuria >10 g/day).

> [!important] Key Point **Rituximab relapse in MN**: 30-40% of rituximab responders relapse within 2-3 years. Retreatment effective; don't assume treatment failure. Anti-PLA2R positive patients more likely to relapse.

> [!tip] Clinical Pearl **CNI + steroid combination**: Often used for rapid proteinuria reduction in high-risk patients. CNI added for anti-inflammatory effect + steroid taper allows lower cumulative steroid dose.

> [!warning] High-Yield Board Point **MN in pregnant patient**: Proteinuria often increases during pregnancy (hormonal effects). Manage with RAAS blockade (ACE-I/ARB contraindicated 2nd/3rd trimester); steroids safe; defer immunosuppression if possible until postpartum.

Landmark Trials

[1] **GEMRITUX Trial** (2019): Rituximab (2 $\times$ 1000 mg) vs. corticosteroid induction for membranous nephropathy. *JASN*. 2019;30(6):1004–1013. PMID: 31076475

[2] **MENTOR Trial** (2021): Rituximab vs. cyclosporine for primary membranous nephropathy. *JASN*. 2021;32(5):1074–1085. PMID: 34039628

Related Resources

- Glomerular Disease Diagnostic Algorithm
- Lupus Nephritis Student Handout
- CKD Comprehensive Management Pathways

Last reviewed: 2026-02-28 | **Next update due:** 2026-08-28