MEMBRANOUS NEPHROPATHY: Treatment in the Modern Era

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A 71 year old man is found to have the Nephrotic Syndrome (Urine protein excretion of 11.2gms/d; serum albumin of 2.2gms/dL). His serum creatinine is 1.50mg/dL (132µM/L; eGFR- CKD-EPI-creatinine=46ml/min/1.73m2). He has no past history of illnesses other than a myocardial infarction and a deep venous thrombosis 5 years ago. He is a former heavy smoker. He takes a “baby” aspirin daily.

Blood pressure is 156/92mmHg. 2+ pitting edema of ankles is present
A renal biopsy reveals thickened capillary walls, no proliferation. IF shows 4+ granular IgG along the outer aspect of capillary wall. No mesangial deposits seen, C3 is present in a similar distribution. C1q is negative. IgM and IgA are weakly +. EM shows thickened basement membrane, spikes and extensive electron dense deposits along the subepithelial space.

IgG subclass shows extensive deposits of IgG4, and weaker deposits of IgG1, 2 and 3. A PLA2R1 antigen is 4+ along the capillary walls.
QUESTION #1A

Which ONE of the following would you now request?

A. Anti-nuclear antibody and anti-dsDNA assay
B. Serum Hepatitis B surface antigen
C. Spiral Chest X-Ray
D. Prostate Specific Antigen
E. None of the Above
QUESTION #1A

The correct answer is **E-None of the Above.** The immunopathological features IgG4+, C1q negative, PLA2R ag positive are sufficient to make a positive diagnosis of **Primary Membranous Nephropathy**
The Regimens used in Treatment of Primary Membranous Nephropathy have undergone a thorough Evidence-Based Evaluation—New Paradigms Represent the Modern Era of Management—but these Paradigms are in a constant state of evolution.
The KDIGO Clinical Practice Guidelines for Glomerulonephritis will be used as the Reference-Point for Discussion (Kidney International Supplements Volume 2 [June] 2012)
Recommendation 7.2

- Perform appropriate investigations to exclude secondary causes of biopsy-proven MN
Primary ("Idiopathic")
Membranous Nephropathy:

Diagnostic Criteria-2014

- A renal biopsy lesion showing exclusively epi-membranous deposits by EM, predominantly containing $IgG_4$ and lesser amount of $IgG_{1,2,3}$. PLA2R1 Antigen, C4d, C3 and MBL commonly present in deposits in active disease, $C1q$ always negative by IF.

- No recognizable underlying disease (especially SLE, HBV, drugs, heavy metal exposure and neoplasia)

- PLA2R1 auto-antibody + in 80%-Normal serum $C3$ and $C4$ concentration
Secondary MN

- Lupus Nephritis (Class V) and other autoimmune diseases
- Infections (mainly Hepatitis B viral infection; uncommonly other viral infections)
- Neoplasia (mainly Lung, Stomach, Breast, Colon, Bladder and Hematological malignancies (such as CLL)
- Drugs (NSAID, gold, mercury)
- Other
Secondary MN

- A renal biopsy showing MN can be proven to be due to a Secondary cause in 20-60% of adults – depending on region and endemic diseases (68% in China; 20% in France and 38% in USA)

- Children with MN have a higher likelihood to have Secondary MN (mainly auto-immune disease)

- Neoplasia accounts for 3-10% of Secondary MN, but as much as 25% of cases in subjects over 60 years of age

- Neoplasia, Hepatitis B infection or Auto-immune disease accounts for about 85% of all Secondary forms of MN
Standard Evaluation for Secondary MN-

**PLA2R Ag Negative**

- FANA, anti-dsDNA antibody, C3 level in subjects <40 years

- Hepatitis B surface antigen, Hepatitis B core antibody in all

- Careful history for drug use (including skin lightening creams containing Hg)

- Careful history and physical exam for signs of neoplasia + stool for occult blood, spiral CT of chest, mammogram (female), PSA (male), colonoscopy (if not done recently as a part of routine surveillance)
Role of IgG4 dominance; anti-PLA2R antibody and PLA2R antigen in detecting Secondary MN

*Primary MN is characterized by;*

- IgG4 subclass dominance (IgG1/3 dominant in Secondary MN)

- Circulating anti-PLA2R auto-antibody in 80%+ (and <10% of secondary MN)

- PLA2R1 expression enhanced in podocytes by IF (but seldom in Secondary MN)
Membranous Nephropathy:  
**IgG Subclass Distribution**

<table>
<thead>
<tr>
<th>Condition</th>
<th>IgG₁</th>
<th>IgG₂</th>
<th>IgG₃</th>
<th>IgG₄</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Idiopathic</strong></td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Lupus</strong></td>
<td>++++</td>
<td>++</td>
<td>++++</td>
<td>±</td>
</tr>
<tr>
<td><strong>Neoplasia</strong></td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>±</td>
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Membranous Nephropathy: PLA2R antibody and PLA2R antigen
(adapted from Svobodova B, et al NDT 2013; 28: 1839-1844)

<table>
<thead>
<tr>
<th>PLA2R Antibody Positive in Circulation</th>
<th>PLA2R Antigen in Glomeruli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive Active 1° (90%)</td>
</tr>
<tr>
<td>Negative</td>
<td>Resolving 1° (86%)</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative Active 2° or Inactive 1°</td>
</tr>
<tr>
<td>Negative</td>
<td>? FP (uncommon)</td>
</tr>
</tbody>
</table>
CONCLUSION

With a combination of *anti-PLA2R auto-antibody* testing (ELISA or IIF), and examination of the renal biopsy for dominant deposits of *IgG4, C1q and PLA2R1* antigen it should be possible to “diagnose” primary MN with an accuracy of over 95%
Recommendation 7.2.1

- We recommend that initial therapy be started ONLY in patients with Nephrotic Syndrome (NS) AND when at least ONE of the following conditions are met:

  - Urine protein excretion persistently exceeds 4g/d AND remains over 50% of the baseline value AND does not show a progressive decline during an observation period of at least 6 months

  - Presence of severe, disabling or life-threatening symptoms related to the NS

  - Scr has risen by 30% or more within 6-12 months from the time of diagnosis but is not less than 25ml/min/1.73m² AND this change is not explained by superimposed complications
Primary Membranous Nephropathy; “Natural” History

- Numerous anecdotal and observational studies suggested that MN pursues an *indolent* course
- Over 15-20 years:
  - Spontaneous Remission - 30%
  - Persistent Low-grade Proteinuria/ Stable Renal Function-- 30%
- Progression to ESRD- 40%
Time Averaged Proteinuria and Decline of eGFR (Males)
(Cattran D, et al NDT 23:2247-2253, 2008)

Proteinuria (gms/d)

- IgA Nephropathy
- Focal Glomerular Sclerosis
- Membranous Nephropathy
Primary Membranous Nephropathy: "Spontaneous" Remissions
Primary Membranous Nephropathy: “Natural” History in Adults

![Graph showing the percentage of patients with ESRD/DEATH and CR and PR over different time periods (5yr, 10yr, 15yr, 20+yr).]
Anti-PLA2R auto-antibody (ELISA) and outcomes
(n=79- all PLA2R1 +)
What about PLA2R1 antibody in decision making for Initial therapy

- A declining anti-PLA2R1 auto-antibody level may "herald" a spontaneous remission

- Monitoring of PLA2R1 levels prior to initiation of "specific" therapy might be worthwhile (not yet proven in a RCT)
"Restrictive" Treatment Strategy for Primary MN
(van den Brand, et al JASN 2014; 25: 150-158)

- 254 patients with primary MN initially treated according to a strategy similar to that advocated by KDIGO were examined for long-term outcomes (median 57 months)
- 96% of patients received RAS inhibiting therapy
- Oral anti-coagulation was given to 36% of patients
- 130 (51%) received conservative therapy only, while 124 (49%) eventually received immunosuppressive therapy (typically oral CYC + Prednisone)
Partial (Solid line) and Complete Remissions (Dotted Line) with Conservative (Thin) and IS Therapy (Bold)
"Restrictive" Treatment Strategy for Primary MN
(van den Brand, et al JASN 2014; 25: 150-158)

- **Conservative:**
  - Deaths- 4/130
  - Any Scr >3.0mg/dL – 5/130
  - ESRD- 1/130

- **Immunosuppressive:**
  - Deaths- 13/124
  - Any Scr >3.0mg/dL- 17/124
  - ESRD- 5/124
Recommendation 7.2.2

Do not use immunosuppressive therapy in patients with a Scr persistently >3.5mg/dL or an eGFR <30ml/min/1.73m2 AND a reduction of kidney size by US OR those with concomitant severe or potentially life-threatening infections
Recommendation 7.3

- For initial therapy of MN-

  - 6 month course of alternating monthly cycles of oral and IV corticosteroids and oral alkylating agents (cyclophosphamide preferred over chlorambucil)

  - Observe patients conservatively for at least 6 months after completion of regimen, unless kidney function is deteriorating or severe symptoms related to NS are present

  - Continuous daily oral cyclophosphamide may also be beneficial but can be associated with toxicity, especially if continued for >6 months

  (IV cyclophosphamide was not recommended and all doses of alkylating agents need to be adjusted for impaired renal function)
Alkylating Agent Treatment
(Ponticelli, 10 y FU)

CR
PR
NR
ESRD
DEATH

Treated
Control
Recommendation 7.4

Alternative Initial Regimens for MN

- Cyclosporine or Tacrolimus (CNI) for a period of at least 6 months (patient preference or contra-indications to use of alkylating agents)

- CNI discontinued if no response after 6 months

- Reduce dosage of CNI at intervals of 4-8 weeks to 50% of starting dosage if remission is obtained and maintained and no nephrotoxicity observed. Continue treatment for 12 months

- Suggest (but not recommend) that CNI blood levels be monitored, especially when there is an unexplained rise in Scr (>20%) during CNI therapy
Cyclosporin in MN: Complete and Partial Remissions
(Cattran, et al KI, 2001)

Remissions (% CR + PR)

- 26 wks
  - Cyclosporin: 80%
  - Placebo: 20%

- 52 wks
  - Cyclosporin: 70%
  - Placebo: 30%

- 78 wks
  - Cyclosporin: 60%
  - Placebo: 40%
Primary MN and MCD-
Time to CR patients achieving a CR under treatment with a CNI
(Fritsche L, et al NDT, 1999)

Fig. 1. Time to complete remission of proteinuria (CR) in patients with nephrotic syndrome due to membranous glomerulopathy (MGN) or minimal change lesions (MC) during treatment with cyclosporine A. (Patients not reaching CR excluded).
A comparison of Chlorambucil or Cyclosporine for IMN with Impaired Renal Function

Primary MN-

108 patients randomly assigned to receive cyclical Chlorambucil (starting dose 0.5mg/kg/d- Ponticelli regimen X6 months ) or Cyclosporine (starting does 5mg/kg/d) without steroids x 12 months) or “supportive” therapy only. 106 patients analyzed by ITT.

All subjects had IMN, NS and at least a 20% decline in estimated Ccr prior to randomization (eCcr= 50ml/min

Primary EP= further 20% decline in eCcr
Primary MN-
A comparison of Chlorambucil or Cyclosporine for IMN with Impaired Renal Function
Primary MN-

*Treatment of patients with impaired renal function*

- A Cyclical alkylating agent + prednisone regimen is the *preferred* approach (but dosage reductions and frequent leukocyte monitoring are required to avoid myelotoxicity)

- Calcineurin agents *should be avoided* (or used with great caution and in reduced initial dosage with close monitoring of blood levels)
Recommendation 7.5

- Use of corticosteroid monotherapy is **NOT recommended**

- Use of monotherapy with MMF is **NOT suggested**
Primary MN-

**Biological agents**

- Rituximab (chimeric anti-CD20 monoclonal antibody) (Genentech)

- Adrenocorticotropic hormone (ACTH)- Natural (porcine) (Questcor); synthetic 1-24 peptide (Synacthen-not available in USA)
RITUXIMAB in Primary MN

- Used since 2002 for treatment of IMN (As “rescue” for patients failing other regimens in USA or as initial treatment in Europe - primarily Northern Italy). Effectiveness in patients with impaired renal function not well understood.

- No RCT yet completed (MENTOR in progress comparing RTX with CsA).

- Extensive observational studies strongly support efficacy and safety, using surrogate end-points, but not approved for use in Nephrotic Syndrome in USA.
A retrospective stay of 100 consecutive patients with IMN and NS treatment with Rituximab (68 as initial “first-line” therapy; 32 as “second line” therapy after failure of another regimen)

Baseline Scr = 1.2mg/dL (0.97-1.70mg/dL) - 44 patients had an elevated Scr

Baseline 24 hour protein = 9.1gms (5.8-12.8gm/d)

RTX given as 4 weekly 375mg/m2 doses IV or B-cell count modified dosage regimen
RITUXIMAB in Primary MN

![Graph showing remission rates](image)

<table>
<thead>
<tr>
<th>Remission Type</th>
<th>Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>100  94  78  56  41  32  20  17  13  12  10</td>
</tr>
<tr>
<td>Partial remission</td>
<td>100  84  63  47  37  26  21  19  15  12  11</td>
</tr>
<tr>
<td>Complete or Partial remission</td>
<td>100  67  40  23  13  4   2   2   1   0   0</td>
</tr>
</tbody>
</table>
RITUXIMAB in Primary MN
RITUXIMAB in Primary MN:

**Notable Points**

- Lower proteinuria and Scr at BL predicted *better CR/PR outcomes*; PLA2R1 antibody levels fall with treatment
- 65% CR or PR rate at median time of 7.1 months; *100% of those followed for 4 years or more achieved a CR or PR*
- Only 4 subjects progressed to ESRD during the observation period
- eGFR increased (13ml/min/1.73m2) in those with a CR
- 18/65 (28%) of patients achieving a CR or PR relapsed; 11/18 (61%) retreated patients achieved a CR or PR.
- RTX was well tolerated with minimal side-effects
**RITUXIMAB** is an important addition to the treatment armamentarium for Primary MN. Patients wishing to avoid the side effects of alkylating agents or CNI may choose it as initial therapy, but knowledge of long-term efficacy and safety requires further studies. The mechanism of action could be on B-cells or directly on podocytes, or both. (a RCT-MENTOR- is in Progress in the USA)
ACTH in Primary MN

- ACTH appears to have beneficial effects on proteinuria in Primary MN. These effects have been proven in a small RCT for synthetic ACTH (Synacthen- ACTH 1-24) compared to cyclical alkylating agents plus steroid.

- Long-acting Natural ACTH (ACTHAR gel), containing intact (porcine) ACTH (1-39) + melanocortin fragments may have similar beneficial effects, but so far these have not been demonstrated in a RCT (CHART – in progress-- is designed to provide this information).
Synthetic ACTH vs MP + CP in Primary MN: *Outcome at 24 months*

ACTHAR GEL®
(Questcor, Inc)

- A natural (porcine) product “purified” by a proprietary method. Primarily 1-34 ACTH polypeptide but contains other propriono-melanocortin products

- Only drug approved by the FDA* in the USA for induction of remissions (or proteinuria) in patients with Nephrotic Syndrome (without uremia) due to Primary Membranous Nephropathy (and other Primary forms of Nephrotic Syndrome) and Lupus Nephritis

(* not based on RCT)
ACTHAR GEL in Primary MN
Prolonged treatment with ACTHAR Gel (80 units twice weekly s.c. for 6 months) appears capable of inducing CR or PR in about 75-80% of patients with Primary MN, despite their resistance to other treatment regimens.

The long-term outcomes (relapses and ESRD) are largely unknown. Side effects are skin pigmentation, mild Cushing syndrome and new onset of aggravation of pre-existing diabetes.

The mechanism(s) of action are uncertain but not likely due to adrenal steroidogenesis. Direct effects on the podocyte (via MCR) are likely.
Can be used in *treatment naïve and non-treatment naïve patients* with nephrotic syndrome but guidelines do not currently recommend its use as initial therapy (a RCT is in progress in the USA)

The effect of impaired kidney function on responsiveness *not well understood*. Not approved for use if “uremia” (ill-defined) present. Effect of concomitant drug use (e.g. MMF or CNI) not understood

Generally safe and well tolerated but expensive *(most insurance covers costs and discount programs available)*
Response to ACTHAR Gel According to Baseline eGFR
(Bombback, 2011; n=21)

<table>
<thead>
<tr>
<th>eGFR at Baseline</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30ml/min</td>
<td>Complete Remission: 2</td>
</tr>
<tr>
<td></td>
<td>Partial Remission: 3</td>
</tr>
<tr>
<td></td>
<td>No Remission: 2</td>
</tr>
<tr>
<td></td>
<td>Did Not Qualify: 2</td>
</tr>
<tr>
<td>&lt;30ml/min</td>
<td>Complete Remission: 1</td>
</tr>
<tr>
<td></td>
<td>Partial Remission: 6</td>
</tr>
<tr>
<td></td>
<td>No Remission: 1</td>
</tr>
<tr>
<td></td>
<td>Did Not Qualify: 4</td>
</tr>
</tbody>
</table>
Mycophenolate Mofetil (MMF) or Mycophenolic Acid (MPA) in Primary Membranous Nephropathy

- Observational and limited RCT suggest efficacy in Primary but only when used with steroids.
- Long-term benefits on ESRD unknown.
- Pharmacokinetics highly variable and influenced by serum albumin levels (drug levels may be required for optimal management).
- At usual dosing (2-3gms daily, divided dosage for 6-12 months) generally well tolerated. GI side effects, CMV but not bone marrow suppression. Low risk of neoplasia. Feto-toxic.
MMF (+ steroids) v Ponticelli Protocol in Primary MN

Remission
MMF = 64%
Pont = 80%
Treatment of Primary MN

Relapse rate high both during and post-MMF treatment
MMF in Treatment of Primary MN

- MMF (or MPA) + steroids tends to be as effective as CYC or CNI for induction of remissions (CR or PR) when used as initial therapy (but is not recommended for use as initial therapy by KDIGO)

- Requires concomitant steroids for any efficacy (MMF monotherapy is ineffective in RCT)

- Very high relapse rate

- No long term studies to evaluate efficacy for avoidance or delay of ESRD
**AXIOM:**

Treatment of CYC/CNI “resistant” patients with Primary MN with Rituximab, ACTH or MMF

- “Resistance” to initial (or rescue) therapy *does not reliably predict* resistance to therapy with another agent of a different class

- Choice of agent for “resistant” cases is largely driven by *side-effect profile* and patient desires
Recommendation 7.6

- **Suggest** that patients with resistance to alkylation-agent based regimens receive a CNI or patients with CNI-resistance be treated with an alkylation-agent based therapy.
Recommendation 7.7

**Suggest** that relapses of NS be treated by reinstitution of the same regimen used to induce the initial remission (but only one additional course of therapy for alkylating agent based regimens)
Relapses in Primary MN

- following "spontaneous remissions" = 5-12% 
- following Alkylating agent therapy = 22-30%
- following CNI therapy = 40-70% (depending on duration of therapy)
- following MMF therapy = 90-100%
- following Rituximab therapy = 25-30%
- following ACTH therapy = unknown
Recommendation 7.9

- **Suggest** that patients with MN and NS with Salb level of <2.5gm/dL AND addition risks for thrombosis be considered for prophylactic anticoagulation using oral Warfarin (*if no contraindications exist*)
Risks for Thrombosis

- Prior DVT or pulmonary emboli
- Obesity
- Immobilization
- CHF
- Concomitant cancer
- Hereditary “thrombophilic” state (Factor V Leiden, Thrombocytosis, Protein C or S deficiency
- Recent abdominal, orthopedic or gynecologic surgery
- Oral contraceptive usage
Primary MN and Thrombo-embolic Events

- Primary MN with Nephrotic Syndrome is associated with an increased risk for DVT, Renal Vein Thrombosis and Pulmonary Embolism.

- The magnitude of the risk greatly increases when [Salb] fall below 2.8gms/dL, regardless of the urine protein excretion rate.

- Although no RCT have yet been performed, Markov Decision Analysis favors prophylactic anticoagulants (Warfarin or Heparin only, not newer anti-thrombin agents [“gatrans’]) when risk of VTE is high (based on Salb and other risk factors) and bleeding risk is low.
CONCLUSIONS:

Primary MN Therapy in 2014-1

- The *great majority* of patients can be induced into a CR or PR by judicious use of a sequential therapeutic regimen involving CYC and/or CNI as initial therapy with Rituximab, ACTH or MMF reserved for “rescue” therapy; but any of these can be used initial therapy in selected cases.

- Resistance to *one* agent does not define resistance to *all* agents.

- Spontaneous remissions are *common* (20-30%) and adequate opportunities should be given for such remissions to occur, unless severe disease prompts early active treatment.
CONCLUSIONS:

**Primary MN Therapy in 2014- II**

- ESRD is *very uncommon* in those with lasting CR or PR

- Relapses are common (20-40%), depending on the initial regimen chosen and often easily treatable

- Second-line treatments (Rituximab, ACTH or MMF) can be used for initial therapy if patients are unwilling or unable to take recommended initial therapy regimens (CYC or CNI)

- Prophylactic anticoagulants (Heparin or Warfarin) are indicated if Salb is <2.8gms/dL, risk of bleeding complications are low, especially if additional risk factors are present
A 71 year old man is found to have the Nephrotic Syndrome (Urine protein excretion of 11.2gms/d; serum albumin of 2.2gms/dL). His serum creatinine is 1.50mg/dL (132µM/L; eGFR- CKD-EPI- creatinine= 46ml/min/1.73m2). He has no past history of illnesses other than a myocardial infarction 5 years ago. He is a former heavy smoker. He takes a “baby” aspirin daily.

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IgG subclass shows extensive deposits of IgG4, and weaker deposits of IgG1, 2 and 3. A PLA2R1 antigen is 4+ along the capillary walls.
QUESTION #1B

Which ONE of the following treatments would you recommend?

A. Observe for up to 6 months while receiving an angiotensin converting enzyme inhibitor and diuretic
B. Give Cyclosporine 5mg/kg/d plus 20mg/d of prednisone
C. Give cyclical oral cyclophosphamide at 1-1.5mg/Kg alternating with IV methyl prednisolone and oral prednisone
D. Give 1000mg of Rituximab twice at an interval of two weeks
E. Give MMF 1.0gm twice daily
F. Give 80 units of ACTH gel twice weekly
The Correct answer is \textit{C- Cyclical cyclophosphamide and prednisone.}

He is unlikely to respond to RAS inhibition and is a high risk of a thrombo-emboilic event (Salb 2.2gms/dL) which might be life-threatening. If his risk of serious bleeding is low he should also receive anti-coagulants (heparin followed by warfarin).
Primary MN Therapy - Uncertainties

- What is the role of anti-PLA2R antibody measurement in therapeutic decision making (initiating and withdrawing treatment)?

- How to treat anti-PLA2R “negative” subjects with advanced lesions? When to re-biopsy to determine “futility”

- When to use Rituximab, ACTH or MMF as initial therapy? (likely to be answered by RCT in progress)

- How best to manage patients with mild-moderate but infrequent relapses?

- Can recurrences of the same disease in the allograft (occurring in 20-40% of patients) be predicted or prevented?