Nephrotic Syndrome
-membranous nephropathy-

APSN Continuing Medical Education (CME) course
July 2nd, 2014
Yokohama, Japan

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This presentation is constructed in reference to the educational course entitled ‘MEMBRANOUS NEPHROPATHY: Treatment in the Modern Era.’ presented by Dr. Richard Glassock, in KDIGO-Mumbai Nephrology Summit, Mumbai, India 2014.

I tried to review the evidence from Asian countries, including China, Korea, India and Japan.

The management can be different in different regions.

APSN CME 2014 YOKOHAMA

Case 1 (1).

A 80-year-old man visits our hospital because of persistent ankle edema for 4 months. His urine protein excretion is 7.89 g/day and urine sediments show 10-30 RBC/hpf.

His serum albumin is 2.0 gms/dL, and serum creatinine is 0.8 mg/dL. He has been treated with CCB for ten years.

He has past history of early gastric cancer which was cured by endoscopic mucosal resection 6 years ago.

Upper gastrointestinal endoscopy performed last year showed no malignancy.

Blood pressure is 150/75mmHg. 2+ pitting edema of ankles is present.

Abdominal CT shows no abnormality.

Q1.
Which kind of renal pathology would you expect?

Q2.
Would you perform renal biopsy?

Clin Exp Nephrol (2012) 16:557–563
DOI 10.1007/s10157-012-0593-7

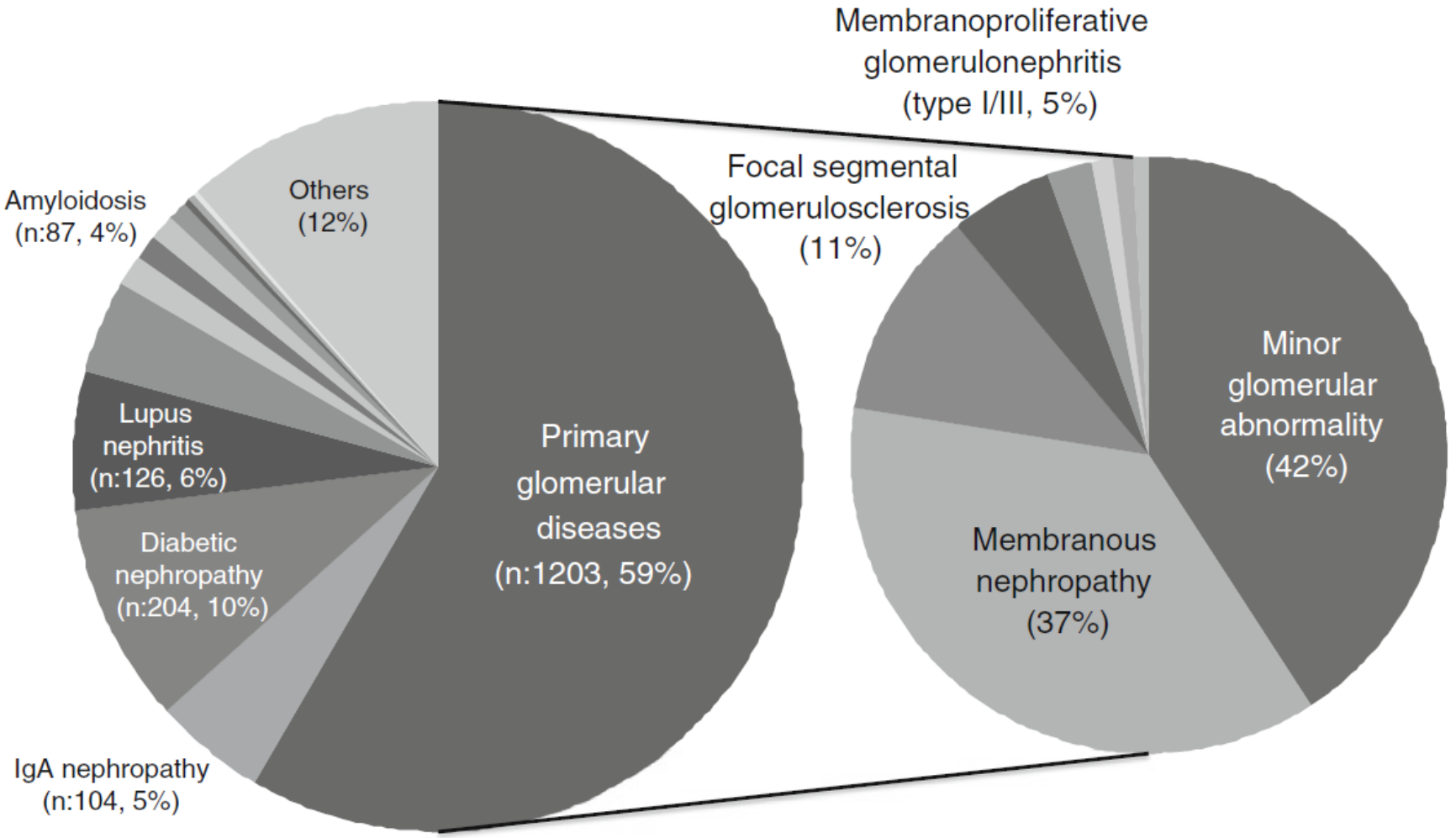
ORIGINAL ARTICLE

Membranous nephropathy in Japan: analysis of the Japan Renal Biopsy Registry (J-RBR)

Clin Exp Nephrol. 2012 Dec;16(6):903-20.

Hitoshi Yokoyama · Takashi Taguchi · Hitoshi Sugiyama · Hiroshi Sato ·
On behalf of the Committee for the Standardization of Renal Pathological Diagnosis
and for Renal Biopsy and Disease Registry in the Japanese Society of Nephrology

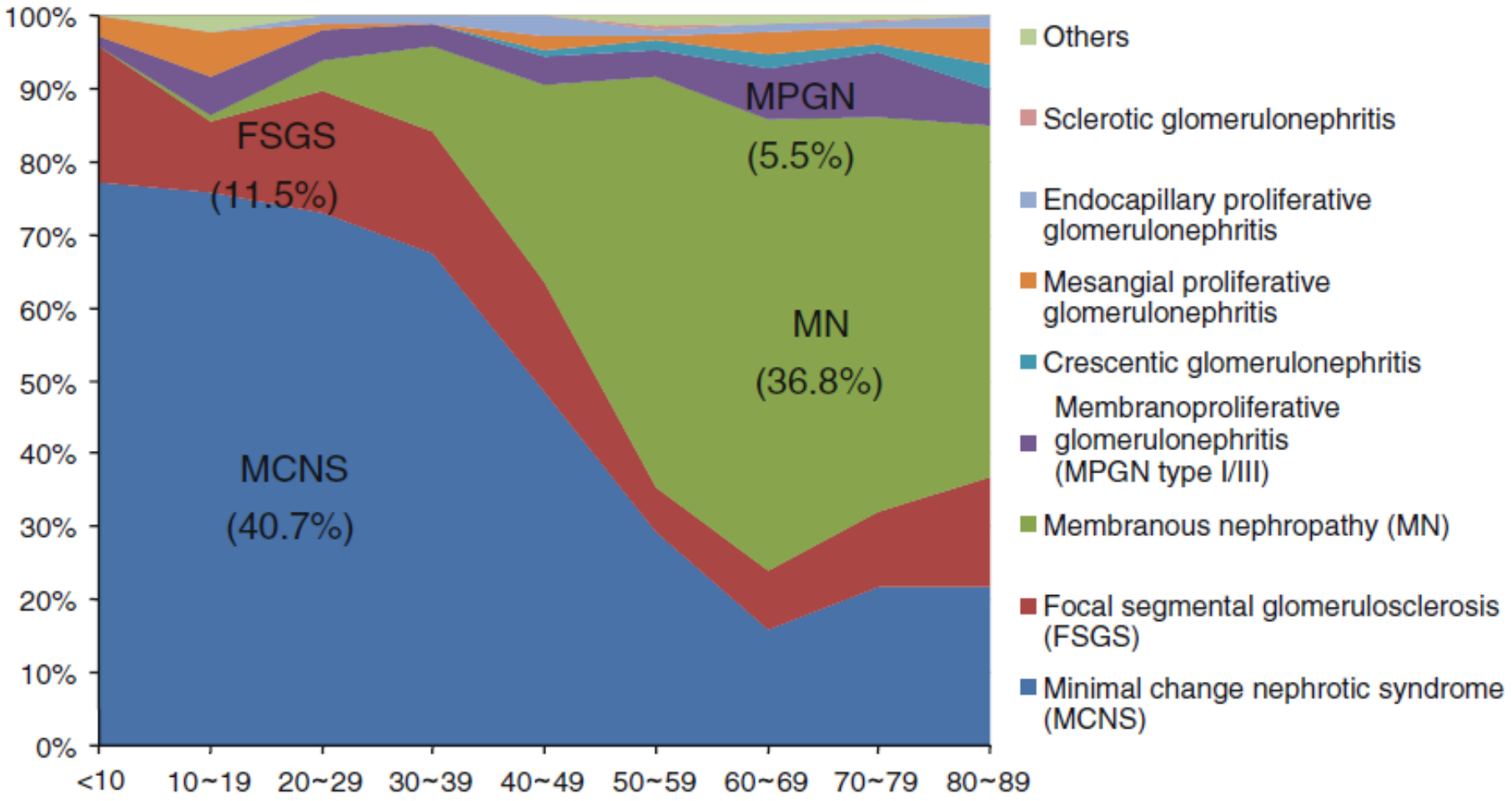
Nephrotic Syndrome in Japan



Glomerular lesions of nephrotic syndrome patients in Japan. J-RBR 2007–2010 registry: 2066 cases in total; 1203 cases of primary glomerular disease. Membranous nephropathy accounted for 37% of the idiopathic nephrotic syndrome cases in Japan.

Clin Exp Nephrol (2012) 16:557–563

Idiopathic nephrotic syndrome patients in Japan



Glomerular lesions of idiopathic nephrotic syndrome patients in Japan according to age. J-RBR 2007–2010 registry: 1203 cases of primary glomerular disease excluding IgA nephropathy.

Clin Exp Nephrol (2012) 16:557–563

Clin Exp Nephrol (2012) 16:903–920
DOI 10.1007/s10157-012-0673-8

ORIGINAL ARTICLE

Renal disease in the elderly and the very elderly Japanese: analysis of the Japan Renal Biopsy Registry (J-RBR)

Hitoshi Yokoyama · Hitoshi Sugiyama · Hiroshi Sato · Takashi Taguchi · Michio Nagata · Seiichi Matsuo · Hirofumi Makino · Tsuyoshi Watanabe · Takao Saito · Yutaka Kiyohara · Shinichi Nishi · Hiroyuki Iida · Kunio Morozumi · Atsushi Fukatsu · Tamaki Sasaki · Kazuhiko Tsuruya · Yukimasa Kohda · Makoto Higuchi · Hideyasu Kiyomoto · Shin Goto · Motoshi Hattori · Hiroshi Hataya · Shoji Kagami · Norishige Yoshikawa · Yuichiro Fukasawa · Yoshihiko Ueda · Hiroshi Kitamura · Akira Shimizu · Kazumasa Oka · Naoki Nakagawa · Takafumi Ito · Shunya Uchida · Kengo Furuichi · Izaya Nakaya · Satoshi Umemura · Keiju Hiromura · Mitsuhiro Yoshimura · Nobuhito Hirawa · Takashi Shigematsu · Masafumi Fukagawa · Makoto Hiramatsu · Yoshio Terada · Osamu Uemura · Tetsuya Kawata · Akira Matsunaga · Aki Kuroki · Yasukiyo Mori · Koji Mitsuiki · Haruyoshi Yoshida

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Clin Exp Nephrol (2012) 16:903–920

Table 7 Pathological diagnoses of nephrotic syndrome in the very elderly Japanese (≥80 years old)

	n	%
Primary nephrotic syndrome (male:female)	95 (37:58)	59.4
Membranous nephropathy	45	28.1
Minimal change nephrotic syndrome	19	11.9
Focal segmental glomerulosclerosis	12	7.5
Membranoproliferative glomerulonephritis (type I/III)	4	2.5
Mesangial proliferative glomerulonephritis except for IgA nephropathy	4	2.5
Crescentic glomerulonephritis	2	1.3
Endocapillary proliferative glomerulonephritis	2	1.3
IgA nephropathy	7	4.4

Clin Exp Nephrol (2012) 16:903–920

Secondary nephrotic syndrome except for IgA nephropathy (male:female)	65 (33:32)	40.6
Diabetic nephropathy	10	6.3
Amyloid nephropathy	19	11.9
Lupus nephritis	1	0.6
Infection-related nephropathy	3	1.9
Nephrosclerosis	4	2.5
Purpura nephritis	0	0.0
MPO-ANCA-positive nephritis	3	1.9
Others	25	15.6
Total cases (male:female)	160 (70:90)	100

Clin Exp Nephrol (2012) 16:903–920

Q1.
Which kind of renal pathology would you expect?

1. Membranous nephropathy
2. MCD
3. FSGS
4. MPGN
5. IgA-N
6. Amyloidosis
7. Infection related GN
8. Lupus Nephritis
9. Others

Q2.
Would you perform renal biopsy?

Yes

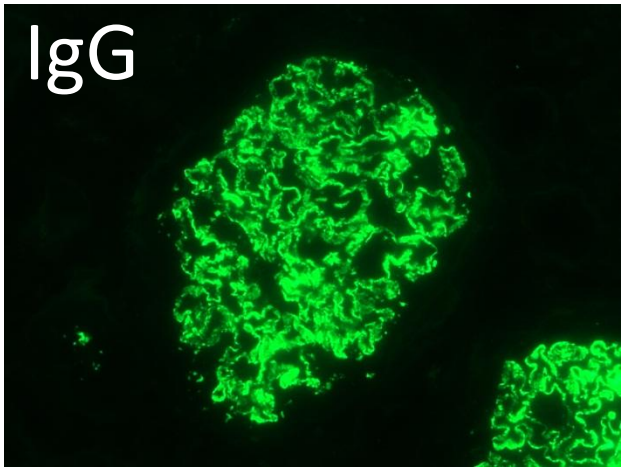
Q3
Before performing renal biopsy, which of the following would you request?

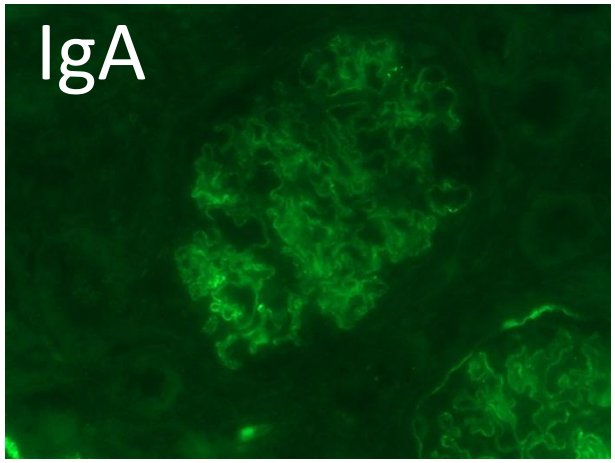
A. Anti-nuclear antibody and anti-dsDNA assay
B. Serum Hepatitis B surface antigen
C. HCV Ab
D. Serum Protein Electrophoresis
E. Complement C3 and C4

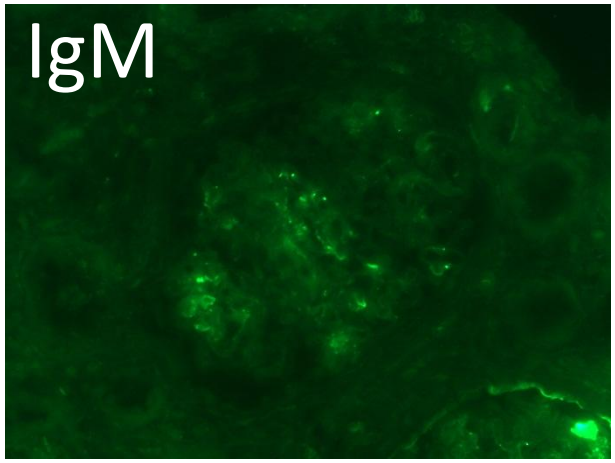
Answer.
I would order all of the above.

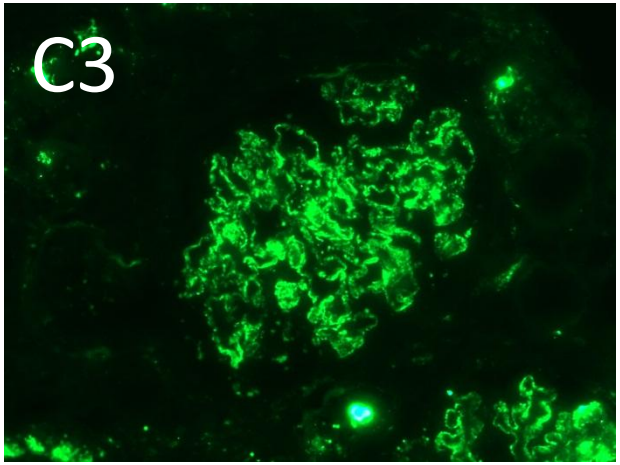
The test results are all negative or normal.

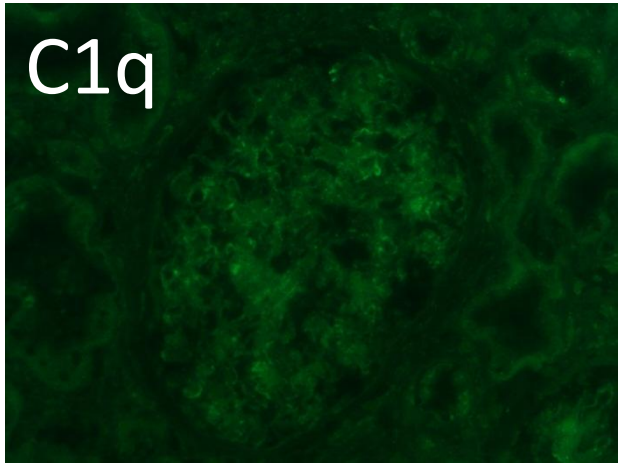
Case 1(2)
A renal biopsy was performed.
Light microscopy reveals slightly thickened capillary walls, without proliferation.
IF shows 3+ granular IgG and 2+ granular C3 along the glomerular capillary wall. No mesangial deposits is seen. IgA and C4 are weakly positive (+). IgM and C1q are negative.
EM shows thickened basement membrane, spikes and electron dense deposits along the subepithelium.

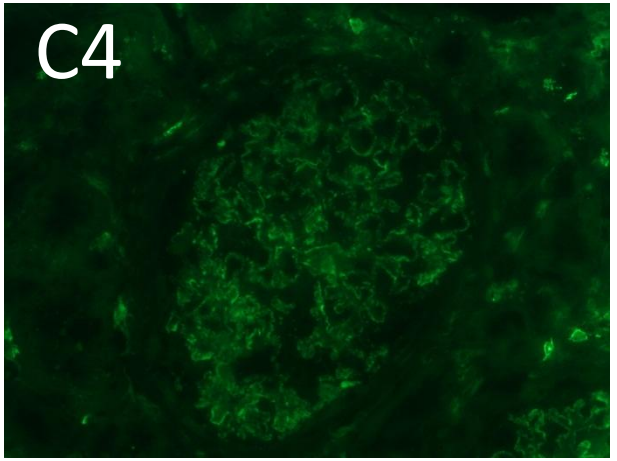

IgG

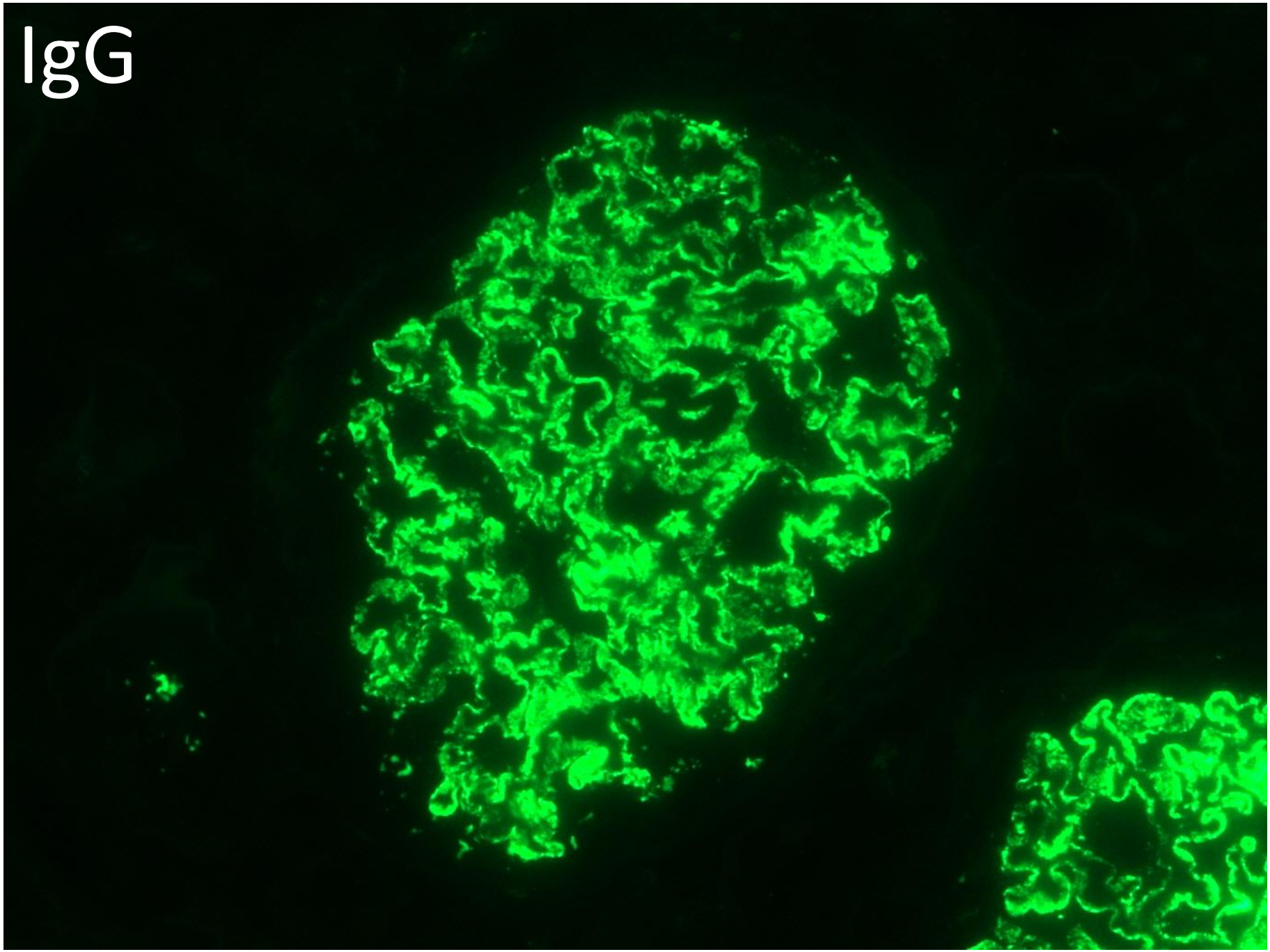

IgA

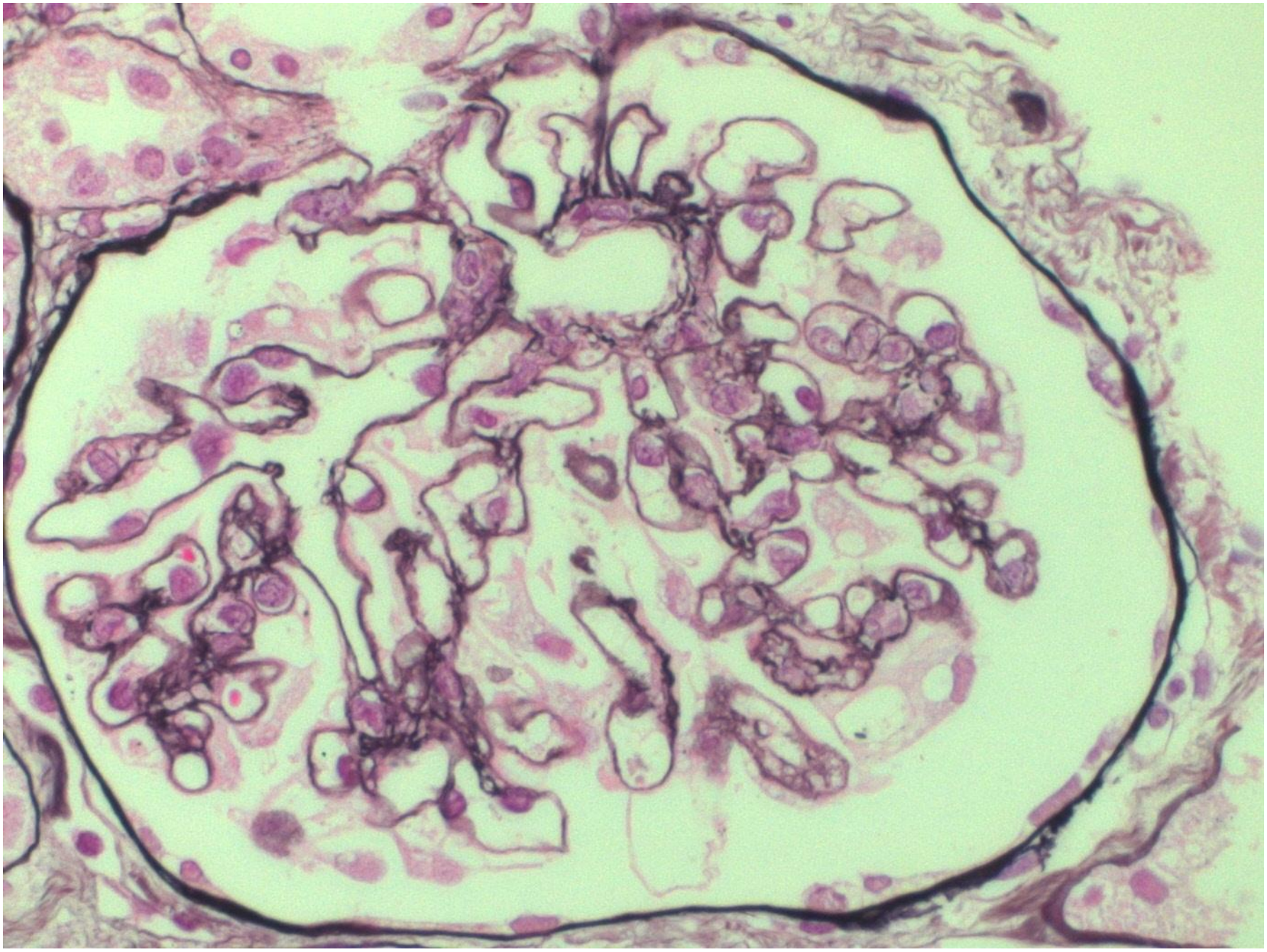

IgM

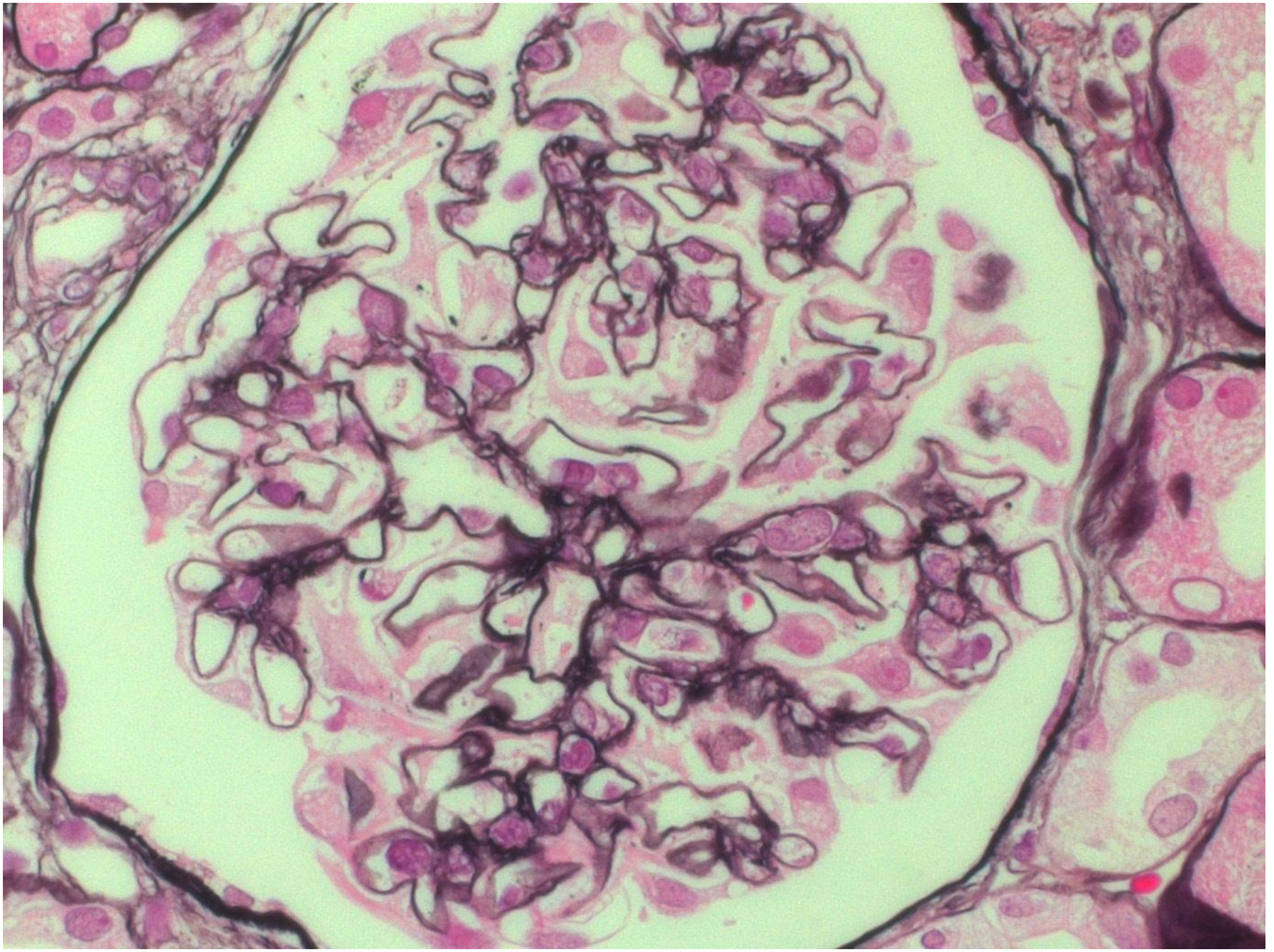

C3


C1q


C4

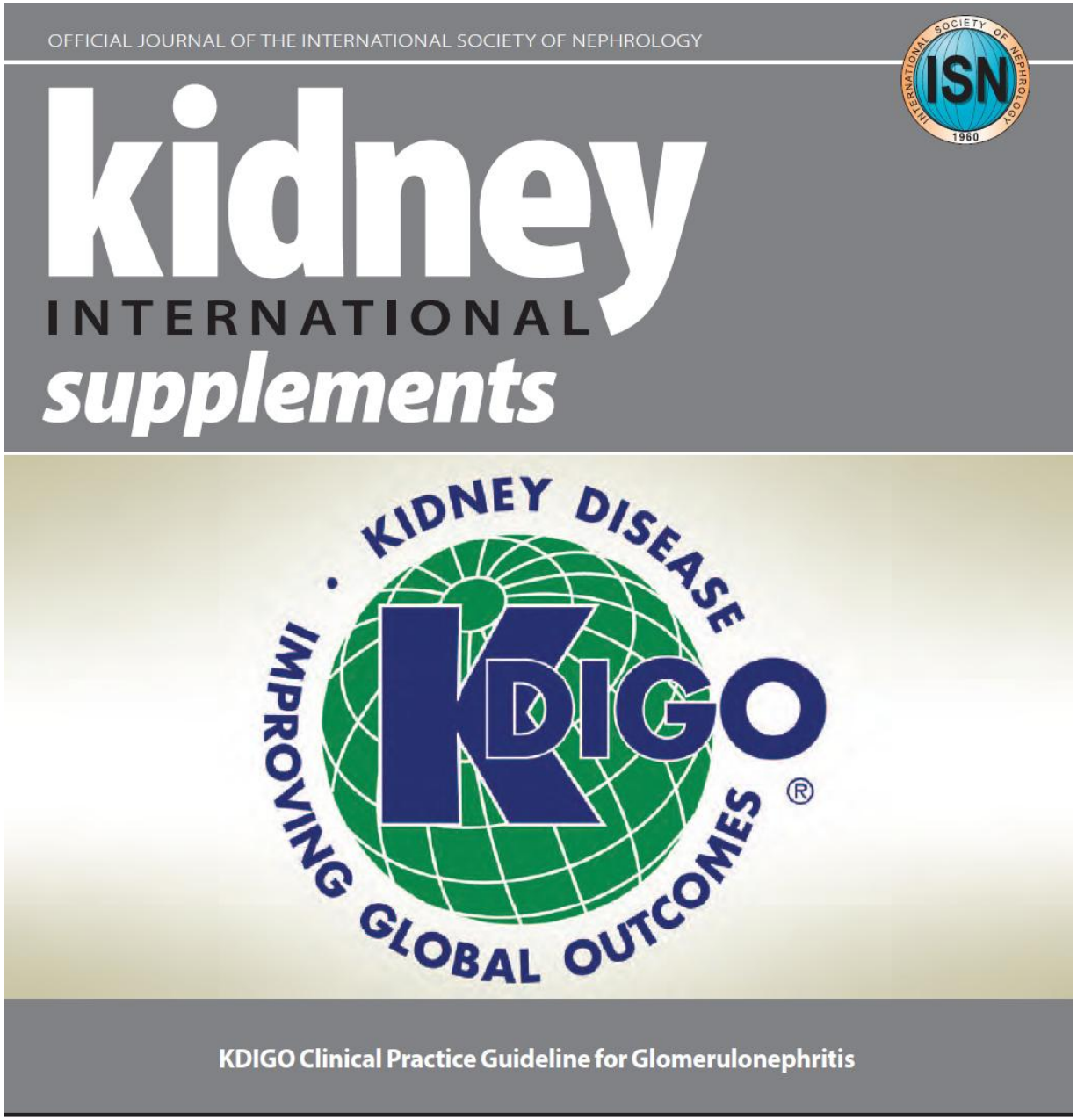

IgG





Q4.
Which of the following would you now request?

A. IgG subclass staining
B. Congo Red Staining
C. PLA2R Ab measurement
D. IgG κ and IgG λ staining
E. Additional sections stained with PAM



KDIGO Clinical Practice Guideline for Glomerulonephritis

7.1: Evaluation of MN

7.1.1: Perform appropriate investigations to exclude secondary causes in all cases of biopsy-proven MN. (Not Graded)

Table 12 | Reported causes of secondary MN (% in adults)

Cause	China Zeng *et al.*[196] (*n*=390)	Japan Abe *et al.*[191] (*n*=137)	France Cahen *et al.*[192] (*n*=82)	Finland Honkanen[197] (***n*=82**)	United States Ehrenreich *et al.*[198] (*n*=167)
IMN	31.8	65.0	79.3	69.8	62.3
Secondary MN	68.2	35.0	20.7	30.2	37.7
Autoimmune diseases	50.0	25.5	6.1	17.7	7.2
Infections	12.0	5.1	2.5		2.4
Tumors	3.1	1.5	4.9	2.1	1.8
Drugs or toxins	3.1	2.2	6.1	10.4	4.2

IMN, idiopathic membranous nephropathy; MN, membranous nephropathy.

Abe *et al.*, Cahen *et al.*, and Ehrenreich *et al.* also reported diabetes as a secondary cause of MN, accounting for 0.7%, 1.2%, and 16.8% of secondary MN cases, respectively.

Reprinted from Zeng CH, Chen HM, Wang RS *et al.* Etiology and clinical characteristics of membranous nephropathy in Chinese patients. *Am J Kidney Dis* 2008; 52: 691–698 with permission from National Kidney Foundation;[196] accessed http://www.ajkd.org/article/S0272-6386(08)01058-5/fulltext.

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Cause	China Zeng *et al.*[196] (*n*=390)	Japan Abe *et al.*[191] (*n*=137)
IMN	31.8	65.0
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Autoimmune diseases	50.0	25.5
Infections	12.0	5.1
Tumors	3.1	1.5
Drugs or toxins	3.1	2.2

IMN, idiopathic membranous nephropathy; MN, membranous nephropathy.

Etiology and Clinical Characteristics of Membranous Nephropathy in Chinese Patients

China

Study Design

Case series.

Setting & Participants

Patients with biopsy-proven MN at the Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China.

Results

390 patients with MN were identified from 1985 to 2005. Of 390 patients with MN, 124 (31.8%) had idiopathic MN and 266 had secondary MN (68.2%). Of patients with idiopathic MN. Common presentations of idiopathic MN were 60.5% with proteinuria (39.5% of whom presented with nephrotic syndrome), 29.8% with hypertension, 17.7% with hematuria, and 0.8% with decreased kidney function. In patients with secondary MN, causes were autoimmune diseases (73.3%), infections (17.7%), tumors (4.5%), and drugs or toxins (4.5%). Systemic lupus erythematosus was the most common autoimmune disease (predominately in younger women). Hepatitis B predominated in younger men. Greater levels of proteinuria were found in patients who presented with drugs or toxins compared with patients with other secondary MNs ($P < 0.05$).

Am J Kidney Dis 2008; 52: 691–698.

Table 13 | Reported causes of secondary MN

Autoimmune	Infections
Autoimmune diseases	Hepatitis B
Systemic lupus erythematosus	Hepatitis C
Rheumatoid arthritis	Human immunodeficiency virus
Mixed connective tissue disease	Malaria
Dermatomyositis	Schistosomiasis
Ankylosing spondylitis	Filariasis
Systemic sclerosis	Syphilis
Myasthenia gravis	Enterococcal endocarditis
Bullous pemphigoid	Hydatid disease
Autoimmune thyroid disease	Leprosy
Sjögren's syndrome	
Temporal arteritis	
Crohn's disease	
Graft-versus-host disease	

Table 13 | Reported causes of secondary MN

Drugs/Toxins	Miscellaneous
Gold	Diabetes mellitus (association or cause?)
Penicillamine	Sarcoidosis
Bucillamine	Sickle cell disease
Mercury compounds	Polycystic kidney disease
Captopril	α1-antitrypsin deficiency
Probenicid	Weber-Christian disease
Trimethadione	Primary biliary cirrhosis
Nonsteroidal anti-inflammatory drugs	Systemic mastocytosis
Cyclooxygenase-2 inhibitors	Guillain-Barre syndrome
Clopidogrel	Urticarial vasculitis
Lithium	Hemolytic-uremic syndrome
Formaldehyde	Dermatitis herpetiformis
Hydrocarbons	Myelodysplasia

KDIGO Clinical Practice Guideline for Glomerulonephritis

Mercury-Induced Membranous Nephropathy: Clinical and Pathological Features

China

Shi-Jun Li, Su-Hua Zhang, Hui-Ping Chen, Cai-Hong Zeng, Chun-Xia Zheng, Lei-Shi Li, and Zhi-Hong Liu

Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, P.R China

Table 1. General clinical characteristics and etiology in patients of mercury-induced MN

Case	Gender	Age, yr	Primary Disease	Etiology of Mercury Poisoning	Duration of Mercury Exposure, mo	Urinary Mercury Concentration, μg/L	Duration of Renal Symptoms, mo
1	F	24	rheumatoid arthritis	antirheumatoid pill	60	>400	12
2	F	45	rheumatoid arthritis	antirheumatoid pill	6	200	7
3	F	42	rheumatoid arthritis	antirheumatoid pill	5	48	2
4	M	15	still disease	antirheumatoid pill	60	22	2
5	F	37	no	skin-lightening cream	12	100	6
6	F	39	no	skin-lightening cream	8	12	1
7	F	33	no	skin-lightening cream	4	120	4
8	F	43	no	skin-lightening cream	8	18	3
9	F	38	no	mercury-containing hair dye	36	27	12
10	F	30	tuberculosis of breast	mercury-containing drugs	2	>400	2
11	F	18	no	mercury vapor	7	35	3

Clin J Am Soc Nephrol 5: 439–444, 2010.

Mercury-Induced Membranous Nephropathy

China

Table 3. Immunofluorescence findings in patients with mercury-induced MN

Case	IgG	IgA	IgM	C3	C4	C1q	IgG1	IgG3	IgG4
1	1+	N	N	2+	1+	1+	2+	N	1+
2	2+	1+	1+	1+	1+	1+	2+	N	1+
3	2+	N	N	2+	N	N	2+	1+	1+
4	2+	N	N	2+	1+	N	2+	N	1+
5	2+	1+	1+	2+	1+	1+	2+	N	N
6	2+	N	N	2+	N	N	1+	1+	1+
7	2+	N	N	1+	1+	1+	2+	N	1+
8	2+	N	N	2+	1+	N	2+	N	1+
9	2+	N	N	1+	N	N	2+	N	N
10	2+	N	N	2+	1+	1+	2+	N	1+
11	2+	N	N	1+	1+	1+	2+	N	1+

N, negative.

1. History of mercury exposure
2. Urine test for mercury excretion
3. IgG1>IgG4>IgG3

Patients should abstain from the mercury exposure, and immune suppression should be carefully avoided.

Clin J Am Soc Nephrol 5: 439–444, 2010.

Table 13 | Reported causes of secondary MN

Malignancies	
Carcinomas	*Noncarcinomas*
Lung	Hodgkin's lymphoma
Esophageal	Non-Hodgkin's lymphoma
Colon	Leukemia (chronic lymphocytic leukemia)
Breast	
Stomach	Mesothelioma
Renal	Melanoma
Ovary	Wilm's tumor
Prostate	Hepatic adenoma
Oropharynx	Angiolymphatic hyperplasia
	Schwannoma
	Neuroblastoma
	Adrenal ganglioneuroma

Major Causes of Secondary MN

1. Infection
    - hepatitis B and hepatitis C
    - malaria, schistosomiasis, TB, leprosy
    - Syphilis
2. Diseases associated with MN
    - Autoimmune
        - Lupus Nephritis
        - Rheumatoid arthritis
        - Sjogren's syndrome
    - Diabetes mellitus
    - sickle cell disease.
3. Drugs
    - gold, bucillamine, penicillamine,
    - NSAIDs, captopril
4. Malignancy

Nephrol Dial Transplant (2004) 19: 574–579
DOI: 10.1093/ndt/gfg616

Nephrology
Dialysis
Transplantation

Original Article

Japan

Distribution of glomerular IgG subclass deposits in malignancy-associated membranous nephropathy

Hiroshi Ohtani[1], Hideki Wakui[1], Atsushi Komatsuda[1], Shin Okuyama[1], Rie Masai[1], Nobuki Maki[1], Akihiro Kigawa[1], Ken-ichi Sawada[1] and Hirokazu Imai[1,2]

[1]The Third Department of Internal Medicine, Akita University School of Medicine, Akita and
[2]The Department of Nephrology and Rheumatology, Aichi Medical University, Aichi, Japan

Nephrol Dial Transplant (2004) 19: 574–579

Japan

Table 3. IF intensity of glomerular IgG subclass deposits in 10 patients with M-MN and 15 patients with idiopathic MN

Case no.	IgG1	IgG2	IgG3	IgG4
1	0.0	0.5	0.0	1.0
2	1.0	2.0	0.5	0.0
3	2.0	2.0	1.0	2.0
4	3.0	3.0	0.5	0.5
5	1.0	0.5	1.0	2.0
6	2.0	1.0	1.0	0.5
7	3.0	3.0	0.5	3.0
8	2.0	2.0	0.5	0.5
9	0.0	1.0	0.0	2.0
10	1.0	1.0	0.5	0.5
11	2.0	1.0	0.0	3.0
12	1.0	0.0	0.0	2.0
13	0.0	1.0	0.0	2.0
14	0.0	0.0	0.0	2.0
15	1.0	0.0	0.0	1.0
16	1.0	1.0	0.5	3.0
17	1.0	1.0	1.0	3.0
18	0.5	2.0	0.0	3.0
19	0.5	0.5	0.5	3.0
20	0.0	0.0	1.0	0.0
21	0.0	0.0	0.0	1.0
22	0.5	1.0	0.0	3.0
23	0.5	1.0	0.0	2.0
24	0.0	1.0	0.0	1.0
25	0.5	0.5	1.0	3.0

Case nos 1–10, malignancy group; case nos 11–25, idiopathic group.

Nephrol Dial Transplant (2004) 19: 574–579

IgG Subclass Distribution in Membranous Nephropathy

	IgG1	IgG2	IgG3	IgG4
Idiopathic	++	+	+-	+++
Lupus	+++	++	+++	+-
Neoplasia	+++	+++	++	+~-

Am J Kidney Dis.1994 Mar;23(3):358-64.
Clin Exp Immunol. 1984 Oct;58(1):57-62.

Clin Nephrol. 1983 Apr;19(4):161-5.

Nephrol. Dial. Transplant. (2004) 19 (3): 574-579.

Kidney International (1997) **51**, 270–276

Pathological findings suggesting secondary MN

1. LM — Proliferative lesion → SLE, MPGN？

2. IF — Full house (including C1q) → SLE?
Vascular and TBM staining → SLE?
IgG1, 3 > IgG4 → SLE?
IgG1, 2 > IgG4 → malignancy?

3. EM — Subendothelial deposits
Mesangial deposits

4. IHC — No granular staining for PLA2R Ag along GBM

Glomerular Diseases: Membranous Nephropathy—A Modern View

Claudio Ponticelli* and Richard J. Glassock†

Table 1. Investigations suggested to detect/exclude an underlying cancer in a patient with apparently idiopathic (primary) MN and repeatedly negative serologic tests for anti-PLA2R1 autoantibody and/or absence of PLA2R1 or IgG4 in glomerular deposits

Cancer Type	Young Adult	Older Patient
Lung	Chest x-ray	Computed tomography
Kidney	Ultrasonography, malignant cells in the urine	Ultrasonography, malignant cells in the urine
Breast	Physical examination	Mammography
Stomach	Fecal occult blood?	Gastroscopy
Colon	Fecal occult blood?	Colonoscopy
Prostate	Rectal digital examination, percentage PSA	Ultrasonography, prostate biopsy
Uterus	Gynecologic examination	Colposcopy

In young patients, fecal occult blood is usually searched for only in the case of anemia. MN, membranous nephropathy; PLA2R1, phospholipase A2 receptor 1; PSA, prostate specific antigen.

The association of MN with cancer is frequent, although not always clear cut. A French review showed that 24 of 240 (10%) patients with MN had a malignancy at the time of renal biopsy or within a year thereafter. The frequency of malignancy in MN increased with age up to 20%–25% after age 60 years. The solid organ cancers are particularly frequent, mainly in the lung, colon, breast, prostate, oruterus. An evaluation for underlying cancer is recommended for patients with MN, particularly for older individuals (Table 1).

Clin J Am Soc Nephrol 9: 609–616, 2014

Case 1

In the mean time・・・・・

Abdominal CT: normal
Chest CT: normal
PSA: normal
Urinary cytodiagnosis: no malignancy
Fecal occult blood: negative

Q4.
Which of the following would you now request?

A. IgG subclass staining
B. Congo Red Staining
C. PLA2R Ab measurement
D. IgG κ and IgG λ staining
E. Additional sections stained with PAM

Answer.
I would order A (and C).

Case 1 (2)

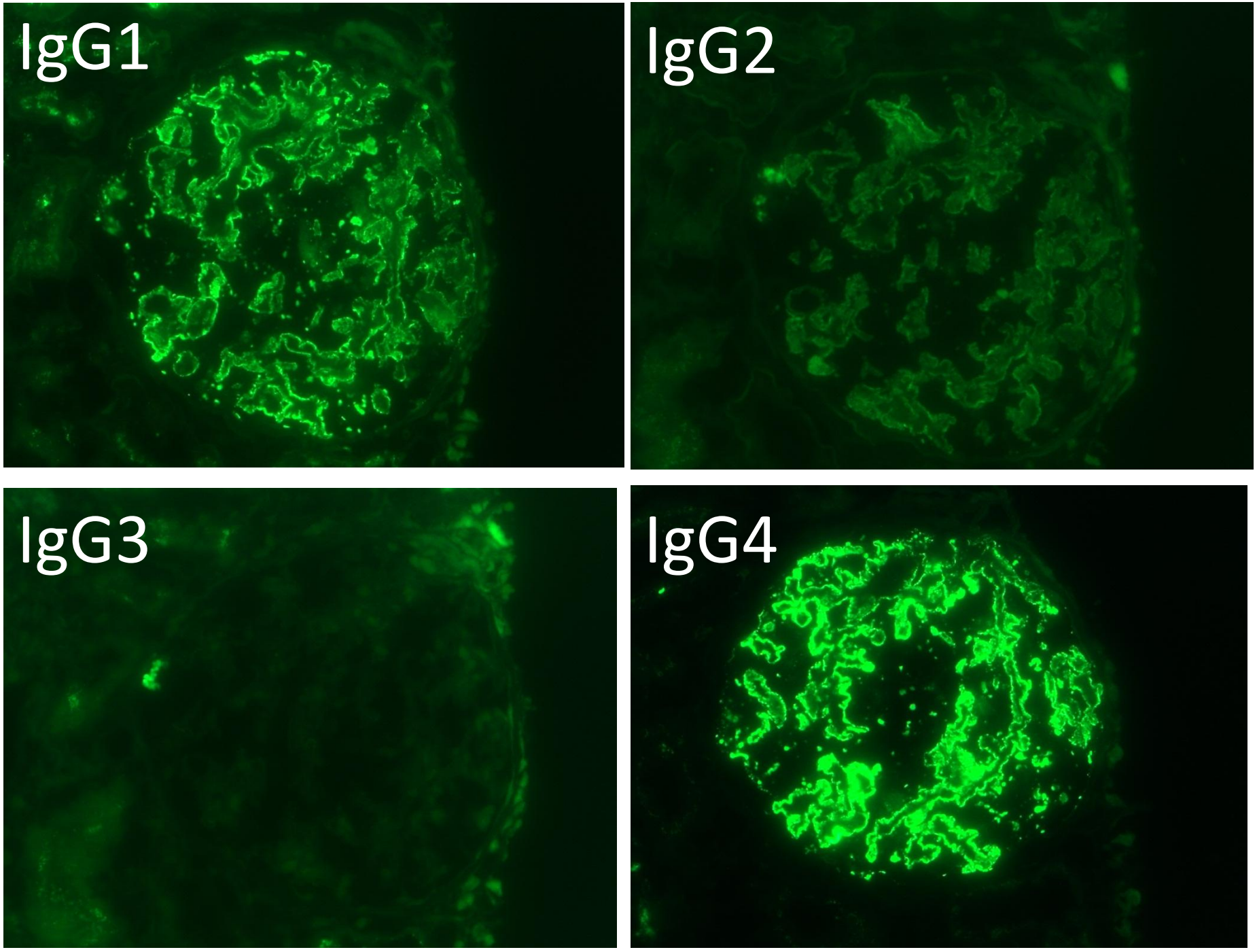
A renal biopsy was performed.

Light microscopy reveals slightly thickened capillary walls, without proliferation.

IF shows 4+ granular IgG and 3+ granular C3 along the glomerular capillary wall. No mesangial deposits is seen. IgA and IgM are weakly positive (+). C1q and C4 are negative.

EM shows thickened basement membrane, spikes and electron dense deposits along the subepithelium.

IgG subclass shows IgG4>>IgG1> IgG2. IgG3 is negative.


IgG1
IgG2
IgG3
IgG4

Target antigens in Membranous Nephropathy

1. α-enolase

Circulating antibodies against a-enolase in patients with primary membranous nephropathy (MN).

Wakui H, Imai A. et al. Clin Exp Immunol 1999; 118:445-450

2. NEP: neutral endopeptidase

Alloantigen involved in neonatal cases of membranous nephropathy that occur in newborns from neutral endopeptidase-deficient mothers.

Debiec H, Ronco P. N. Engl J Med 2002, Lancet 2004

3. PLA2R: M-type phospholipase A2 receptor

The first autoantigen identified in idiopathic MN in the adult.

Beck and Salant. N Engl J Med 2009;361:11-21.

4. Cationic BSA

Target Antigen in Early childhood MN.

Debiec H, Ronco P. N. N Engl J Med 2011;364:2101-10.

5. AR and SOD2:

Specific anti–aldose reductase (AR) and anti–manganese superoxide dismutase (SOD2) IgG4 were detected in sera of MN patients.

J Am Soc Nephrol 21: 507–519, 2010

6. Others:

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 2, 2009 VOL. 361 NO. 1

M-Type Phospholipase A_2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy

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CONCLUSIONS

A majority of patients with idiopathic membranous nephropathy have antibodies against a conformation-dependent epitope in PLA_2R. PLA_2R is present in normal podocytes and in immune deposits in patients with idiopathic membranous nephropathy, indicating that PLA_2R is a major antigen in this disease.

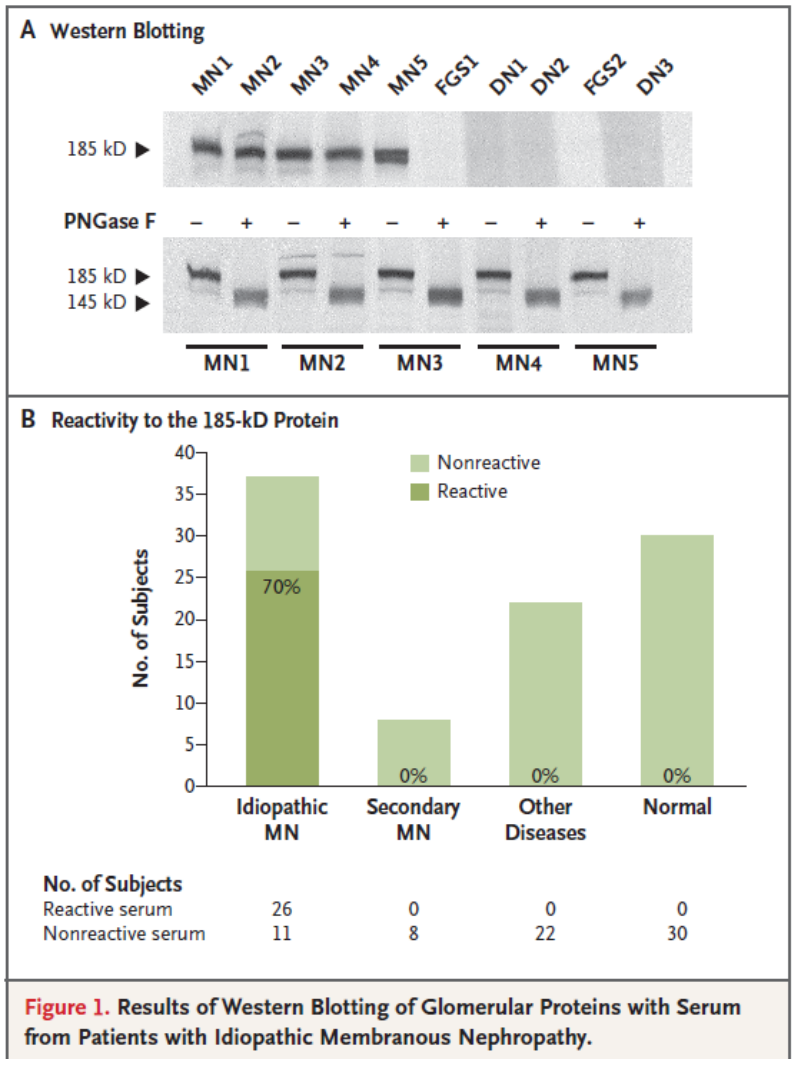

Figure 1. Results of Western Blotting of Glomerular Proteins with Serum from Patients with Idiopathic Membranous Nephropathy.

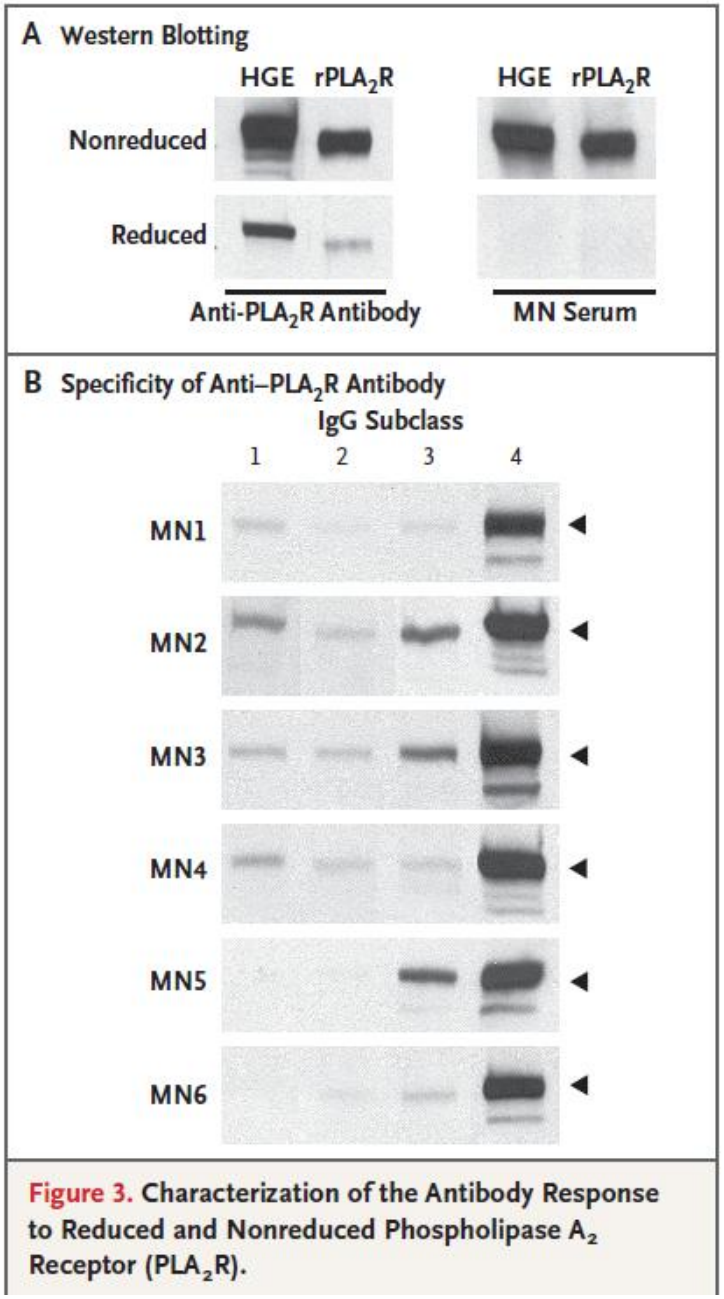

Figure 3. Characterization of the Antibody Response to Reduced and Nonreduced Phospholipase A_2 Receptor (PLA_2R).

Anti-Phospholipase A_2 Receptor Antibodies Correlate with Clinical Status in Idiopathic Membranous Nephropathy

Julia M. Hofstra, Laurence H. Beck, Jr.,† David M. Beck,† Jack F. Wetzels,* and David J. Salant†*

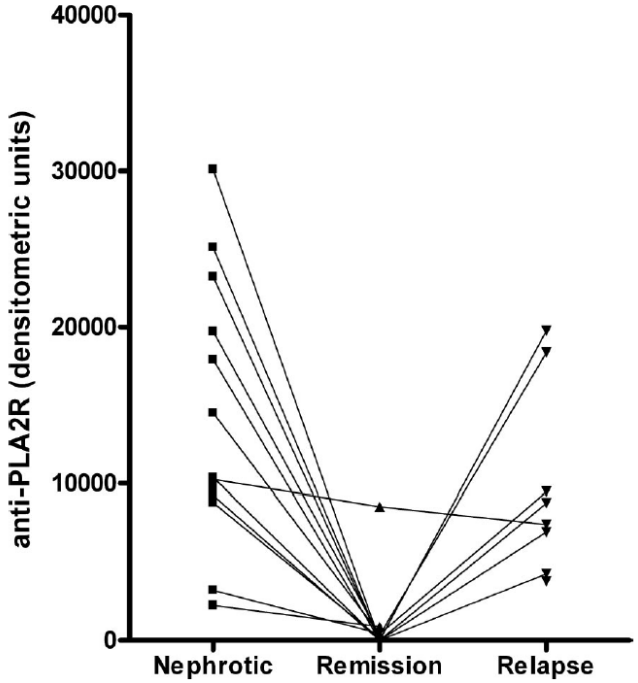

Figure 2. | Anti-PLA_2R-autoantibody levels during the clinical course of 13 anti-PLA_2R-positive patients with remission of proteinuria during follow-up. Nephrotic, sample taken during period of proteinuria >3.5 g/d with serum albumin <3.0 g/dl; Remission, sample taken during clinical remission with proteinuria <3.5 g/d; Relapse, sample taken during clinical relapse of proteinuria >3.5 g/d after a period of remission.

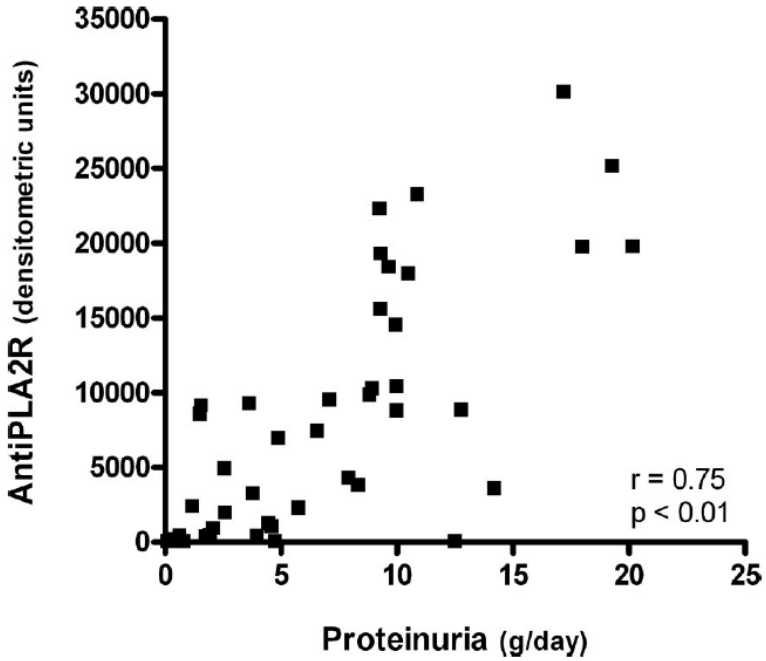

Figure 3. | Correlation between the anti-PLA_2R antibody level and proteinuria. All of the samples were taken during the clinical course (n = 46) from 14 patients with positive aPLA_2R antibodies at baseline.

Rituximab-Induced Depletion of Anti-PLA_2R Autoantibodies Predicts Response in Membranous Nephropathy

Laurence H. Beck, Jr.,* Fernando C. Fervenza,†
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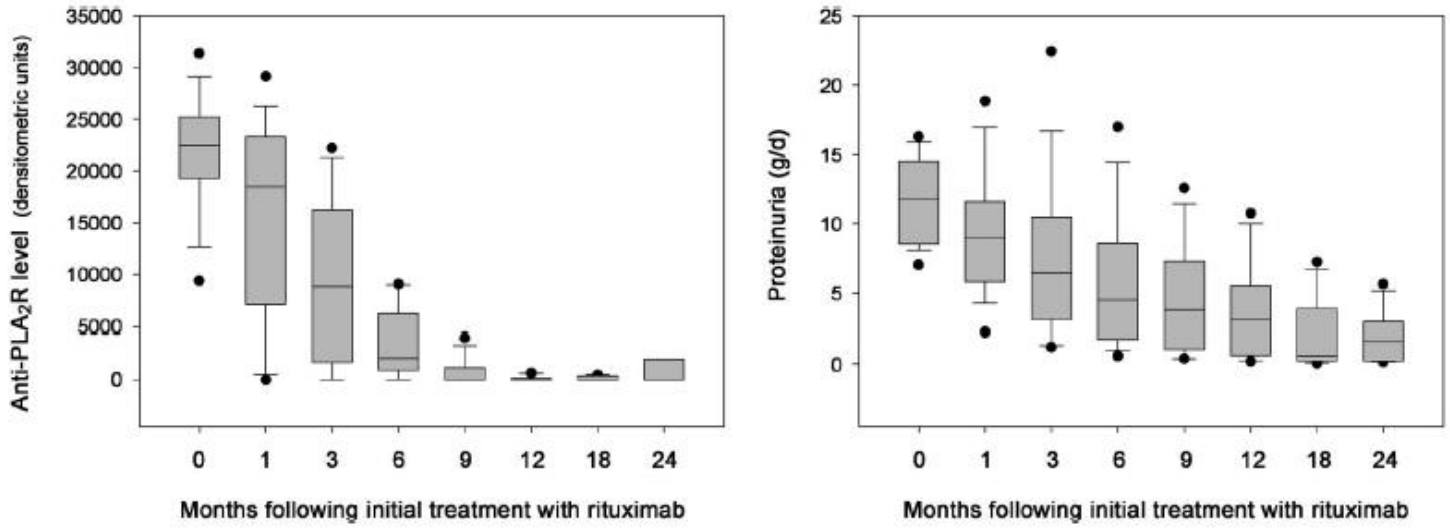

Figure 3. Anti-PLA_2R (left box plot) declines in advance of a more gradual decline of proteinuria (right) in those patients who cleared anti-PLA_2R. Boxes represent median (line) and 25th and 75th percentiles, with whiskers to the 10th and 90th percentiles. Outliers are represented by filled circles.

J Am Soc Nephrol 22: 1543–1550, 2011.

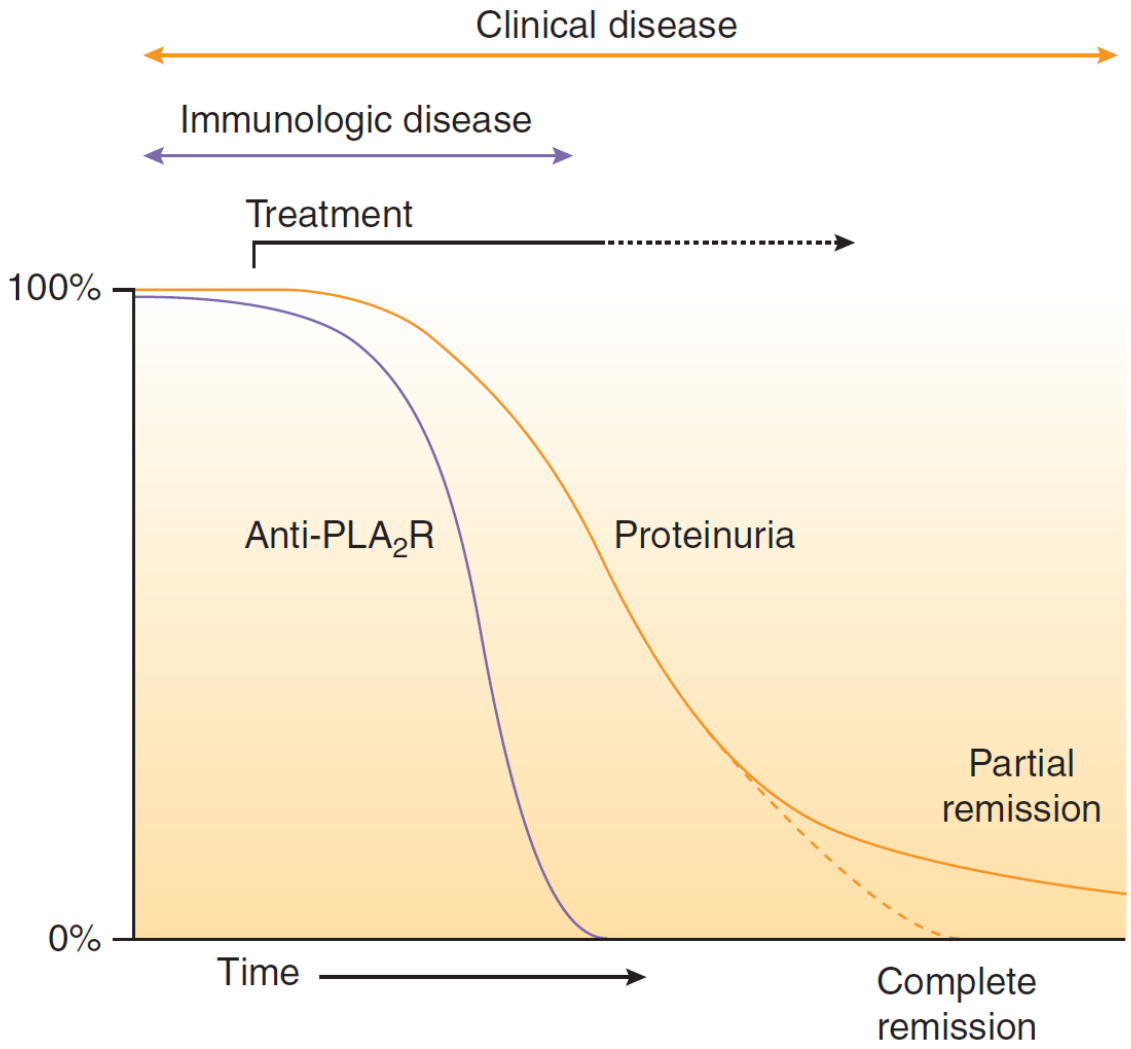

Figure 1 | Relationship between clinical disease (proteinuria) and immunological activity (circulating anti-PLA2R) in idiopathic membranous nephropathy.

Beck and Salant *Kidney International* (2010) **77**, 765–770

Antiphospholipase A_2 Receptor Antibody Titer and Subclass in Idiopathic Membranous Nephropathy

Anti-PLA2R auto-antibody (ELISA) and outcomes (n=79- all PLA2R1 +)

Table 1. Baseline characteristics (*n*=117)

	All (*n*=117)	Paris (*n*=20)	Nijmegen (*n*=77)	Manchester (*n*=20)
Sex (male/female)	91/26	13/7	64/13	14/6
Age at diagnosis (yr)	51±16	54±19	51±16	47±11
Serum creatinine (μmol/L)	95 (51–320)	97 (61–259)	95 (51–320)	91 (60–261)
Serum albumin (g/L)	22.5±6.3	17.3±7.0	23.4±5.7	24.8±4.6
Proteinuria (g/d)	10.2 (3.6–37.9)	9.0 (4.1–24.0)	11.0 (3.6–37.9)	9.2 (3.8–20.1)
eGFR (ml/min per 1.73 m^2)	73±27	69±25	73±28	77±26
Interval Bx serum sample (mo)	2 (−2 to 6)	0	2 (0–6)	1 (−2 to 5)
Follow-up (mo)	54 (2–277)	38 (9–104)	56 (2–148)	85 (4–277)

In the French cohort, all serum samples were collected at time of renal biopsy. One patient was from a non-Manchester UK cohort.[5] Data are mean ± SD or median (range). eGFR was calculated using the MDRD formula. Bx, renal biopsy.

Table 3. Outcome in aPLA$_2$R antibody-positive patients (*n*=79): outcome in different tertiles of antibody titer (ELISA)

Outcome	aPLA$_2$R=41–175 U/ml (*n*=26)	aPLA$_2$R=176–610 U/ml (*n*=26)	aPLA$_2$R>610 U/ml (*n*=27)	*P* Value
Partial remission	11 (42%) **Low**	8 (31%) **middle**	11 (41%) **High**	NS
Complete remission	7 (27%)	9 (35%)	8 (30%)	NS
Renal failure	1 (4%)	3 (12%)	5 (19%)	NS
Persistent proteinuria	7 (27%)	6 (23%)	3 (11%)	NS
Spontaneous remission[a]	10 (38%)	8 (31%)	1 (4%)	<0.01

Definitions of remission are in the text.
[a]No treatment with immunosuppressive agents.

Hofstra JM, et al JASN 23:1735-1743, 2012

Antiphospholipase A_2 Receptor Antibody Titer and Subclass in Idiopathic Membranous Nephropathy

Anti-PLA2R auto-antibody (ELISA) and outcomes (n=79- all PLA2R1 +)

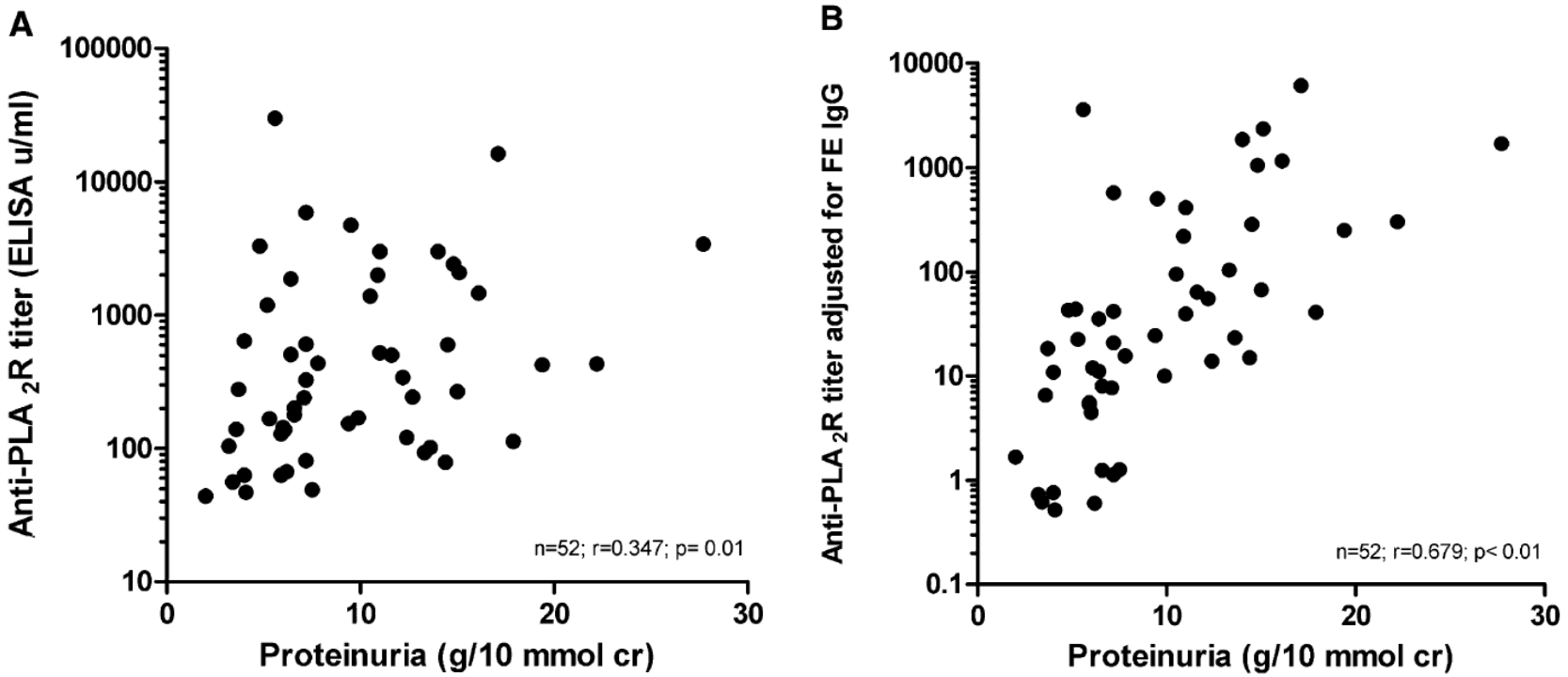

Figure 2. Correlation between anti-PLA2R levels measured with an ELISA technique and proteinuria in patients of the Dutch cohort. (A) Unadjusted analysis. (B) Anti-PLA2R levels adjusted for fractional excretion of IgG.

Hofstra JM, et al JASN 23:1735-1743, 2012

Anti-Phospholipase A2 Receptor Antibody in Membranous Nephropathy

China

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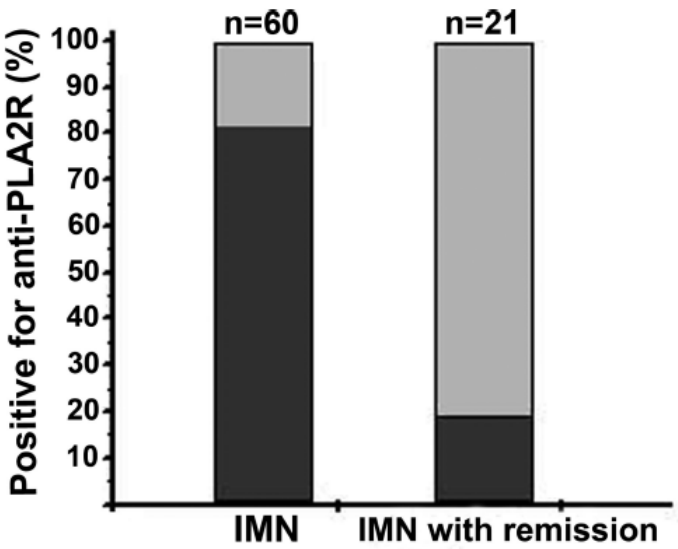

Figure 4. The prevalence of anti-PLA2R in idiopathic MN (IMN) in remission is low by comparison to IMN patients with nephrotic syndrome. The prevalence of anti-PLA2R seropositivity was compared in the 60 patients with nephrotic syndrome to 21 additional patients in remission (see Supplemental Tables 2 and 3 for details), using the standard assay.

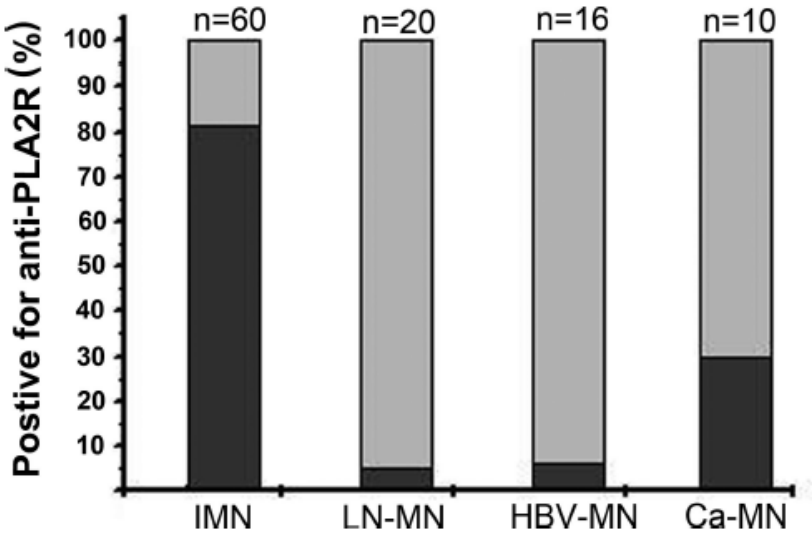

Figure 5. Anti-PLA2R is detected infrequently in secondary MN. The dark bars represent the prevalence of anti-PLA2R detected in patients with idiopathic (IMN), lupus-associated (LMN), hepatitis B—associated (HBV-MN), and cancer-associated (Ca-MN) membranous nephropathy, using the standard Western blot assay.

J Am Soc Nephrol 22: 1137–1143, 2011.

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PLOS ONE

Autoantibodies against Phospholipase A_2 Receptor in Korean Patients with Membranous Nephropathy

Korea

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Abstract

The data were presented in abstract form at the 45th meeting of the American Society of Nephrology, October 30-November 04 2012, San Diego, CA, USA. Circulating autoantibodies against M-type phospholipase A_2 receptor (PLA_2R) are important pathogenic antibodies of idiopathic membranous nephropathy (MN) in adults. However, previous studies on the clinical impact of anti-PLA_2R antibodies demonstrated several limitations, including insufficient numbers of study subjects and different time points and methods for anti-PLA_2R antibody measurement. To verify the clinical significance of anti-PLA_2R antibodies in Korean patients with MN, we measured autoantibodies in serum samples obtained at the time of biopsy from a total of 100 patients with idiopathic MN who had not yet received immunosuppressive treatment. We detected anti-PLA_2R antibody in 69 patients, and we observed that autoantibody reactivity reflected the severity of disease activity. Proteinuria and hypoalbuminemia were more severe in patients with anti-PLA_2R than in those without the autoantibodies (2.95 g/g vs. 6.85 g/g, $P=0.003$; 3.1 g/dL vs. 2.5 g/dL, $P=0.004$, respectively). Additionally, the clinical severities worsened proportionally as the levels of anti-PLA_2R antibodies increased ($P=0.015$ and P *for trend* <0.001 for proteinuria and hypoalbuminemia, respectively). However, neither the levels nor the presence or absence of anti-PLA_2R antibody showed a significant correlation with clinical outcomes, such as remission rate and time to remission. In conclusion, we observed that anti-PLA_2R antibodies are highly prevalent in Korean patients with idiopathic MN and that they reflect the clinical disease activity before the administration of immunosuppressive treatment. However, the levels of anti-PLA_2R antibody at the time of kidney biopsy may not predict the clinical outcomes in current clinical practice.

Citation: Oh YJ, Yang SH, Kim DK, Kang S-W, Kim YS (2013) Autoantibodies against Phospholipase A_2 Receptor in Korean Patients with Membranous Nephropathy. PLoS ONE 8(4): e62151. doi:10.1371/journal.pone.0062151

PLoS ONE 8(4): e62151. 2013

Korea

Table 3. Clinical outcomes and general characteristics of patients with idiopathic MN according to anti-PLA_2R reactivity.

		Positive	Negative	
	Total	**Anti-PLA_2R(+)**	**Anti-PLA_2R(-)**	***P* value**
Number of patients	77	56	21	
Age	55±13.9	55±13.1	58±15.9	0.438
Male	40 (51.9%)	31 (55.4%)	9 (42.9%)	0.328
Total cholesterol (mg/dL)	281±99	286±105.1	265±83.4	0.397
Serum creatinine (mg/dL)	0.92±0.35	0.90±0.33	0.97±0.40	0.447
eGFR (mL/min/1.73 m^2)	89±29	90±24.3	85±39.4	0.527
Serum albumin (g/dL)	2.5±0.6	2.5±0.5	2.8±0.7	0.036
uPCR (g/g)	6.80 (4.80–9.98)	6.87 (4.97–9.99)	5.35 (2.29–9.90)	0.106
uPCR >3.5 g/g	66 (85.7%)	52 (92.9%)	14 (66.7%)	0.007
RAS blocker	64 (83.1%)	48 (85.7%)	16 (76.2%)	0.325
Statin	69 (89.6%)	51 (91.1%)	18 (85.7%)	0.676
Anti-coagulation	4 (5.2%)	4 (7.1%)	0 (0%)	0.570
Immunosuppressive treatment	52 (67.5%)	38 (67.9%)	14 (66.7%)	0.921
Steroid	18 (34.6%)	14 (36.8%)	4 (28.6%)	
Steroid + Cyclosporine	14 (26.9%)	8 (21.1%)	6 (42.8%)	
Steroid + Tacrolimus	2 (3.8%)	2 (5.3%)	0 (0%)	
Steroid + Cyclophosphamide	16 (30.8%)	12 (31.6%)	4 (28.6%)	
Steroid + Mycophenolate mofetile	2 (3.8%)	2 (5.3%)	0 (0%)	
Remission rate	63 (81.8%)	45 (80.4%)	18 (85.7%)	0.746
Treatment-induced	46 (73.0%)	33 (73.3%)	13 (72.2%)	
Spontaneous	17 (27.0%)	12 (26.7%)	5 (27.8%)	
Time to remission (months)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–5.5)	0.580
Relapse	7 (9.1%)	5 (8.9%)	2 (9.5%)	1.000

The data are expressed as the number (%) or median (25–75% interquartile range) or the mean±SD. MN, membranous nephropathy; Anti-PLA_2R, anti-phospholipase A_2 receptor antibody. eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease formula; uPCR, urine protein-creatinine ratio; RAS blocker, renin angiotensin systemic blocker.

doi:10.1371/journal.pone.0062151.t003

PLoS ONE 8(4): e62151. 2013

Korea

Table 4. Clinical outcomes of patients with idiopathic MN according to anti-PLA_2R levels.

	Negative	Low	middle	High	
Clinical outcomes	**Anti-PLA_2R levels**				
	0 (Negative), N = 21	**1:100 (+)[a], N = 11**	**1:2000 (++)[b], N = 22**	**1:8000 (+++)[c], N = 23**	**P value**
Remission	18 (85.7%)	10 (90.9%)	16 (72.7%)	19 (82.6%)	0.540
Treatment-induced	13 (61.9%)	5 (45.5%)	13 (59.1%)	15 (65.2%)	
Spontaneous	5 (23.8%)	5 (45.5%)	3 (13.6%)	4 (17.4%)	0.380
Time to remission (months)	2.0 (1.0–5.5)	3.0 (1.3–4.0)	1.5 (1.0–4.8)	2.0 (1.0–5.3)	0.895

MN, membranous nephropathy; Anti-PLA_2R, anti-phospholipase A_2 receptor antibody; N, number of patients.
[a]Group of patients whose serum samples showed anti-PLA_2R reactivity at dilutions of 1:25 or 1:100 with negative results at dilutions over 1:100; [b]Group of patients whose serum samples showed anti-PLA_2R reactivity at dilutions of 1:500 or 1:2000 with negative results at dilutions over 1:2000; [c]Group of patients whose serum samples showed anti-PLA_2R reactivity at dilutions up to 1:8000.
doi:10.1371/journal.pone.0062151.t004

No relationship was observed between anti-PLA1R titer and remission rate.

PLoS ONE 8(4): e62151. 2013

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Nephrol Dial Transplant (2012) 0: 1–5
doi: 10.1093/ndt/gfs439

NDT
Nephrology Dialysis Transplantation

Original Article

Kidney biopsy is a sensitive tool for retrospective diagnosis of PLA2R-related membranous nephropathy

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Nephrol Dial Transplant. 2013 Jul;28(7):1839-44.

Membranous Nephropathy: PLA2R antibody and PLA2R antigen

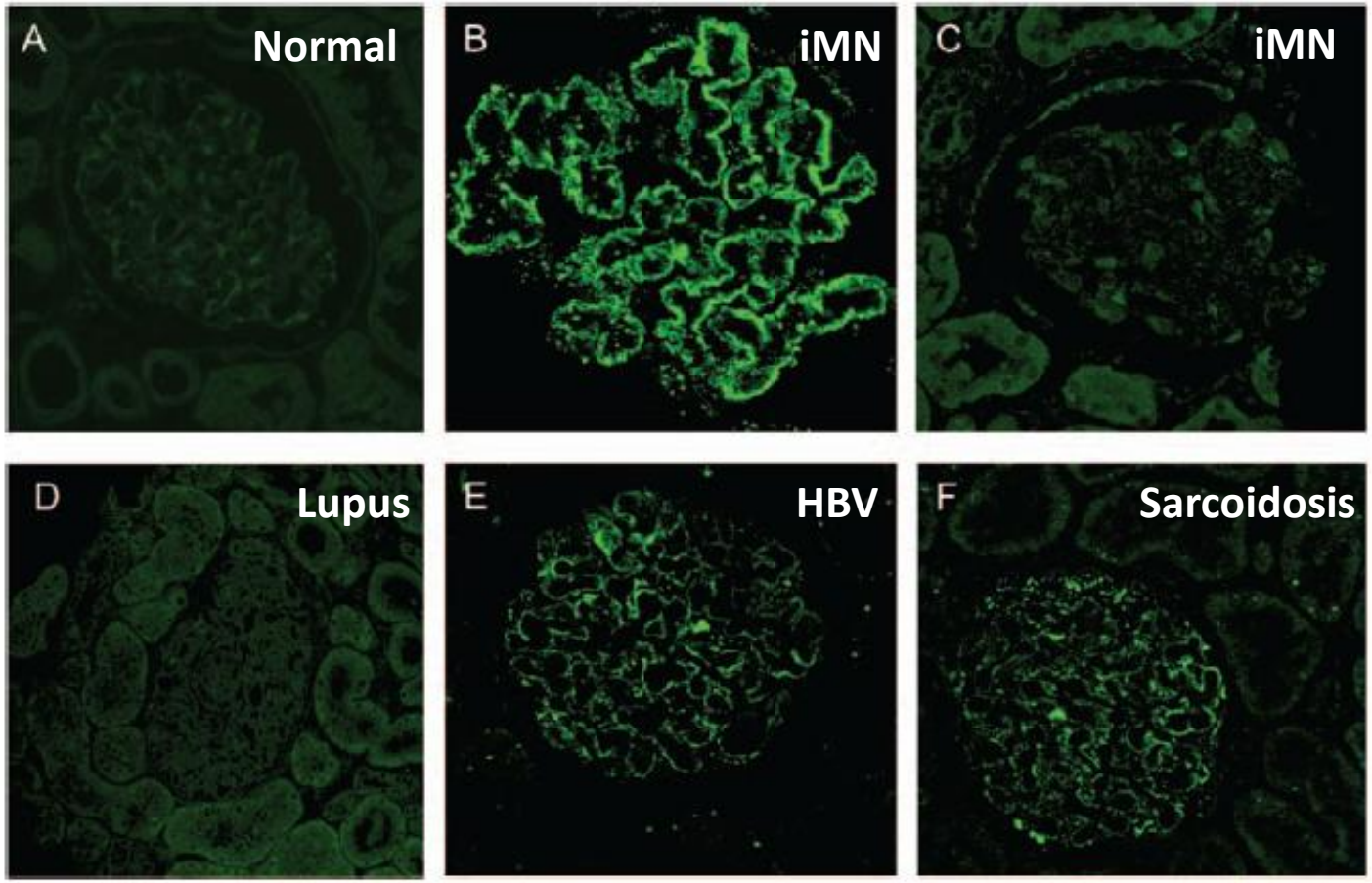

Fig. 2. Expression of PLA2R in glomeruli. Confocal microscopic analysis of paraffin kidney biopsy specimens show: a very weak expression of PLA2R in normal kidneys podocytes (**A**); the presence of PLA2R in sub-epithelial deposits along glomerular capillary loops in patient with iMN (one representative image from 45 patients) (**B**); and its absence in other group of patients with iMN (one representative image from 20 patients) (**C**); patients with lupus associated MN had no PLA2R in immune deposits (**D**); patients with secondary MN as hepatitis B and sarcoidosis had PLA2R in immune deposits (**E** and **F**).

Nephrol Dial Transplant. 2013 Jul;28(7):1839-44.

Membranous Nephropathy: PLA2R antibody and PLA2R antigen

Table 2. PLA2R in glomerular immune deposits and circulating anti-PLA2R autoantibodies in sera sampled at the time of active disease

	Number of patients	PLA2R		Time from renal biopsy to PLA2R-AB (months)
		Biopsy	Serum	
iMN	13	+	+	0
	3	+	–	0
	1	–	+	0
	3	–	–	0
iMN relapse	4	+	+	16–45
or PP	3	+	–	4–85
	1	–	–	85
Secondary	HepB1	+	+	0
MN	HepB2	+	–	0
	Sarc 1	+	+	5

PP, persistent proteinuria; HepB, hepatitis B; Sarc, sarcoidosis.

Nephrol Dial Transplant. 2013 Jul;28(7):1839-44.

Membranous Nephropathy: PLA2R antibody and PLA2R antigen

Table 3. PLA2R in glomerular immune deposits and circulating anti-PLA2R antibodies in sera sampled from iMN patients at the time of partial or complete remission

Number of patients	PLA2R		Time from renal biopsy to PLA2R-AB (months)	Proteinuria
	Biopsy	Serum		
7	+	+	3–44	7PR
15	+	–	6–168	6PR, 9CR
1	–	+	48	CR
14	–	–	5–164	4PR, 10PR

Nephrol Dial Transplant. 2013 Jul;28(7):1839-44.

Enhanced expression of the M-type phospholipase A2 receptor in glomeruli correlates with serum receptor antibodies in primary membranous nephropathy

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Kidney International (2012) **82**, 797–804

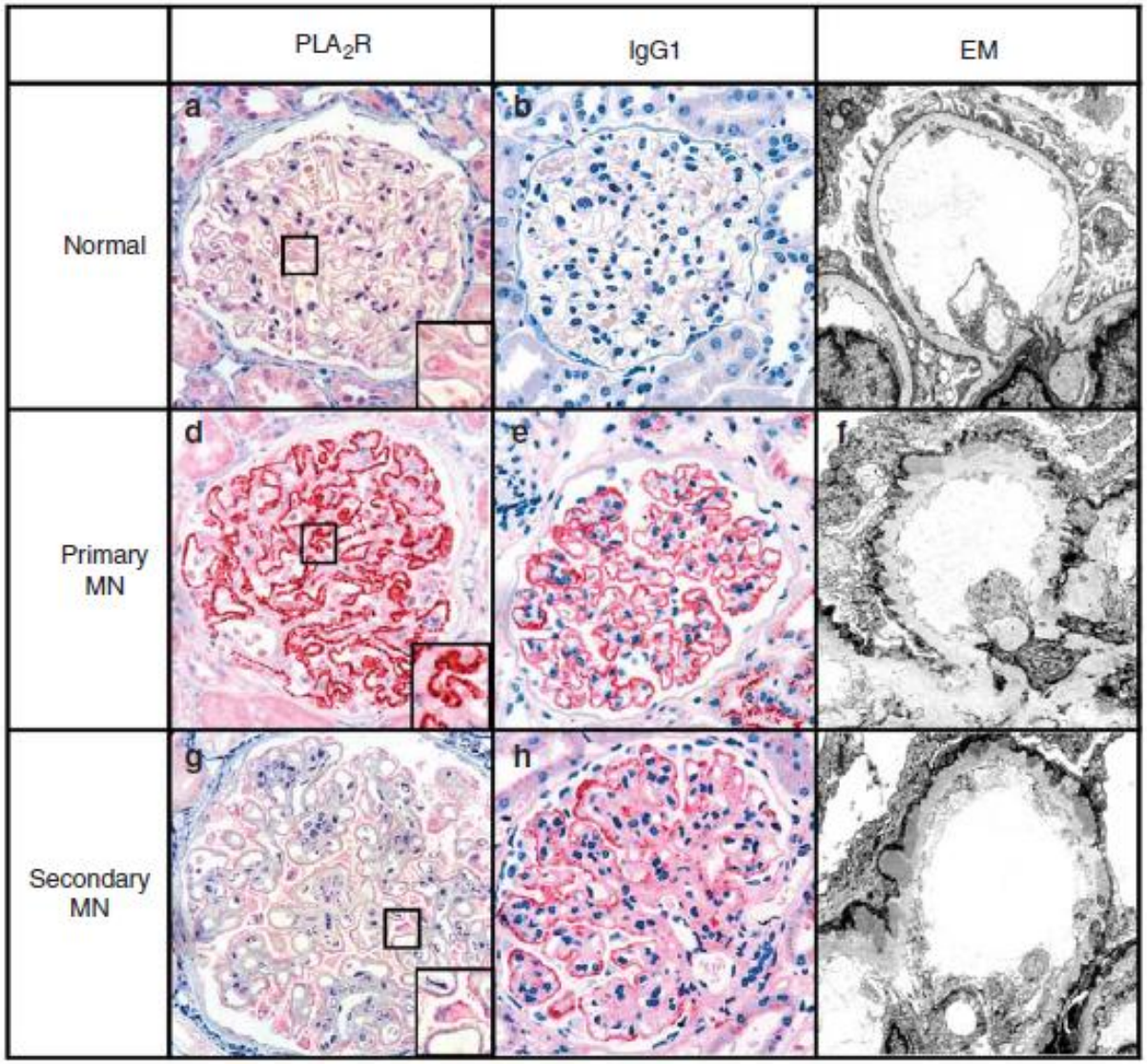


Figure 1 | Histology of the various forms of membranous nephropathy. Immunohistochemical staining (APAAP method; original magnification × 1.140) of phospholipase A2 receptor (PLA_2R) and IgG1 and transmission electron microscopy (EM; original magnification × 7.000) of renal biopsies from a normal kidney (**a**–**c**), from a patient with primary membranous nephropathy (MN) (**d**–**f**), and from a patient with secondary MN (**g**–**i**). The gallery shows that only PLA_2R staining but not immunoglobulin G1 (IgG1) staining or EM allows to differentiate between primary and secondary MN.

Case 1 (2)

A renal biopsy was performed.

Light microscopy reveals slightly thickened capillary walls, without proliferation.

IF shows 4+ granular IgG and 3+ granular C3 along the glomerular capillary wall. No mesangial deposits is seen. IgA and IgM are weakly positive (+). C1q and C4 are negative.

EM shows thickened basement membrane, spikes and electron dense deposits along the subepithelium.

IgG subclass shows IgG4>IgG1> IgG2. IgG3 is negative.

Western blotting revealed that anti-PLA2R1 Ab is present in his serum.

Primary ("Idiopathic") Membranous Nephropathy: Diagnostic Criteria-2014

A renal biopsy lesion showing exclusively epimembranous deposits by EM, predominantly containing IgG4 and lesser amount of IgG1,2,3.

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.

Glassock R, KDIGO- Mumbai Nephrology Summit, Mumbai, India 2014

Standard Evaluation for Secondary MN

PLA2R Ag Negative

ANA, 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).

Glassock R, KDIGO- Mumbai Nephrology Summit, Mumbai, India 2014

PLA2R Ab

With a combination of anti-PLA2R autoantibody testing, 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%

Glassock R, KDIGO- Mumbai Nephrology Summit, Mumbai, India 2014

Q5.

Serum creatinine has gradually increased from 0.8mg/dL to 1.1 mg/dL.Which ONE of the following treatments would you recommend?

A. Observe for up to 6 more months while receiving an angiotensin converting enzyme inhibitor and diuretic

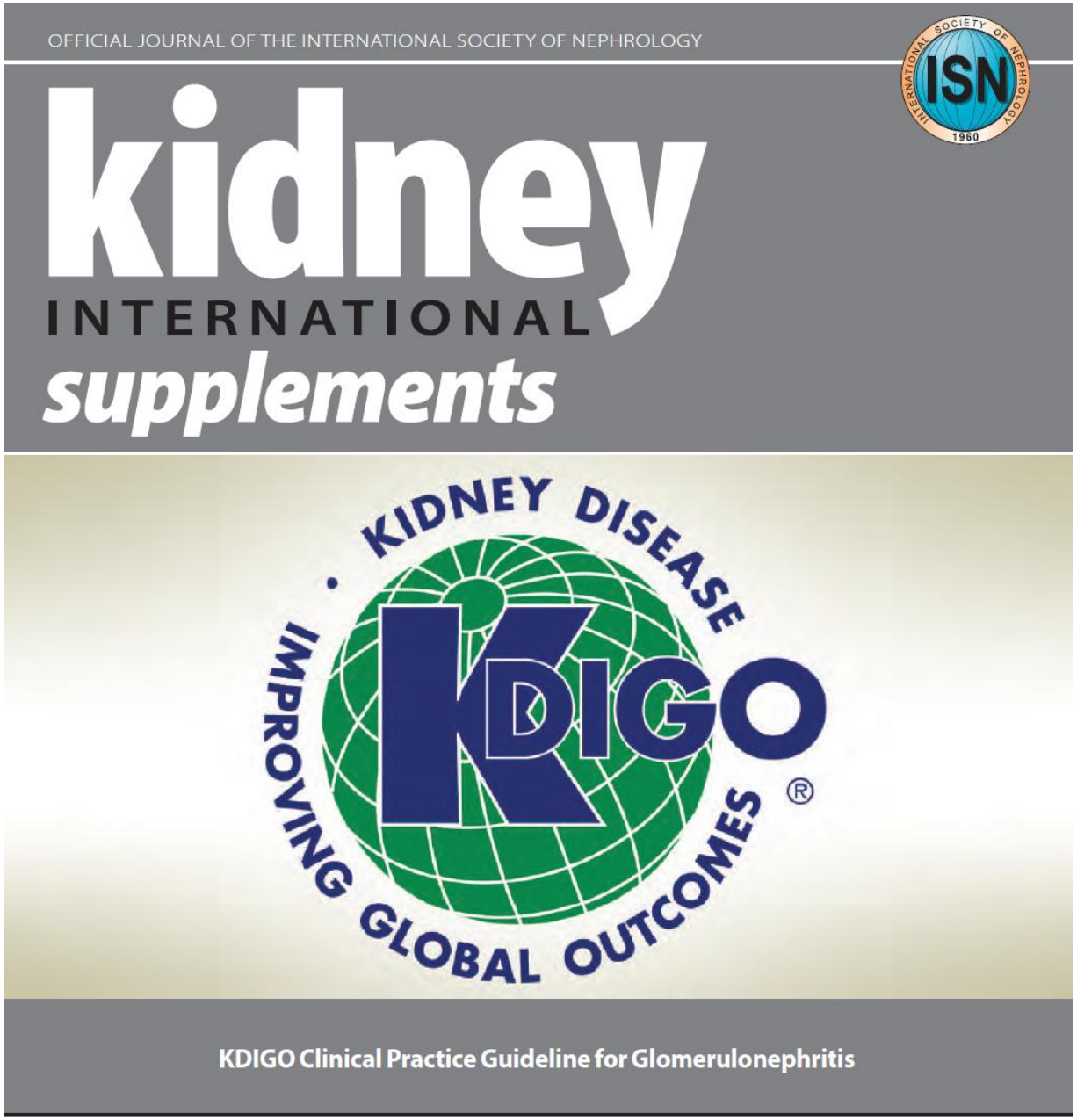
B. Give Cyclosporine 2~4mg/kg/d plus 30mg/d of prednisone

C. Give cyclical oral cyclophosphamide at 1-1.5mg/Kg alternating with IV methyl prednisolone and oral prednisone

D. Give 40mg of prednisone

E. Give 1000mg of Rituximab twice at an interval of two weeks

F. Give MMF 1.0gm twice daily



KDIGO Clinical Practice Guideline for Glomerulonephritis

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:

1. 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

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

3. 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

CLINICAL EPIDEMIOLOGY www.jasn.org

Long-Term Outcomes in Idiopathic Membranous Nephropathy Using a Restrictive Treatment Strategy

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A large cohort of patients with idiopathic membranous nephropathy treated according to a restrictive treatment policy. Participants are 254 patients who visited our outpatient clinic between 1995 and 2009.

J Am Soc Nephrol 25: 150–158, 2014

Restrictive Treatment Strategy for Primary MN

254 patients with primary MN initially treated according the 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.
91/124 (73%) were given oral CYC + Prednisone and 33/124 (27%) others.

J Am Soc Nephrol 25: 150–158, 2014

Restrictive Treatment Strategy for Primary MN

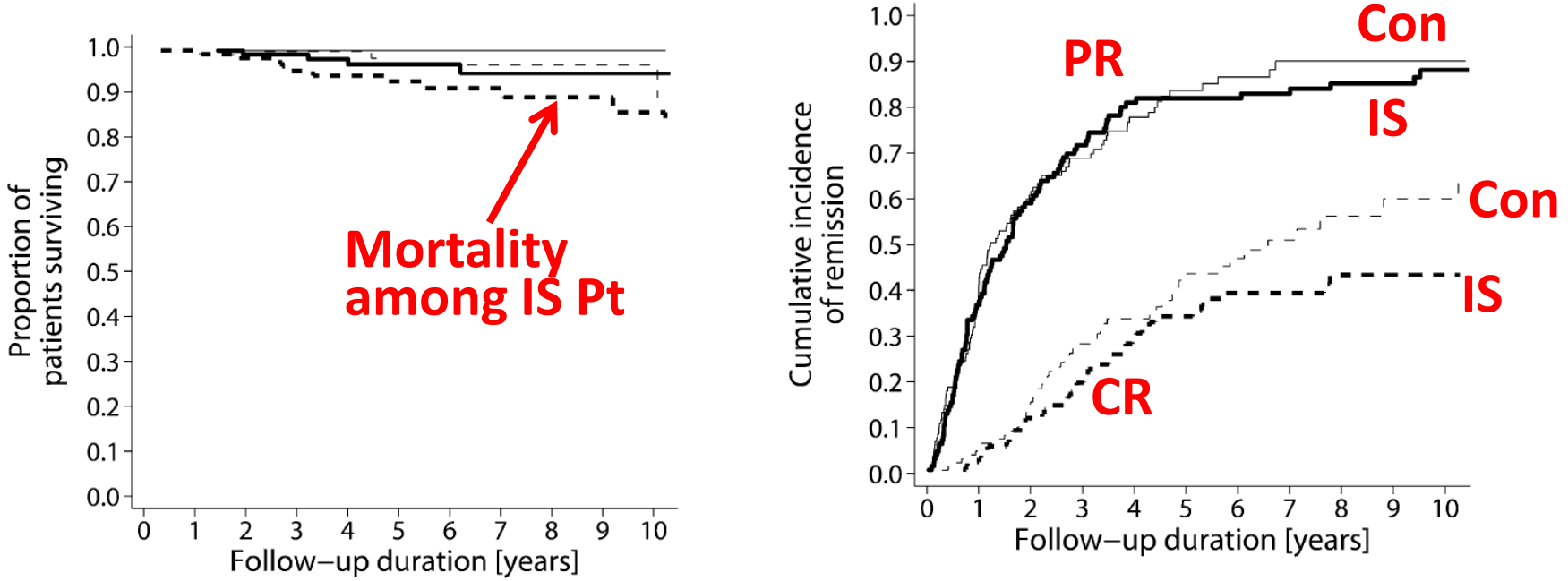

Figure 2. Renal replacement and all-cause mortality rates were higher in the treated patients (top panel). Partial remission rates were similar. However, complete remission rate was lower in the treated patients (bottom panel). The thick lines represent patients treated with immunosuppressive drugs, and the thin lines represent patients treated conservatively. The top panel shows survival until renal replacement therapy (solid lines) and mortality (dotted lines). Death was considered competing for renal replacement therapy in the analyses. The bottom panel shows the cumulative incidence of partial (solid lines) and complete remission (dotted lines). Severe kidney failure was considered competing for remission.

J Am Soc Nephrol 25: 150–158, 2014

Restrictive Treatment Strategy for Primary MN

Conservative:

Deaths- 4/130

Any Scr >3.0mg/dL – 13/130

PR 90/130, CR 60/130

ESRD- 1/130

Immunosuppressive:

Deaths- 15/124

Any Scr >3.0mg/dL- 20/124

PR 88/130, CR 45/130

ESRD- 6/124

J Am Soc Nephrol 25: 150–158, 2014

Restrictive Treatment Strategy for Primary MN

In conclusion, a restrictive therapeutic regimen yields favorable long-term outcomes. Additionally, it results in half of the patients not requiring toxic drugs. Short-term and long-term adverse effects remain an important issue, and risks of adverse effects should be balanced against the potential benefits of treatment. Overall, our study supports the recommendations in the recently published KDIGO guideline.

J Am Soc Nephrol 25: 150–158, 2014

7.3: Initial therapy of IMN

7.3.1: We recommend that initial therapy consist of a 6-month course of alternating monthly cycles of oral and i.v. corticosteroids, and oral alkylating agents (see Table 15). (1B)

7.3.2: We suggest using cyclophosphamide rather than chlorambucil for initial therapy. (2B)

7.3.5: Adjust the dose of cyclophosphamide or chlorambucil according to the age of the patient and eGFR. (Not Graded)

Table 15 | Cyclical corticosteroid/alkylating-agent therapy for IMN (the "Ponticelli Regimen")

Month 1: i.v. methylprednisolone (1 g) daily for three doses, then oral methyprednisolone (0.5 mg/kg/d) for 27 days
Month 2: Oral chlorambucil (0.15–0.2 mg/kg/d) or oral cyclophosphamide (2.0 mg/kg/d) for 30 days[a]
Month 3: Repeat Month 1
Month 4: Repeat Month 2
Month 5: Repeat Month 1
Month 6: Repeat Month 2

IMN, idiopathic membranous nephropathy.

[a]Monitor every 2 weeks for 2 months, then every month for 6 months, with serum creatinine, urinary protein excretion, serum albumin, and white blood cell count. If total leukocyte count falls to $<3500/mm^3$, then hold chlorambucil or cyclophosphamide until recovery to $>4000/mm^3$.

Table 17 | Contraindications to the use of the cyclical corticosteroid/alkylating-agent regimen in IMN

Untreated infection (HIV, hepatitis B and C, tuberculosis, fungal infection, etc.)
Neoplasia (lung, skin [except squamous cell]), breast, colon, etc.
Urinary retention
Inability to comply with monitoring
Pre-existing leukopenia (<4000 leukocytes/mm^3)
SCr >3.5 mg/dl (>309 μmol/l)

HIV, human immunodeficiency virus; MN, membranous nephropathy; SCr, serum creatinine.

A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy

CLAUDIO PONTICELLI, PIETRO ZUCCHELLI, PATRIZIA PASSERINI, BRUNO CESANA, FRANCESCO LOCATELLI, SONIA PASQUALI, MAURO SASDELLI, BRUNO REDAELLI, CLAUDIO GRASSI, CLAUDIO POZZI, DANIELA BIZZARRI, and GIOVANNI BANFI

Division of Nephrology and Dialysis, IRCCS, Ospedale Maggiore Milano, Ospedale Malpighi Bologna, Ospedale Civile Lecco, Ospedale Civile Arezzo, Ospedale San Gerardo dei Tintori Monza, and Ospedale Predabissi Melegnano, Italy

Kidney International, Vol. 48 (1995), pp. 1600—1604

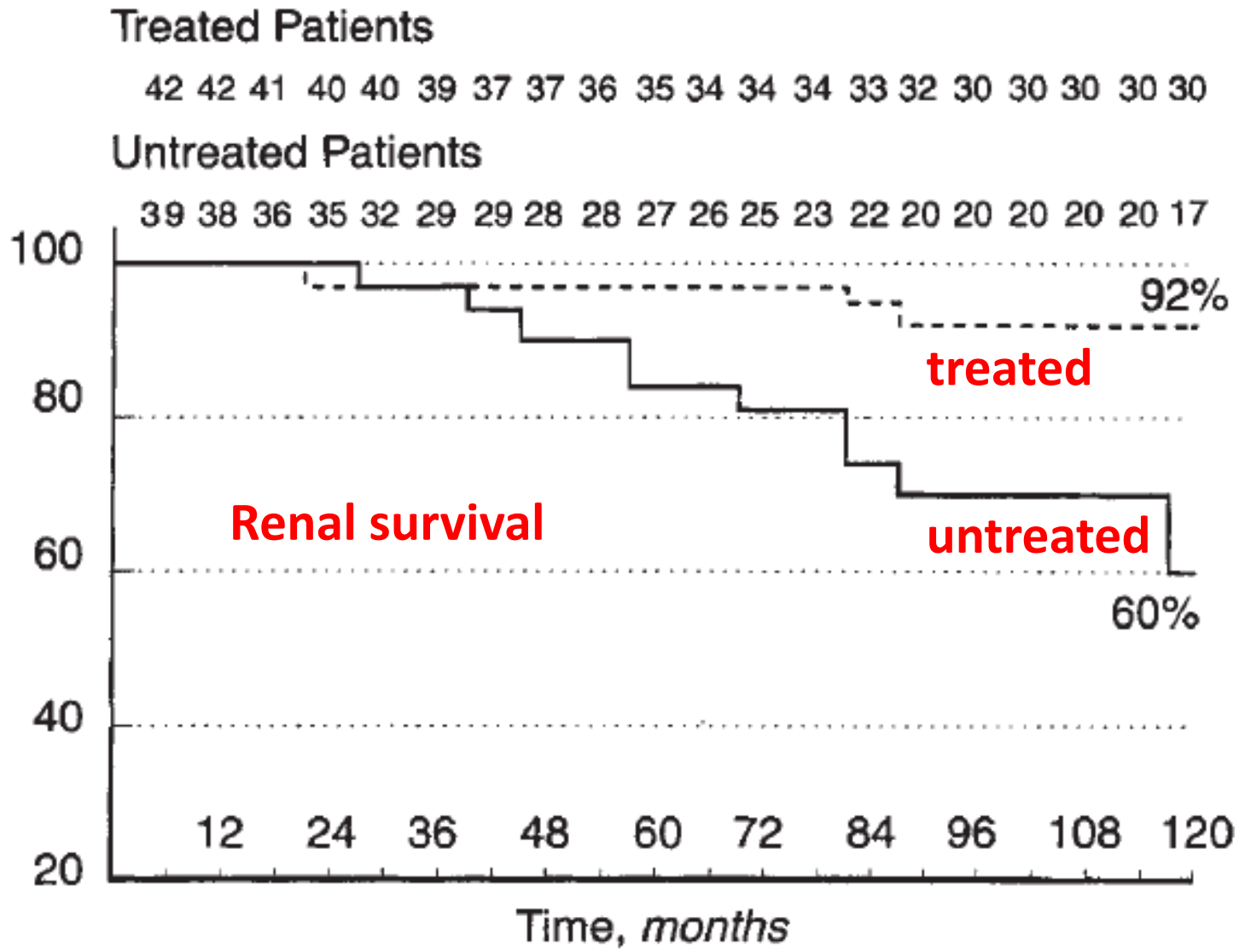

Fig. 1. *Cumulative probability of survival without dialysis in patients who received treatment (- - -) and in untreated controls (——).* The difference is significant ($P = 0.0038$).

Kidney International, Vol. 48 (1995), pp. 1600—1604

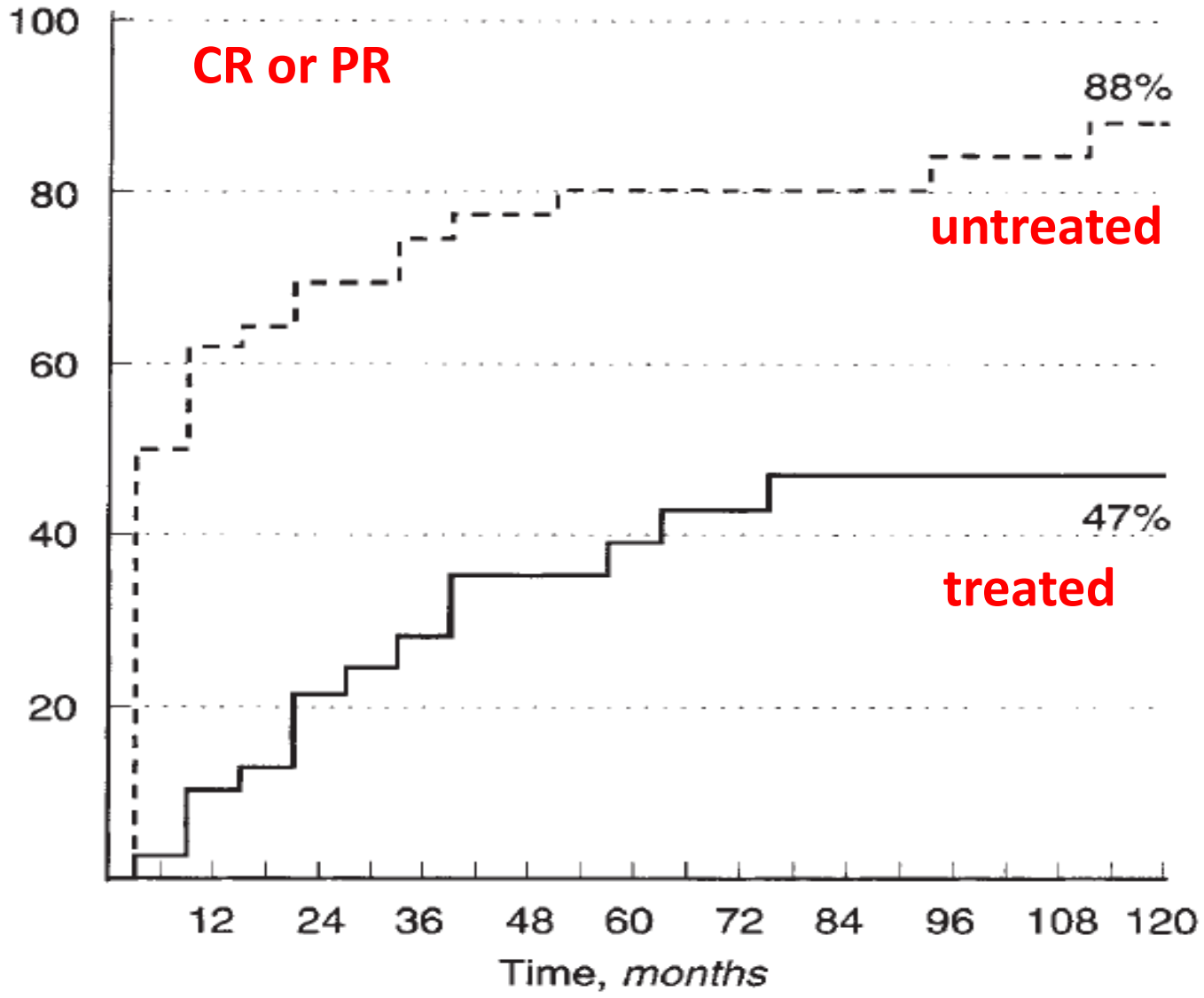

Fig. 3. *Probability of complete or partial remission of the nephrotic syndrome as a first event in the treated group (- - -) and in control group (——).* The difference between the two curves is statistically significant (P = 0.0000).

Kidney International, Vol. 48 (1995), pp. 1600—1604

India

A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy.

Patients:
biopsy-proven IMN of at least 6 mo duration.
Intervention:
Group2(n=47):
a 6-mo course of alternate months of steroid and cyclophosphamide.
Control:
Group1(N=46):
supportive therapy
Outcomes:
doubling of serum cre, development of ESRD, or patient death.
(PR, CR, Quality of life)

Jha V, Ganguli A, Saha TK et al. J Am Soc Nephrol 2007; 18: 1899–1904.

A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy.

India

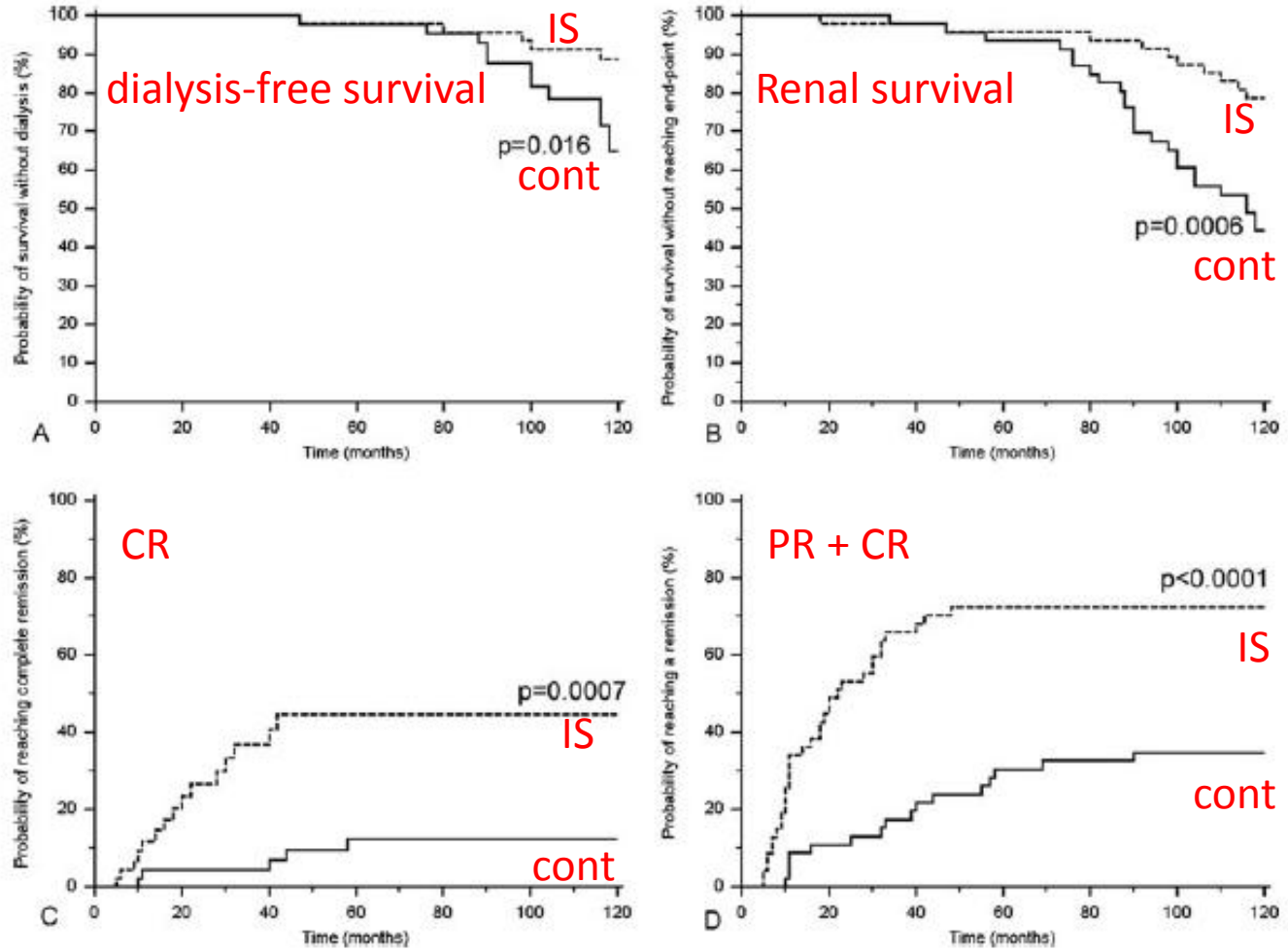

Figure 1. Kaplan-Meier plots showing probabilities of dialysis-free survival (A), survival without reaching either end point (B), complete remission (C), and complete or partial remission (D). Solid line, group 1; dashed line, group 2.

Jha V, Ganguli A, Saha TK et al. J Am Soc Nephrol 2007; 18: 1899–1904.

Table 16 | Risks and benefits of the cyclical corticosteroid/alkylating-agent regimen in IMN

Risks
Enhanced risk of opportunistic infection
Reactivation of viral hepatitis
Alopecia
Gonadal damage (aspermatogenesis, ovulation failure)
Hemorrhagic cystitis (cyclophosphamide only)
Neoplasia (myelodysplastic syndrome, acute myelogenous leukemia
Transitional cell carcinoma of the bladder, ureter or pelvis
Toxic hepatitis

Benefits
Prevention of CKD and ESRD
Avoidance of complications of nephrotic syndrome (thrombosis, accelerated atherogenesis)
Prolongation of life; improved quality of life

CKD, chronic kidney disease; ESRD, end-stage renal disease; MN, membranous nephropathy.

7.4: Alternative regimens for the initial therapy of IMN: CNI therapy

7.4.1: We recommend that **cyclosporine** or **tacrolimus** be used for a period of at least 6 months in patients who meet the criteria for initial therapy (as described in Recommendation 7.2.1),
but who choose not to receive the cyclical corticosteroid/alkylating-agent regimen or who have contraindications to this regimen. (1C)

Table 18 | CNI-based regimens for IMN

***Cyclosporine*:** 3.5–5.0 mg/kg/d given orally in two equally divided doses 12 hours apart, with prednisone 0.15 mg/kg/d, for 6 months. We suggest starting at the low range of the recommended dosage and gradually increasing, if necessary, to avoid acute nephrotoxicity (Sandimmune®, Neoral®, and generic cyclosporin considered equivalent).

***Tacrolimus*:** 0.05–0.075 mg/kg/d given orally in two divided doses 12 hours apart, without prednisone, for 6–12 months. We suggest starting at the low range of the recommended dosage and gradually increasing, if necessary, to avoid acute nephrotoxicity.

IMN, idiopathic membranous nephropathy.
Note: Monitoring of blood levels during therapy is discussed in the text.

Cyclosporine in patients with steroid-resistant membranous nephropathy: A randomized trial

DANIEL C. CATTRAN, GERALD B. APPEL, LEE A. HEBERT, LAWRENCE G. HUNSICKER, MARC A. POHL, WENDY E. HOY, DOUGLAS R. MAXWELL, and CHERYL L. KUNIS, for the NORTH AMERICAN NEPHROTIC SYNDROME STUDY GROUP

Department of Medicine, University of Toronto, Toronto, Ontario, Canada; Departments of Medicine, Columbia Presbyterian Medical Center, New York, New York, Ohio State University, Columbus, Ohio, University of Iowa Hospitals, Iowa City, Iowa, Cleveland Clinic Foundation, Cleveland, Ohio, Lovelace Medical Foundation, Albuquerque, New Mexico, and Indiana University School of Medicine, Indianapolis, Indiana, USA

Table 1. Baseline demographic and laboratory data of the 51 randomized patients

Initial	Placebo $N = 23$	Cyclosporine $N = 28$
Age *range*	49 ± 14	47 ± 11
Gender *M/F*	16/7	26/2
Blood pressure *mm Hg*		
Systolic	138 ± 16	137 ± 18
Diastolic	84 ± 9	84 ± 7
Racial group *N* (%)		
Caucasians	20 (87)	24 (86)
African American	0 (0)	1 (4)
Other/Mixed	3 (13)	2 (10)
Serum albumin *g/dL*	2.7 ± 0.6	2.8 ± 0.6
Serum creatinine *mg/dL*[a]	1.1 ± 0.3	1.3 ± 0.5
Creatinine clearance *mL/min/1.73 m²*	95 ± 37	90 ± 27
Proteinuria *g/day*	8.8 ± 4.7	9.7 ± 5.3
Urine urea *g/day*	9.5 ± 3.6	10.3 ± 4.0

Data that are ± values are standard deviations.
[a] To convert to μmol/L, multiply by 88.4

Kidney International, Vol. 59 (2001), pp. 1484–1490

Cyclosporin in MN: Complete and Partial Remssions

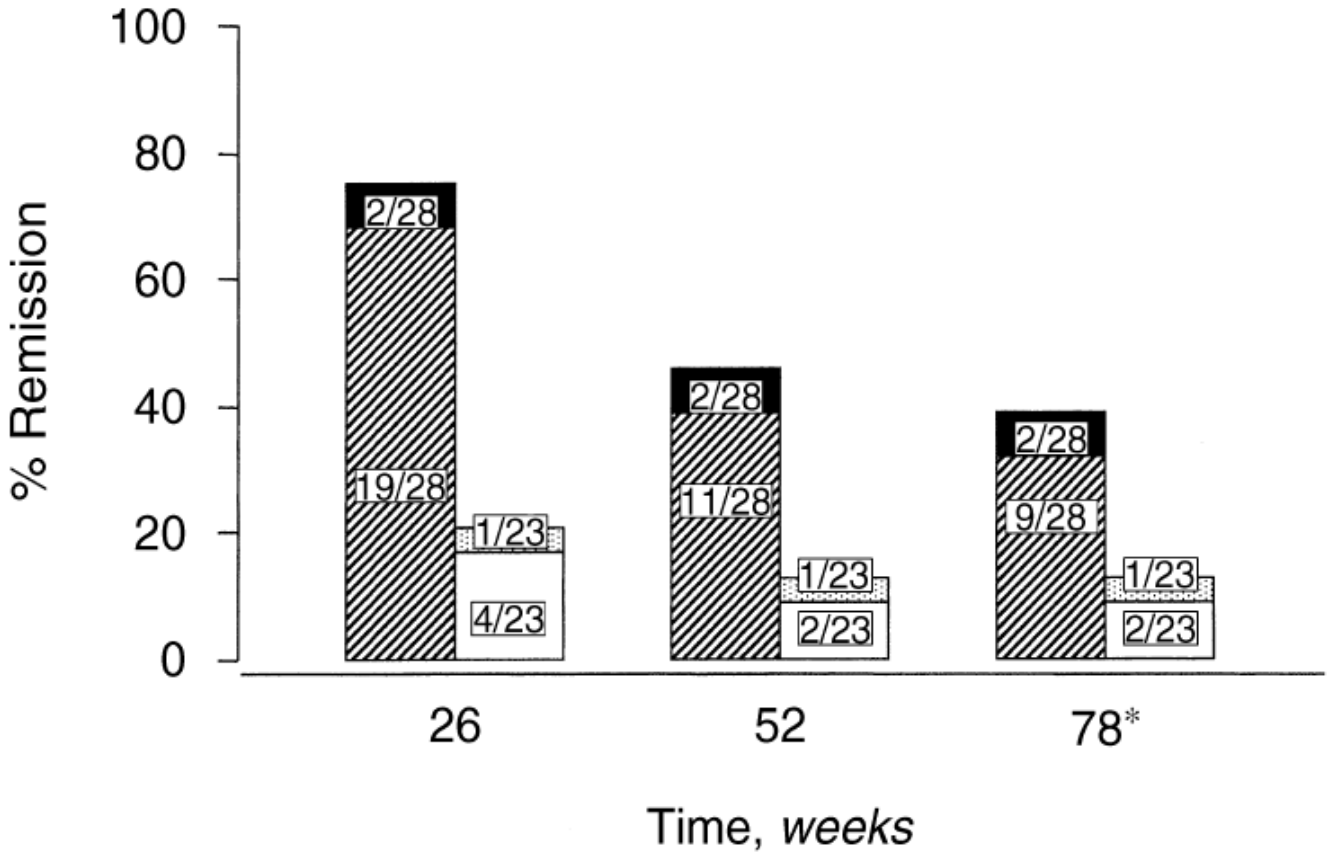

Fig. 1. Remissions in proteinuria in the cyclosporine patients [(▨) partial, (■) complete] compared with the placebo-treated [(▩) complete, (□) partial] at different time points of the study. At week 26, $P = 0.001$; at week 52, $P = 0.004$; and week 78, $P = 0.007$. Early stops (*) were assessed at the last follow-up.

Kidney International, Vol. 59 (2001), pp. 1484–1490

Cyclosporin in MN: Complete and Partial Remssions

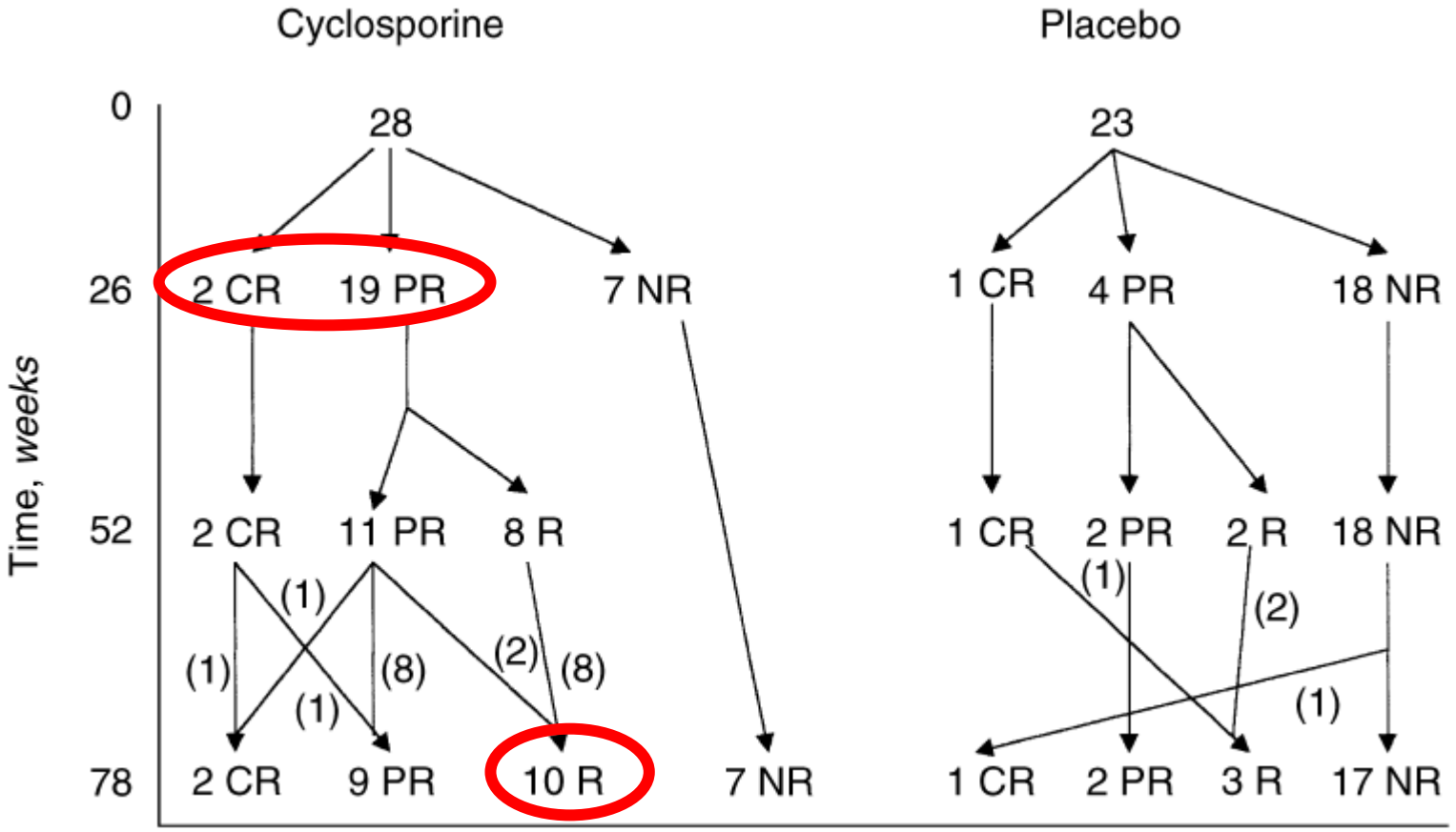

Fig. 2. Remission and relapses in the two groups over the study and follow-up period.

Abbreviations are: CR, complete remission; PR, partial remission; NR, no remission; R, relapse.

Kidney International, Vol. 59 (2001), pp. 1484–1490

Immunosuppression for progressive membranous nephropathy: a UK randomised controlled trial

Andrew Howman, Tracey L Chapman, Maria M Langdon, Caroline Ferguson, Dwomoa Adu, John Feehally, Gillian J Gaskin, David R W Jayne, Donal O'Donoghue, Michael Boulton-Jones, Peter W Mathieson

Patients:
biopsy-proven idiopathic membranous nephropathy
Intervention:
Patients were randomly assigned (1:1:1) by a random number table to receive supportive treatment only, supportive treatment plus 6 months of alternating cycles of prednisolone and chlorambucil, or supportive treatment plus 12 months of ciclosporin.
The primary outcome:
a further 20% decline in renal function from baseline, analysed by intention to treat.

Lancet. 2013 Mar 2;381(9868):744-51.

20% decline in renal function

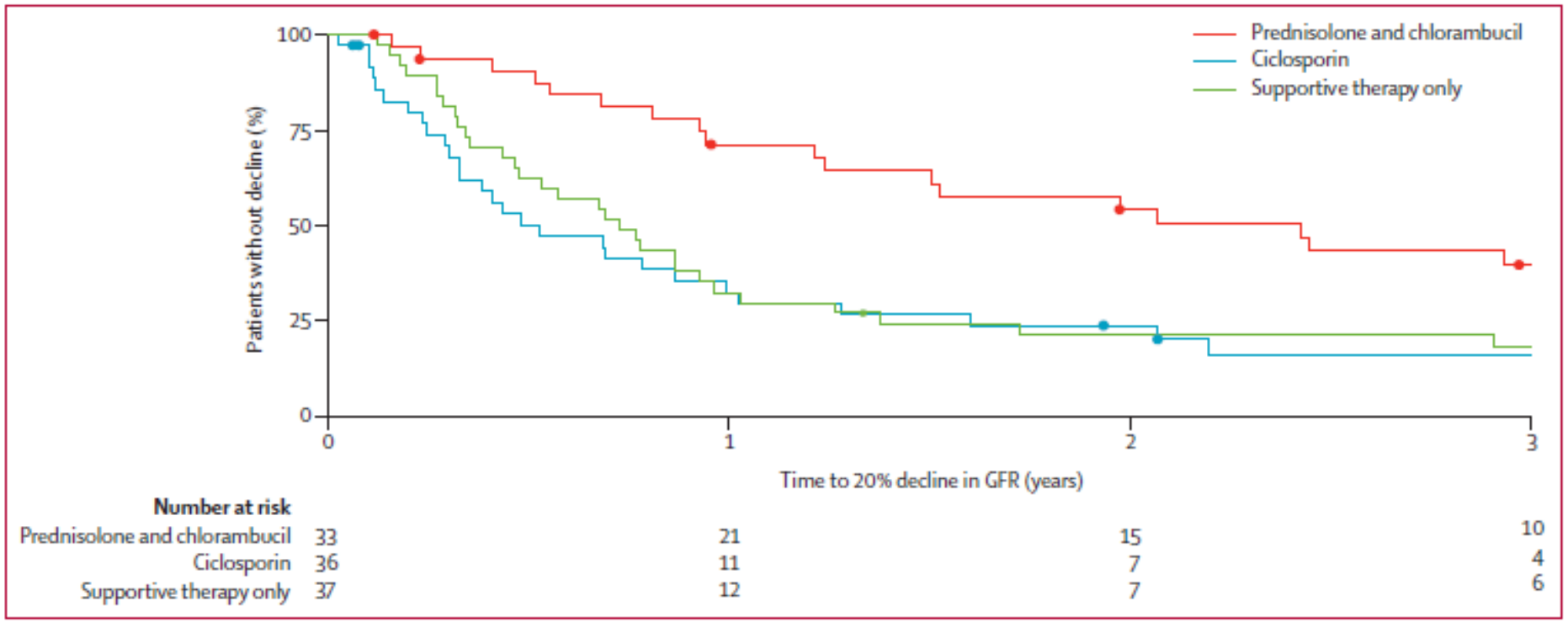

Figure 2: **Kaplan-Meier analysis of further 20% decline in renal function**
Deaths were censored. GFR=glomerular filtration rate.

Patients treated with PSL and chlorambucil showed better survival than those with ciclosporin or supportive therapy.

Is 20% decline appropriate outcome?

Lancet. 2013 Mar 2;381(9868):744-51.

	Prednisolone and chlorambucil	Ciclosporin	Supportive therapy only
Patients with at least one SAE*	20/33 (61%)	18/37 (49%)	16/38 (42%)
Number of SAEs†	56/117 (48%)	37/117 (32%)	24/117 (21%)
Likelihood to be related to treatment‡§			
None/unlikely	20/56 (36%)	18/37 (49%)	24/24 (100%)
Possible	10/56 (18%)	6/37 (16%)	0
Likely	26/56 (46%)	13/37 (35%)	0
Body system affected			
Haematological	28	5	3
Dermatological	4	2	0
Renal	1	5	2
Neurological	3	6	4
Cardiovascular	4	3	3
Metabolic	8	1	5
Gastroenterological	3	3	2
Infection	3	8	2
Other/not specified	2	4	3

Data are number, or number (%). SAE=serious adverse event. *Out of number of patients assigned to each treatment group; includes patients removed from the intention-to-treat analysis because they were deemed ineligible after randomisation. †Out of number of SAEs overall. ‡Out of number of SAEs in each treatment group. §Likelihood was assessed by PWM.

Table 2: **Serious adverse events by treatment and body system affected**

Lancet. 2013 Mar 2;381(9868):744-51.

CLINICAL EPIDEMIOLOGY www.jasn.org

Long-Term Outcomes in Idiopathic Membranous Nephropathy Using a Restrictive Treatment Strategy

Jan A.J.G. van den Brand,* Peter R. van Dijk,† Julia M. Hofstra,* and Jack F.M. Wetzels*

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A large cohort of patients with idiopathic membranous nephropathy treated according to a restrictive treatment policy. Participants are 254 patients who visited our outpatient clinic between 1995 and 2009.

J Am Soc Nephrol 25: 150–158, 2014

Table 3. Adverse events and complications during follow-up

Adverse Event	Cyclophosphamide (*n*=91)	Other Immunosuppression (*n*=33)	Conservative Treatment (*n*=130)
Serious adverse event	35 (38)	11 (33)	12 (9)
Resulting in (prolongation of) hospitalization	13 (14)	3 (9)	2 (2)
Leukopenia	35 (38)	8 (24)	2 (2)
Thrombopenia	7 (8)	2 (6)	0
Liver enzyme abnormalities	7 (8)	0	0
Hyperglycemia	10 (11)	5 (15)	1 (1)
Infection	30 (33)	11 (33)	1 (1)
Hematuria/cystitis	1 (1)	0	0
Cardiovascular/ thrombotic events	18 (20)	7 (21)	8 (6)
Subfertility	0	0	0
Osteonecrosis	0	0	0
Malignancy	14 (15)	2 (6)	4 (3)

Serious adverse events have been defined according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice guidelines. Values are *n* (%).

Malignancies occurred more frequently in cyclophosphamide-treated patients.

J Am Soc Nephrol 25: 150–158, 2014

Nephrol Dial Transplant (2012) 27: 235–242
doi: 10.1093/ndt/gfr220
Advance Access publication 10 May 2011

Idiopathic membranous nephropathy and nephrotic syndrome: outcome in the era of evidence-based therapy

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Cohort Study

Ninety-five consecutive adult patients attending two centres in the UK between 1997 and 2008.

MN Cohort Study in the UK

Table 2. Outcomes for the whole cohort and stratified by whether the patient received IS and if so, which type [Cattran or Ponticelli (Pont) regimen][a]

	All patients $N = 95$	IS $N = 37$	No IS $N = 58$	Cattran $N = 26$	Pont $N = 11$
Any PR (%)	76.4	79.2	69.6	66.7	77.3
Any CR (%)	24.4	22.3	24.3	29.1	21.2
Relapse (%)	32.8	**47.4**	**22.3***	48.2	49.1
Dead (%)	16.8	11.5	19.7	13.5	14.3
RRT (%)	11.9	8.2	13.6	14.5	12.5

[a]Data reported as the actuarial probability (%) of an event at 5 years using Kaplan–Meier analysis. Comparisons made using log-rank test. Items in bold are significant differences between groups. *$P < 0.05$.

Treatment:

IS is considered for patients with prolonged nephrotic syndrome (>6months), serious complications of nephrotic syndrome including venous thromboemboli and intractable oedema or rapidly deteriorating renal function. Choice of immunosuppressive regime has been physician led, with no fixed unit policy but treatment adhered to published protocols. (Cattran or ponticelli)

Nephrol Dial Transplant (2012) 27: 235–242

MN Cohort Study in the UK

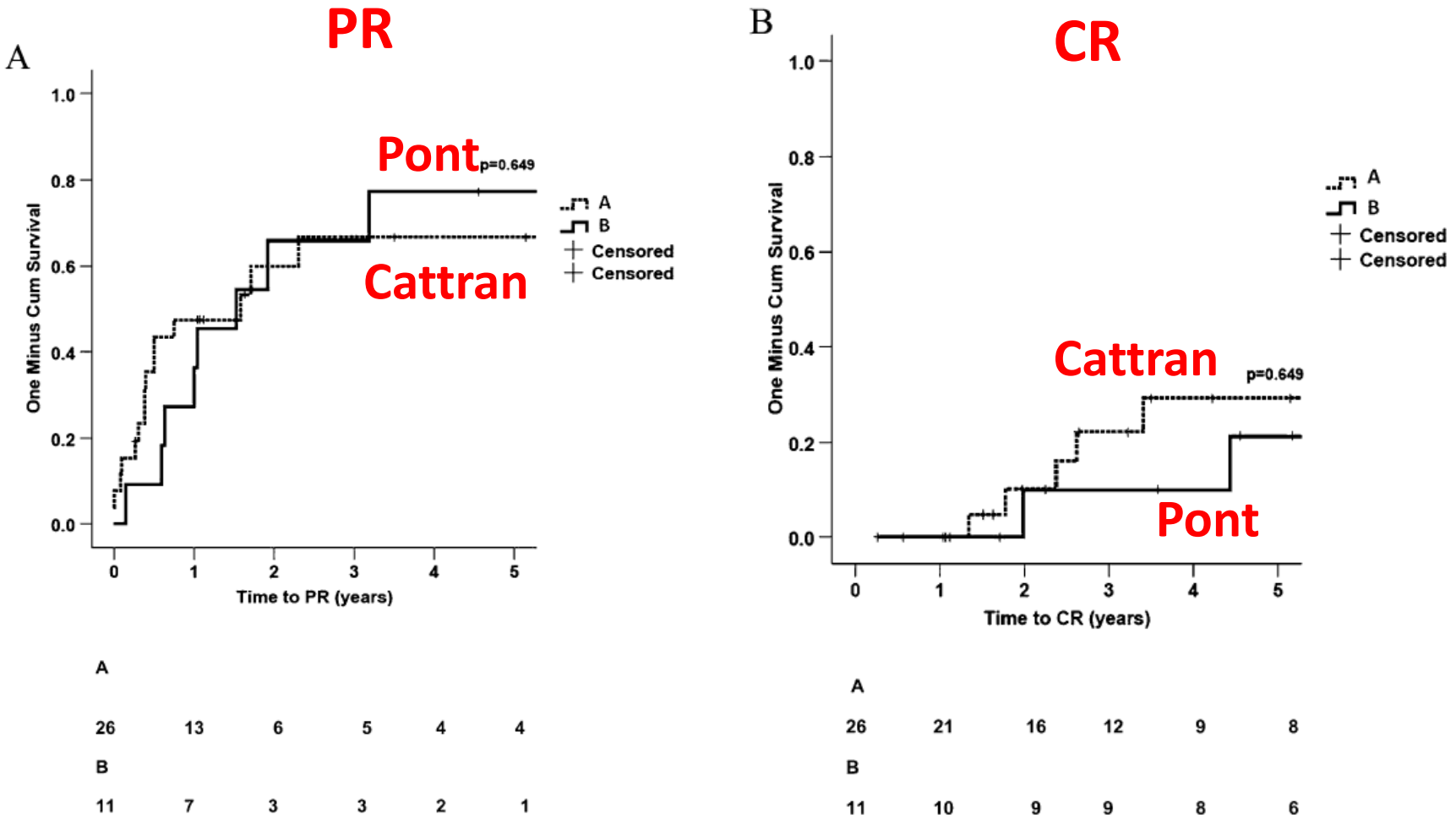

Fig. 3. Kaplan–Meier one-survival plots of outcomes by type of IS.
(A) Cattran regimen (cyclosporine) (interrupted line);
(B) Ponticelli regimen (solid line). Comparison by log-rank test.

Nephrol Dial Transplant (2012) 27: 235–242

MN Cohort Study in the UK

Type of IS used did not have an impact on outcome but the Ponticelli regimen was associated with a higher incidence of side effects than the Cattran regimen.

These findings should help inform physician and patient treatment choice while awaiting the results of the ongoing UK MRC randomized controlled trial of immunosuppressive regimens in patients with IMN.

Nephrol Dial Transplant (2012) 27: 235–242

7.5: Regimens not recommended or suggested for initial therapy of IMN

7.5.1: We recommend that **corticosteroid monotherapy not be used** for initial therapy of IMN. (1B)

7.5.2: We suggest that monotherapy with MMF not be used for initial therapy of IMN. (2C)

Nevertheless, retrospective studies conducted in subjects of Asian (Japanese) ancestry have suggested possible benefits for steroid monotherapy.

Japan

Prognosis and risk factors for idiopathic membranous nephropathy with nephrotic syndrome in Japan

Hideo Shiiki, Takao Saito, Yoshiharu Nishitani, Tetsuya Mitarai, Noriaki Yorioka, Ashio Yoshimura, Hitoshi Yokoyama, Shinichi Nishi, Yasuhiko Tomino, Kiyoshi Kurokawa, and Hideto Sakai, and Members and Coworkers of the Research Group on Progressive Renal Diseases in Japan

First Department of Internal Medicine, Nara Medical University, Nara, Japan; Division of Nephrology and Rheumatology, Department of Internal Medicine, Fukuoka University School of Medicine, Fukuoka, Japan; Fourth Department of Internal Medicine, Saitama Medical Center, Saitama Medical School, Saitama, Japan; Department of Molecular and Internal Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan; Division of Nephrology, Showa University Fujigaoka Hospital, Yokohama, Japan; Division of Blood Purification, Kanazawa University Hospital, Kanazawa, Japan; Blood Purification Center, Niigata University Hospital, Niigata, Japan; Division of Nephrology, Department of Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan; Institute of Medical Sciences, Tokai University School of Medicine, Isehara, Japan; and Division of Nephrology and Metabolism, Department of Internal Medicine, Tokai University School of Medicine, Isehara, Japan

Kidney International, Vol. 65 (2004), pp. 1400–1407

Japan

Table 5. Clinical features at onset and outcome of nephrotic syndrome: comparison of patients with different treatments

Clinical features	Treatment groups		
	Corticosteroids alone	Corticosteroids + cyclophosphamide	Supportive therapy
Number of patients	374	257	161
Male/female	147/227	99/158	58103
Age[a]	51.4 ± 13.1	48.9 ± 12.7	52.3 ± 14.0[b]
Urinary protein (≥10 g/day)	75 (20%)	56 (21.6%)	13 (8.1%)[c]
Hypertension	74 (19.8%)	58 (22.6%)	40 (24.8%)
Increased blood urea nitrogen (≥20 mg/dL)	73 (19.5%)	56 (21.8%)	39 (24.2%)
Increased serum creatinine (≥1.5 mg/dL)	30 (8.0%)	28 (10.9%)	14 (8.7%)
Follow-up period *years*[a]	6.4 ± 4.3	7.6 ± 5.0	6.1 ± 4.4
Outcome of nephrotic syndrome			
Complete remission	179 (47.9%)	106 (41.2%)	61 (37.4%)
Incomplete remission I	95 (25.4%)	65 (25.3%)	37 (23.0%)
Incomplete remission II	52 (13.9%)	47 (18.3%)	31 (19.2%)
No response	48 (12.8%)	39 (15.2%)	32 (19.9%)

[a]Data are mean ± SD (data in parentheses are percentages of patients); [b]$P < 0.05$ vs. cyclophosphamide combined group; [c]$P < 0.001$ vs. corticosteroid alone and cyclophosphamide combined groups.

Kidney International, Vol. 65 (2004), pp. 1400–1407

Japan

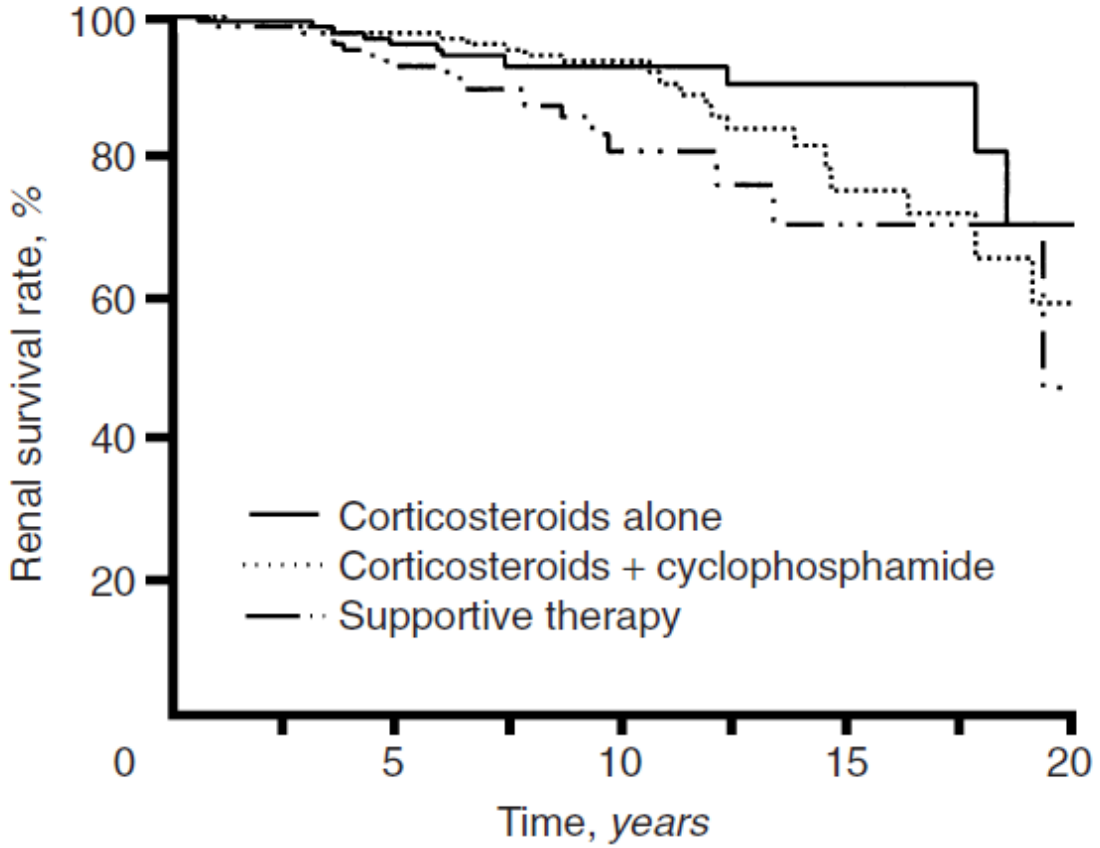

Fig. 2. Renal survival rates: Comparison of patients receiving different treatments. Patients in the corticosteroids-alone and corticosteroids + cyclophosphamide groups showed a significant improvement of renal survival rates compared to those in the supportive therapy group, respectively.

Conclusion.
IMNis a disease with a comparatively good prognosis in Japan even when it is associated with nephrotic syndrome. Steroid therapy, which has not been recommended for IMN in most review articles, seems to be useful at least for Japanese patients. In particular, a remission from heavy proteinuria likely results in a favorable outcome.

Kidney International, Vol. 65 (2004), pp. 1400–1407

Korea

Original Article | http://dx.doi.org/10.3349/ymj.2013.54.4.973
pISSN: 0513-5796, eISSN: 1976-2437 | Yonsei Med J 54(4):973-982, 2013 | YMJ

Stepwise Treatment Using Corticosteroids Alone and in Combination with Cyclosporine in Korean Patients with Idiopathic Membranous Nephropathy

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Yonsei Med J. 2013 Jul;54(4):973-82.

Korea

Table 1. Baseline Characteristics According to Treatment Modalities

Variables	Total (n=179)	Conservative treatment (n=57)	Corticosteroids alone (n=72)	Corticosteroids plus CsA (n=50)	*p* value
Age (yrs)	52.1±13.9	57.5±11.1	47.2±15.3*	52.8±13.9	<0.01
Male (%)	102 (57)	30 (52.6)	47 (65.3)	25 (50)	0.84
MAP (mm Hg)	97.2±31.0	94.8±12.6	94.5±15.7	103.9±53.7	0.19
Follow-up duration (months)	56.9±52.5	48.5±48.7	70.9±58.5	49.6±48.7	0.03
Serum creatinine (mg/dL)	1.1±0.5	1.1±0.5	1.1±0.7	0.99±0.3	0.46
eGFR (mL/min/1.73 m^2)	79.7±27.0	74.6±29.3	81.9±25.6	74.6±29.3	0.22
Serum cholesterol (mg/dL)	306.4±99.5	270.0±74.8	327.9±98.9*	316.6±113.9†	<0.01
Serum albumin (g/dL)	2.7±0.7	2.9±0.6	2.5±0.7*	2.7±0.8	<0.01
Proteinuria (g/day)	7.5±4.2	6.9±3.7	7.9±4.7	7.6±4.1	0.34
Statin use (%)	146 (81.6)	48 (84.2)	54 (75.0)	44 (88.0)	0.67
RAS blockades use (%)	161 (89.9)	54 (94.7)	60 (83.3)	47 (94.0)	0.82
Pathologic stage (%)					0.46
I	51 (28.5)	17 (29.8)	21 (29.2)	13 (26.0)	
II	84 (46.9)	28 (49.1)	32 (44.4)	24 (48.0)	
III	42 (23.5)	12 (21.1)	18 (25.0)	12 (24.0)	
IV	2 (1.1)	0 (0)	1 (1.4)	1 (2.0)	

CsA, cyclosporine A; MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate (by MDRD-4 equation); RAS, renin-angiotensin system; MDRD, Modification of Diet in Renal Disease study.

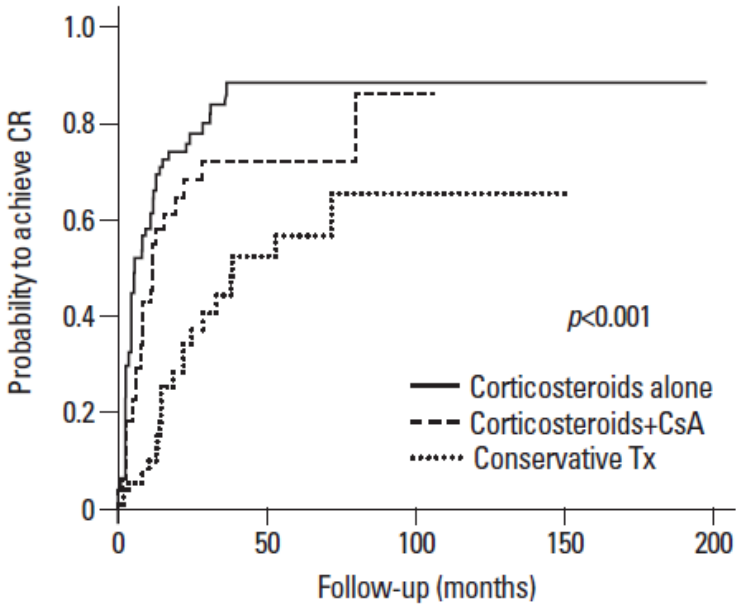
Values are expressed as mean±standard deviation or number (percentage).

*$p<0.01$ vs. conservative treatment.

†$p<0.05$ vs. conservative treatment.

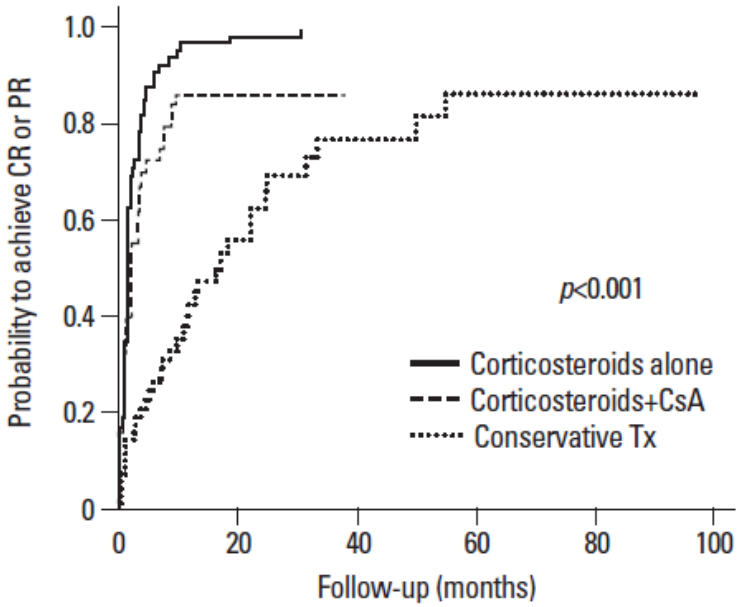
Yonsei Med J. 2013 Jul;54(4):973-82.

Korea



Corticosteroids alone	72	4	4	3	0
Corticosteroids+CsA	50	2	1	0	0
Conservative Tx	57	12	2	1	0

A



Corticosteroids alone	72	1	0	0	0	0
Corticosteroids+CsA	50	2	0	0	0	0
Conservative Tx	57	15	5	3	1	0

B

Fig. 2. Kaplan-Meier plots for cumulative probabilities to achieve complete remission (CR) and to achieve CR or partial remission (PR) according to treatment modalities. (A) Probability to achieve CR was significantly higher in patients treated with corticosteroids alone or with cyclosporine A (CsA) compared to patients with conservative treatment (Tx). (B) Probability to achieve CR or PR was significantly higher in patients treated with corticosteroids alone or with CsA compared to patients with conservative Tx.

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Korea

Table 2. Multiple Cox Regression Analysis for CR, and CR or PR Adjusted for Covariates

Treatment modality	CR		CR or PR	
	HR (95% CI)*	*p* value	HR (95% CI)*	*p* value
Conservative treatment	Reference		Reference	
Corticosteroids alone	4.09 (2.34-7.15)	<0.001	4.74 (2.94-7.64)	<0.001
Corticosteroids plus CsA	2.57 (1.45-4.57)	0.003	3.51 (2.16-5.71)	<0.001

CR, complete remission; PR, partial remission; CsA, cyclosporine A; eGFR, estimated glomerular filtration rate.
*Adjusted for age, sex, blood pressure, baseline eGFR, proteinuria, renin-angiotensin system blockades use, and pathologic stage.

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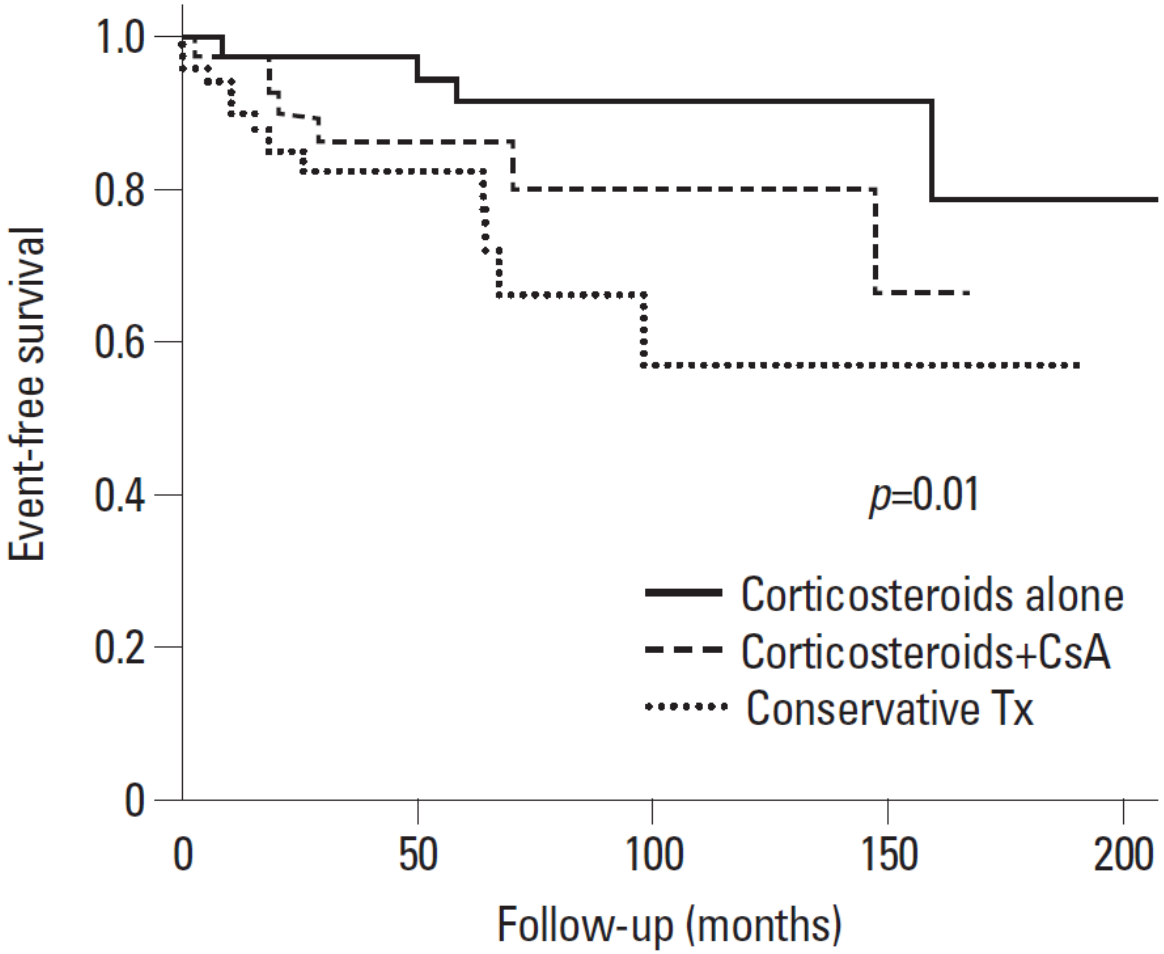
EVENTS: a decline in eGFR >50% or initiation of dialysis, and all-cause mortality.

Korea



Corticosteroids alone	72	36	19	8	4
Corticosteroids+CsA	50	14	9	3	0
Conservative Tx	57	21	6	2	0

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JNSCS as a secondary study of J-KDR

JNSCS: Japan Nephrotic Syndrome Cohort Study

JNSCS

Primary nephrotic syndrome

J-IGACS

Patietns with IgA nephropathy

JRPGN-CS

Rapidly progressive glomerulonephritis

JDNCS

Diabetic nephropathy

J-PKD

Polycystic kidney disease

J-IDCS

Dialysis

Study Design of JNSCS

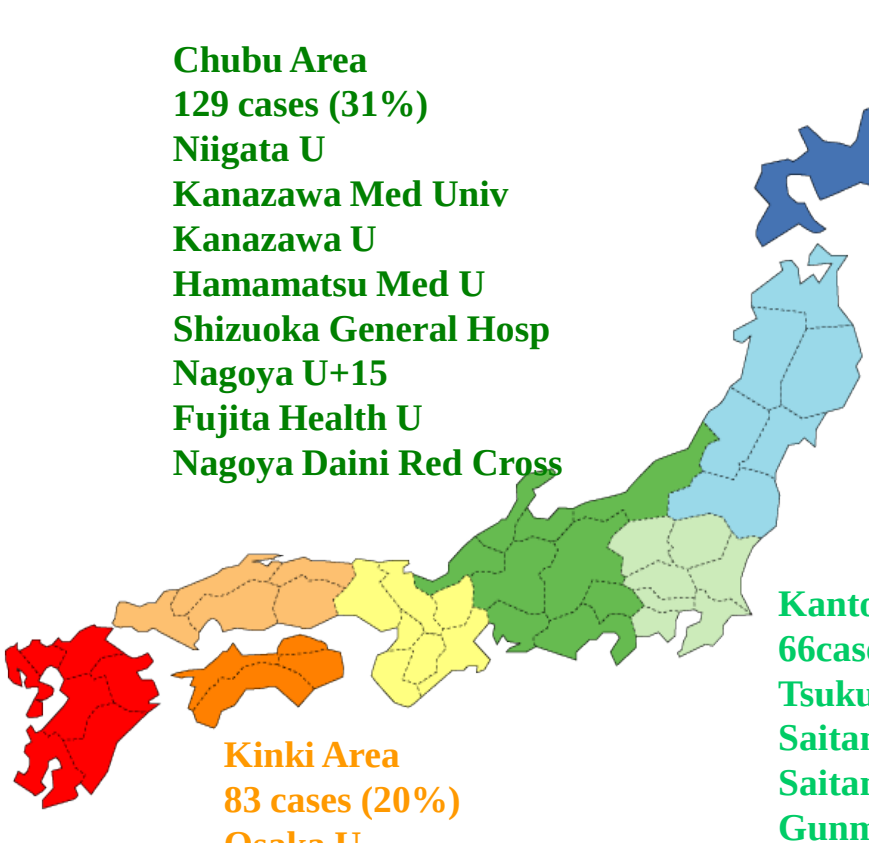
Purpose To disclose the outcomes and practice patterns in patients with primary nephrotic syndrome in Japan

Design Multicenter prospective cohort study

Participants Patients diagnosed histologically by renal biopsy with primary nephrotic syndrome between Jan 2008 and Dec 2010

Definition of nephrotic syndrome:
(1) Urinary protein ≥3.5 g/day
(2) Serum protein <3.0 g/dL

396 cases from 56 medical centers



Chubu Area
129 cases (31%)
Niigata U
Kanazawa Med Univ
Kanazawa U
Hamamatsu Med U
Shizuoka General Hosp
Nagoya U+15
Fujita Health U
Nagoya Daini Red Cross

Hokkaido Tohoku
66 cases (16%)

Hokkaido U
Tohoku U
Sendai Shakaihpoken H
Yamagata U
Fukushima M U

Chugoku
Shikoku area
26 cases (6%)
Kawasaki MU
Okayama U
Shimane U
Kagawa U
Tokushima UJ
Kochi U

Kanto Area
66cases (18%)
Tsukuba U
Saitama Med U
Saitama Med U General Hosp
Gunma U
Tokyo Women's Med U
Juntendo U
Teikyo U
St. Mariana Med U

Kyusyu area
42 cases (10%)
Kyusyu U
East Fukuoka MC
Kurume U
Fukuoka U
Miyazaki U
Nagasaki U

Kinki Area
83 cases (20%)
Osaka U
Osaka City U
Munincipal Toyonaka Hospital
Kitano Hospital
Osaka Prefectural Hospital
Kobe U
Wakayama Med Univ
Nara Medical U

Baseline Characteristics

	MCD N = 165	MN N = 158	FSGS N = 38	Others N = 35
Age (year)	**42 (26-61)**	**66 (59-75)**	**62 (29-73)**	**58 (45-71)**
Male gender (N (%))	95 (57.6)	85 (53.8)	25 (65.8)	20 (57.1)
Edema (N (%))	153 (92.7)	132 (85.2)	36 (94.7)	25 (71.4)
BMI (kg/m^2)	23.9±4.3	23.6±3.6	23.4±3.8	23.0±3.5
Systolic blood pressure (mmHg)	120±16	128±19	134±17	135±15
Diastolic blood pressure (mmHg)	73±11	75±13	80±13	78±11
Serum creatinine (mg/dL)	**0.87 (0.68-1.20)**	**0.86 (0.70-1.14)**	**1.17 (0.93-1.74)**	**1.06 (0.79-1.65)**
Serum albumin (g/dL)	**1.7±0.6**	**2.1±0.6**	**1.9±0.7**	**2.5±0.4**
Total cholesterol (mg/dL)	405±121	307±100	355±124	287±78
HDL-cholesterol (mg/dL)	75±27	63±23	61±20	58±25
Triglyceride (mg/dL)	194 (145-277)	186 (128-263)	224 (152-304)	147 (114-238)
Hemoglobin A1c (%)	5.5±1.3	5.4±0.5	5.5±1.0	5.3±0.5
Urinary protein (g/day)	**6.3 (4.2-10.0)**	**4.6 (3.0-6.4)**	**6.0 (4.2-8.8)**	**5.1 (3.1-6.9)**
UPCR	**7.1 (4.5-10.3)**	**4.6 (3.1-6.4)**	**6.0 (4.2-8.8)**	**5.1 (3.5-7.6)**

Mean±SD, or Median (25% - 75%)

Treatment for NS

	MCD	n	MN	n	FSGS	n
Observation period（year）	**2.3 (1.9 – 3.0)**	**165**	**2.3 (1.7 – 3.0)**	**158**	**2.5 (2.0 – 3.1)**	**38**
Immunosuppressive therapy	**162 (98.2)**		**136 (86.1)**		**35 (92.1)**	
The 1st month		**165**		**158**		**38**
oral glucocorticoids	**158 (95.8)**		**127 (80.9)**		**35 (92.1)**	
methyl predonisolone IV	**47 (28.5)**		**25 (15.9)**		**10 (26.3)**	
Cyclosporine	**24 (14.6)**		**61 (38.9)**		**15 (39.5)**	
Cyclophosphamide	**1 (0.6)**		**6 (3.8)**		**0 (0.0)**	
Mizoribine	**3 (1.8)**		**10 (6.4)**		**0 (0.0)**	
ACEI/ARB	41 (24.9)		119 (75.8)		20 (52.6)	
2-12 months		**162**		**151**		**38**
oral glucocorticoids	**157 (96.9)**		**125 (82.8)**		**35 (92.1)**	
methyl predonisolone IV	**8 (4.9)**		**2 (1.3)**		**1 (2.6)**	
Cyclosporine	**46 (28.4)**		**70 (46.4)**		**20 (52.6)**	
Cyclophosphamide	**0 (0.0)**		**3 (2.0)**		**1 (2.6)**	
Mizoribine	7 (4.3)		20 (13.3)		0 (0.0)	
ACEI/ARB	50 (30.9)		125 (82.8)		28 (82.4)	

In this annual meeting of JSN, we are publishing an "Evidence Based Guideline for Nephrotic Syndrome 2014."

MN

Initial treatment

Oral predonisolone is administered at single daily dose starting at 0.6～0.8 mg/kg/day and continued for 4 weeks. Instead of oral steroid alone, **predonisolone and cyclophosphamide** 50～100 mg/day is administered as starting doses. **Lower oral steroid and cyclosporine** as initial treatment is considered for the cases that are skeptical about steroid adverse effects, such as diabetic patients.

Initial immunosuppressive treatment for idiopathic membranous nephropathy

KDIGO GL	JSN GL
1. Ponticelli treatment	Steroid monotherapy
2. Cyclosporin or Tacrolimus	Cyclophosphamide + PSL
	Cyclosporin + PSL

Rituximab in Idiopathic Membranous Nephropathy

Piero Ruggenenti,*† Paolo Cravedi,* Antonietta Chianca,* Annalisa Perna,* Barbara Ruggiero,* Flavio Gaspari,* Alessandro Rambaldi,‡ Maddalena Marasà,* and Giuseppe Remuzzi*†

*Mario Negri Institute for Pharmacological Research, Clinical Research Center for Rare Diseases, Aldo e Cele Daccò, Villa Camozzi, Ranica, Italy; and †Units of Nephrology and ‡Hematology, Azienda Ospedaliera, Ospedali Riuniti di Bergamo, Bergamo, Italy

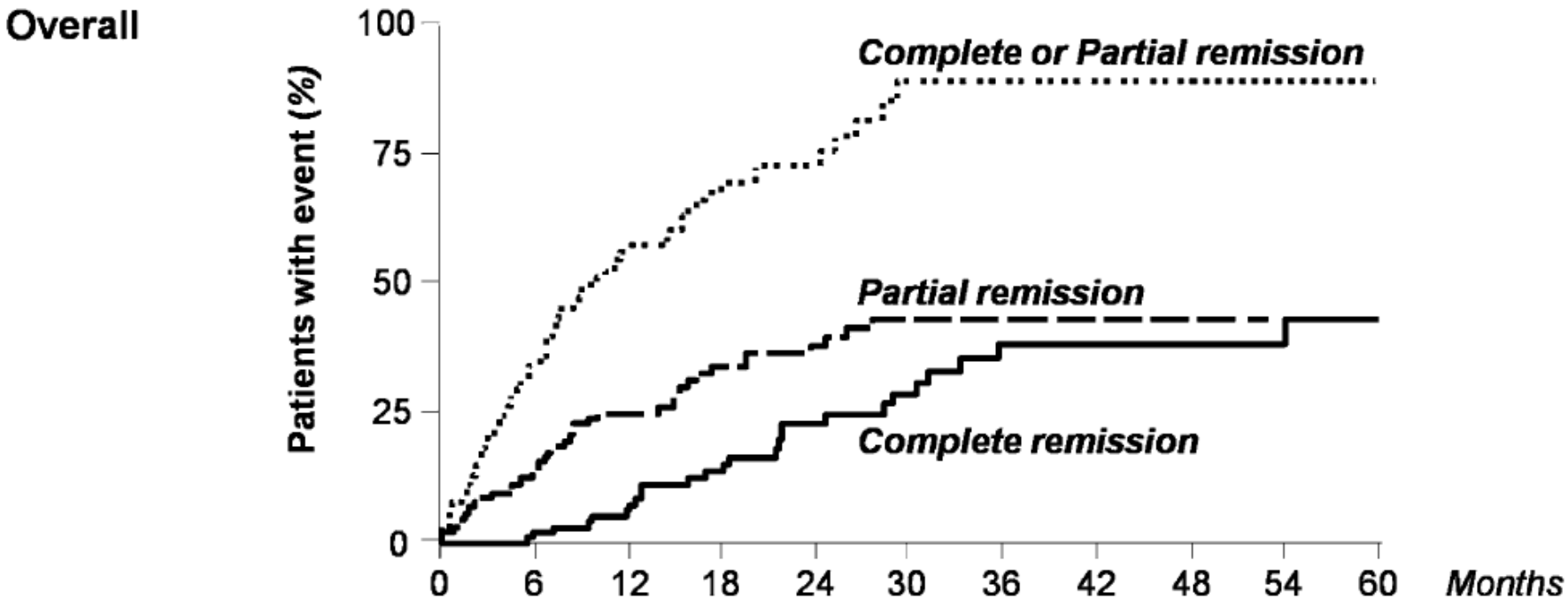
A retrospective stay of 100 consecutive patients with IMN and NS treatment with Rituximab (68 as initial "first-line" therapy; 32 as "second line" therapy after failure of another regimen)
Baseline Scr= 1.2mg/dL (0.97-1.70mg/dL-44 patients had an elevated Scr.)

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

J Am Soc Nephrol 23: 1416–1425, 2012

RITUXIMAB in Primary MN



Patients at risk											
Complete remission	100	94	78	56	41	32	20	17	13	12	10
Partial remission	100	84	63	47	37	26	21	19	15	12	11
Complete or Partial remission	100	67	40	23	13	4	2	2	1	0	0

J Am Soc Nephrol 23: 1416–1425, 2012

RITUXIMAB in Primary MN

Table 3. Number of patients with treatment-related adverse events that were serious and/or required treatment interruption in different series of patients with IMN and the nephrotic syndrome

Adverse Event	Rituximab (*n*=100)	Prednisone + Chlorambucil (*n*=42)	Prednisone + Cyclophosphamide (*n*=47)
Infections	0	1 (2.4)	10 (21.3)
pneumonia	0	1 (2.4)[a]	3 (6.4)
disseminated tuberculosis	0	0	1 (2.1)
other	0	0	6 (12.8)
Other	0	7 (16.7)	0
myelotoxicity	0	2 (4.8)	0
gastric/liver toxicity	0	4 (9.5)[a]	0
diabetes	0	1 (2.4)	0
Total	0	8 (19.0)	10 (21.3)

Data are presented as *n* (%).

[a]Treatment was stopped in four patients because of pneumonia (*n*=1), peptic ulcers (*n*=2), and gastric intolerance to chlorambucil (*n*=1).

J Am Soc Nephrol 23: 1416–1425, 2012

Q5.

Serum creatinine has gradually increased to 1.2 mg/dL.

Which ONE of the following treatments would you recommend?

A. Observe for up to 6 more months while receiving an angiotensin converting enzyme inhibitor and diuretic

B. Give Cyclosporine 2~4mg/kg/d plus 30mg/d of prednisone

C. Give cyclical oral cyclophosphamide at 1-1.5mg/Kg alternating with IV methyl prednisolone and oral prednisone

D. Give 40mg of prednisone

E. Give 1000mg of Rituximab twice at an interval of two weeks

F. Give MMF 1.0gm twice daily

According to the KDIGO GL, the answer is C.

According to the Japanese GL, the answer is either B, C, or D.

I would choose B.