The KDIGO App is downloadable!

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<table>
<thead>
<tr>
<th>Rating Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade</strong></td>
</tr>
<tr>
<td><strong>Level 1</strong></td>
</tr>
<tr>
<td>“We recommend”</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
</tr>
<tr>
<td>“We suggest”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rating Quality of Evidence</th>
</tr>
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<tbody>
<tr>
<td><strong>Grade</strong></td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
</tbody>
</table>

Note: Within each recommendation, the strength of recommendation is indicated as Level 1, Level 2, or Not Graded, and the quality of the supporting evidence is shown as A, B, C, or D.

*The additional category “Not Graded” was used, typically to provide guidance based on common sense or when the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.*
# CLINICAL RELEVANCE OF RATING GUIDELINE RECOMMENDATIONS

<table>
<thead>
<tr>
<th>LEVEL 1</th>
<th>WE RECOMMEND</th>
<th>Most patients should receive the recommended course of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVEL 2</td>
<td>WE SUGGEST</td>
<td>Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision appropriate for them.</td>
</tr>
<tr>
<td>NOT GRADED</td>
<td></td>
<td>Usually provides guidance based on common sense or where the issue does not allow adequate application of evidence</td>
</tr>
</tbody>
</table>
QUALITY OF SUPPORTING EVIDENCE

A 1A (STRONGEST)

B

C

D 2D (WEAKEST)
MEMBRANOUS NEPHROPATHY

Kidney Disease: Improving Global Outcomes
MEMBRANOUS NEPHROPATHY
7.1.1. Perform appropriate investigations to exclude SECONDARY CAUSES in all cases of biopsy proven MN. (NOT GRADED)

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

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.\textsuperscript{196} accessed http://www.ajkd.org/article/S0272-6386(08)01058-5/fulltext.
Distinguishing secondary MN from IMN is very important, since the therapy in the former must be directed at the underlying cause and some of the treatments for IMN are potentially toxic both to the patient and the kidney.

### Table 13 | Reported causes of secondary MN

<table>
<thead>
<tr>
<th>Autoimmune diseases</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Hepatitis B</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Malaria</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Filarialis</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>Enteroococcal endocarditis</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>Hydatid disease</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Leptospirosis</td>
</tr>
<tr>
<td>Temporal arteritis</td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td></td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carcinomas</strong></td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Esophageal</td>
</tr>
<tr>
<td>Colon</td>
</tr>
<tr>
<td>Breast</td>
</tr>
<tr>
<td>Stomach</td>
</tr>
<tr>
<td>Melanoma</td>
</tr>
<tr>
<td><strong>Noncarcinomas</strong></td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Leukemia (chronic lymphocytic leukemia)</td>
</tr>
<tr>
<td>Mesothelioma</td>
</tr>
<tr>
<td>Wilm’s tumor</td>
</tr>
<tr>
<td>Hepatic adenoma</td>
</tr>
<tr>
<td>Angiolymphatic hyperplasia</td>
</tr>
<tr>
<td>Schwannoma</td>
</tr>
<tr>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Adrenal ganglioneuroma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs/Toxins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold</td>
</tr>
<tr>
<td>Penicillamine</td>
</tr>
<tr>
<td>Bucillamine</td>
</tr>
<tr>
<td>Mercury compounds</td>
</tr>
<tr>
<td>Captopril</td>
</tr>
<tr>
<td>Probenecid</td>
</tr>
<tr>
<td>Trimethadione</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Cycoxygenase-2 inhibitors</td>
</tr>
<tr>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Formaldehyde</td>
</tr>
<tr>
<td>Hydrocarbons</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Diabetes mellitus (association or cause?)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
</tr>
<tr>
<td>α1-antitrypsin deficiency</td>
</tr>
<tr>
<td>Weber-Christian disease</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Systemic mastocytosis</td>
</tr>
<tr>
<td>Guillain-Barre syndrome</td>
</tr>
<tr>
<td>Urticarial vasculitis</td>
</tr>
<tr>
<td>Hemolytic-uremic syndrome</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td>Myelodysplasia</td>
</tr>
</tbody>
</table>
• The recognition of the underlying disorder responsible for MN has **important implications for PROGNOSIS and THERAPY**.
• MN is typically a **disease of adults** (fewer than 3% of cases are found in children).
• IMN is often a **“diagnosis of exclusion”**.
• A recent study has shown that about 70–80% of IMN patients exhibit circulating antibodies of IgG4 subtype against a conformation-dependent epitope in the M-type phospholipase A2 receptor.

• Such autoantibodies appear to be absent or very uncommon in patients with secondary MN.

• The IgG4 subclass dominates in the deposits of IMN, while IgG1, IgG2, and/or IgG3 dominate in secondary forms of MN.
M-Type Phospholipase A2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy

Laurence H. Beck, Jr., M.D., Ph.D., Ramon G. Bonegio, M.D., Gérard Lambeau, Ph.D., David M. Beck, B.A., David W. Powell, Ph.D., Timothy D. Cummins, M.S., Jon B. Klein, M.D., Ph.D., and David J. Salant, M.D.

- 75% SENSITIVITY
- 100% SPECIFICITY
MEMBRANOUS NEPHROPATHY
SELECTION OF CANDIDATES FOR TREATMENT WITH IMMUNOSUPPRESSIVE AGENTS

7.2.1: We recommend that initial therapy be started ONLY IN PATIENTS WITH NEPHROTIC SYNDROME AND when at least one of the following conditions is met:

• Urinary protein excretion persistently exceeds 4 g/d AND remains at over 50% of the baseline value, AND does not show progressive decline, during antihypertensive and anti-proteinuric therapy (see during an observation period of at least 6 months; (1B)

• the presence of severe, disabling, or life-threatening symptoms related to the nephrotic syndrome; (1C)

• SCr has risen by 30% or more within 6 to 12 months from the time of diagnosis but the eGFR is not less than 25–30 ml/min/1.73 m2 AND this change is not explained by superimposed complications. (2C)
Kidney Disease: Improving Global Outcomes

NATURAL HISTORY OF MN
RULE OF THIRD

- **SPONTANEOUS REMISSION**
  20-30%

- **PERSISTENT PROTEINURIA**
  30-40%

- **PROGRESSION TO RENAL FAILURE**
  20-30%
NATURAL HISTORY OF MN
RULE OF THIRDS

- **SPONTANEOUS REMISSION**
  20-30%
  - Reasonable to delay specific therapy for at least 6 months utilizing supportive therapy, incl. RAS blockade

- **PERSISTENT PROTEINURIA** 30-40%
  - Related complications: infections, thromboembolic events, accelerated CV disease

- **PROGRESSION TO RENAL FAILURE** 20-30%
The Natural History of the Non-Nephrotic Membranous Nephropathy Patient

Michelle A. Hladunewich, Stephan Troyanov, Jennifer Calafati, and Daniel C. Cattran, for the Metropolitan Toronto Glomerulonephritis Registry
University Health Network, University of Toronto, Toronto, Ontario, Canada

Figure 2. Time (years) for progression from non-nephrotic to nephrotic range proteinuria.

Kidney Disease: Improving Global Outcomes
SPONTANEOUS REMISSION IS COMMON among patients with nephrotic syndrome resulting from MN and carries a FAVORABLE LONG-TERM OUTCOME with a LOW INCIDENCE OF RELAPSE.

A decrease in proteinuria > 50% from baseline during the 1st year PREDICTS SPONTANEOUS REMISSION.
Spontaneous Remission of Nephrotic Syndrome in Idiopathic Membranous Nephropathy

Natalia Polanco,* Elena Gutiérrez,* Adelardo Covarsi,† Francisco Ariza,‡ Agustín Carreño,§ Ana Vigil,‖ José Baltar,‖ Gema Fernández-Fresneda,** Carmen Martín,†† Salvador Pons,‡‡ Dolores Lorenzo,§§ Carmen Bernis,¶ Pilar Arrizabalaga,¶¶ Gema Fernández-Juárez,*** Vicente Barrio,*** Milagros Sierra,††† Ines Castellanos,† Mario Espinosa,‡ Francisco Rivera,§ Aniana Oliet,‖ Francisco Fernández-Vega,‖ and Manuel Praga* for the Grupo de Estudio de las Enfermedades Glomerulares de la Sociedad Española de Nefrología

*Hospital 12 de Octubre, Madrid, Spain; †Hospital San Pedro de Alcántara, Cáceres, Spain; ‡Hospital Reina Sofia, Córdoba, Spain; §Hospital General de Ciudad Real, Ciudad Real, Spain; ¶Hospital Severo Ochoa, Leganés, Spain; ‖Hospital Central de Asturias, Oviedo, Spain; **Hospital Marqués de Valdecilla, Santander, Spain; ††Hospital Virgen del Rocio, Sevilla, Spain; †‡Hospital Clínico, Valencia, Spain; †§Hospital Universitario de A Coruña, A Coruña, Spain; ¶¶Hospital La Princesa, Madrid, Spain; §§Hospital Clinic, Barcelona, Spain; ***Fundación Hospital de Alcorcón, Alcorcón, Spain; and †††Hospital San Pedro, Logroño, Spain

Table 3. Results of univariate and multivariate analyses of independent prognostic factors for the appearance of SR

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio for SR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.8 (1.10 to 3)</td>
<td>0.008</td>
</tr>
<tr>
<td>Baseline serum creatinine (mg/dl)</td>
<td>0.35 (0.18 to 0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline proteinuria (g/24 h)</td>
<td>0.92 (0.86 to 0.98)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Proteinuria decrease &gt;50% in the first year of follow-up</td>
<td>7.08 (3.59 to 13.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACEI/ARB treatment</td>
<td>2 (1.1 to 3.5)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
Spontaneous Remission of Nephrotic Syndrome in Idiopathic Membranous Nephropathy

Natalia Polanco,* Elena Gutiérrez,* Adelardo Covarsi,† Francisco Ariza,‡ Agustín Carreño,§ Ana Vigil,‖ José Baltar,‖ Gema Fernández-Fresnedo,** Carmen Martín,†† Salvador Pons,‡‡ Dolores Lorenzo,§§ Carmen Bernis,‖ Pilar Arrizabalaga,‖ Gema Fernández-Juárez,*** Vicente Barrio,*** Milagros Sierra,+++ Ines Castellanos,† Mario Espinosa,‡ Francisco Rivera,§ Aniana Oliet,‖ Francisco Fernández-Vega,‖ and Manuel Praga* for the Grupo de Estudio de las Enfermedades Glomerulares de la Sociedad Española de Nefrología

Figure 1. Evolution of proteinuria in patients with SR. The line within the box denotes the median and the box spans the interquartile range (25th to 75th percentiles).
• The **LIKELIHOOD OF SPONTANEOUS REMISSION AND PROGRESSION** is dependent upon:
  
  • Age
  
  • Gender
  
  • Degree of proteinuria
  
  • Kidney function at presentation
Original Article

The impact of sex in primary glomerulonephritis

Daniel C. Catran, Heather N. Reich, Heather J. Beanlands, Judith A. Miller, James W. Scholey and Stéphan Trojanov for the Genes, Gender and Glomerulonephritis Group

Department of Nephrology, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada

![Graph showing survival from renal failure with data points for males (134, 70, 29, 15) and females (261, 135, 62, 34). The p-value is 0.05.]
• The **LIKELIHOOD OF SPONTANEOUS REMISSION AND PROGRESSION** is dependent upon:
  
  • Age
  
  • Gender
  
  • Degree of proteinuria
  
  • Kidney function at presentation
Management of Membranous Nephropathy: When and What for Treatment

Daniel Catran

Toronto General Research Institute, University Health Network, Toronto General Hospital, Toronto, Ontario, Canada

Figure 1. Predicting risk of renal disease progression. The algorithm uses a time frame of 6 mo (bar) and the initial and change in creatinine clearance over this period plus the minimum persistent proteinuria value to calculate the "R" (risk) value.
### MEMBRANOUS NEPHROPATHY

**SELECTION OF CANDIDATES FOR TREATMENT WITH IMMUNOSUPPRESSIVE AGENTS**

<table>
<thead>
<tr>
<th>Risk stratification</th>
<th>Proteinuria</th>
<th>Creatinine clearance</th>
<th>Follow-up</th>
<th>Risk of developing chronic kidney disease over 5 years</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>&lt;4 g/day</td>
<td>Remains normal</td>
<td>6 months</td>
<td>&lt;8% over 5 years</td>
<td>Nondisease-specific treatment</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>4–8 g/day</td>
<td>Normal or near normal</td>
<td>6 months</td>
<td>50%</td>
<td>Nondisease specific then disease-specific therapy if not better in 6 months</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;8 g/day</td>
<td>Below normal or decreases during the observation period</td>
<td>3 months</td>
<td>75%</td>
<td>Diseasespecific therapy in addition to non-disease specific</td>
</tr>
</tbody>
</table>

*Table 1: Risk stratification in membranous nephropathy*
MEMBRANOUS NEPHROPATHY
SELECTION OF CANDIDATES FOR TREATMENT WITH IMMUNOSUPPRESSIVE AGENTS

7.2.2: DO NOT USE immunosuppressive therapy in patients with a SCr persistently > 3.5 mg/dl (or an eGFR < 30 ml/min per 1.73 m²) AND reduction of kidney size on ultrasound (e.g., < 8 cm in length) OR those with concomitant severe or potentially life-threatening infections. (NOT GRADED)
• There is no agreed definition of the “point of no return” in the evolution of IMN after which the risks of immunosuppressive drugs become unacceptable and futile.
  – severe tubular interstitial fibrosis, tubular atrophy, and glomerular obsolescence on biopsy, accompanied by
    – persistent elevation of SCr > 3.5 mg/dl (or eGFR < 30 ml/min per 1.73 m²), and
  – reduction in kidney size on ultrasound.
7.3.1: We recommend that initial therapy consist of a 6-month course of alternating monthly cycles of ORAL and IV CORTICOSTEROIDS, and ORAL ALKYLATING AGENTS. (1B)

7.3.2: We suggest using CYCLOPHOSPHAMIDE rather than chlorambucil for initial therapy. (2B)
A Randomized, Controlled Trial of Steroids and Cyclophosphamide in Adults with Nephrotic Syndrome Caused by Idiopathic Membranous Nephropathy

Vivekanand Jha,* Anirban Ganguli,* Tarun K. Saha,* Harbir S. Kohli,* Kamal Sud,* Krishan L. Gupta,* Kusum Joshi,† and Vinay Sakuju*

Departments of *Nephrology and †Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, 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.
• Untreated IMN with nephrotic syndrome is associated with a HIGH RISK OF DETERIORATION of renal function.

• A 6-month regimen of CYCLOPHOSPHAMIDE and STEROIDS induces remissions in a high proportion, arrests progression of renal insufficiency, and improves quality of life.
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 methylprednisolone (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 days³ |
| Month 3: Repeat Month 1 |
| Month 4: Repeat Month 2 |
| Month 5: Repeat Month 1 |
| Month 6: Repeat Month 2 |

IMN, idiopathic membranous nephropathy.

³Monitor 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/mm³, then hold chlorambucil or cyclophosphamide until recovery to >4000/mm³.
### Table 16 | Risks and benefits of the cyclical corticosteroid/alkylating-agent regimen in IMN

<table>
<thead>
<tr>
<th>Risks</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced risk of opportunistic infection</td>
<td>Prevention of CKD and ESRD</td>
</tr>
<tr>
<td>Reactivation of viral hepatitis</td>
<td>Avoidance of complications of nephrotic syndrome (thrombosis, accelerated atherogenesis)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Prolongation of life; improved quality of life</td>
</tr>
<tr>
<td>Gonadal damage (aspermato genesis, ovulation failure)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic cystitis (cyclophosphamide only)</td>
<td></td>
</tr>
<tr>
<td>Neoplasia (myelodysplastic syndrome, acute myelogenous leukemia)</td>
<td></td>
</tr>
<tr>
<td>Transitional cell carcinoma of the bladder, ureter or pelvis</td>
<td></td>
</tr>
<tr>
<td>Toxic hepatitis</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated infection (HIV, hepatitis B and C, tuberculosis, fungal infection, etc.)</td>
</tr>
<tr>
<td>Neoplasia (lung, skin [except squamous cell]), breast, colon, etc.</td>
</tr>
<tr>
<td>Urinary retention</td>
</tr>
<tr>
<td>Inability to comply with monitoring</td>
</tr>
<tr>
<td>Pre-existing leukopenia (≤4000 leukocytes/mm³)</td>
</tr>
<tr>
<td>SCr &gt; 3.5 mg/dl (≥309 µmol/l)</td>
</tr>
</tbody>
</table>

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.

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

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 ($P = 0.0000$).
 Oral cyclophosphamide versus chlorambucil in the treatment of patients with membranous nephropathy and renal insufficiency


From the Department of Medicine, Division of Nephrology, University Hospital Nijmegen, Nijmegen, The Netherlands

- **RENAL FUNCTION** IMPROVED in both groups but was SHORTLIVED IN THE CHLORAMBUCIL group.

- **REMISSIONS OF PROTEINURIA** occurred MORE FREQUENTLY after CYCLOPHOSPHAMIDE treatment.

- **PO CYCLOPHOSPHAMIDE** WAS BETTER TOLERATED.
• Cyclophosphamide has a more favorable side-effect profile compared to chlorambucil.
7.3.3: We recommend patients be managed conservatively for at least 6 months following the completion of this regimen before being considered a TREATMENT FAILURE if there is no remission, unless kidney function is deteriorating or severe, disabling, or potentially life-threatening symptoms related to the nephrotic syndrome are present. (1C)
Table 14 | Definitions of complete and partial remission in IMN

**Complete Remission:** Urinary protein excretion < 0.3 g/d (uPCR < 300 mg/g or < 30 mg/mmol), confirmed by two values at least 1 week apart, accompanied by a normal serum albumin concentration, and a normal SCr.

**Partial Remission:** Urinary protein excretion < 3.5 g/d (uPCR < 3500 mg/g or < 350 mg/mmol) and a 50% or greater reduction from peak values; confirmed by two values at least 1 week apart, accompanied by an improvement or normalization of the serum albumin concentration and stable SCr.

MN, membranous nephropathy; uPCR, urine protein:creatinine ratio. See also Chapter 1. Based on previously published information, Jha et al. and Passerini et al. 204,205
Treatment-induced REMISSIONS are associated with an IMPROVED PROGNOSIS.

<table>
<thead>
<tr>
<th>REMISSION</th>
<th>10-year survival free of kidney failure (%)</th>
<th>Rate of decline in CrCl (mL/min/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPLETE Remission</td>
<td>100</td>
<td>-1.5</td>
</tr>
<tr>
<td>PARTIAL Remission</td>
<td>90</td>
<td>-1.5</td>
</tr>
<tr>
<td>NO Remission</td>
<td>50</td>
<td>-2.0</td>
</tr>
</tbody>
</table>
PREDICTORS OF REMISSION

• Treatment with **RAS BLOCKADE**
• **50% DECLINE OF PROTEINURIA** from baseline during 1\textsuperscript{st} year of follow-up
  • Hypertension
  • Histologic evidence: Interstitial fibrosis and tubular atrophy
  • Persistently elevated Urinary C5b-9
  • Elevated Urinary low or high molecular weight proteins (β2-macroglobulin and IgG)

*STAGING OF MN by histologic criteria has **LIMITED UTILITY** for prediction of outcomes or response to therapy for IMN.*
7.3.4: Perform a **REPEAT KIDNEY BIOPSY** only if the patient has **rapidly deteriorating kidney function** (doubling of SCr over 1–2 month of observation), in the absence of massive proteinuria ( > 15 g/d). (NOT GRADED)

7.3.5: **ADJUST THE DOSE** of cyclophosphamide or chlorambucil according to the **age of the patient** and eGFR. (NOT GRADED)
7.3.6: We suggest that CONTINUOUS DAILY (NONCYCLICAL) use of oral alkylating agents may also be effective, but can be associated with GREATER RISK OF TOXICITY, particularly when administered for 46 months. (2C)
### Table 17 | Contraindications to the use of the cyclical corticosteroid/alkylating-agent regimen in IMN

<table>
<thead>
<tr>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated infection (HIV, hepatitis B and C, tuberculosis, fungal infection, etc.)</td>
</tr>
<tr>
<td>Neoplasia (lung, skin [except squamous cell]), breast, colon, etc.</td>
</tr>
<tr>
<td>Urinary retention</td>
</tr>
<tr>
<td>Inability to comply with monitoring</td>
</tr>
<tr>
<td>Pre-existing leukopenia (&lt; 4000 leukocytes/mm³)</td>
</tr>
<tr>
<td>SCr &gt; 3.5 mg/dl (&gt; 309 μmol/l)</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus; MN, membranous nephropathy; SCr, serum creatinine.
MEMBRANOUS NEPHROPATHY
ALTERNATIVE REGIMENS FOR INITIAL THERAPY: 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, but who choose not to receive the cyclical corticosteroid/alkylating-agent regimen or who have contraindications to this regimen. (1C)
MEMBRANOUS NEPHROPATHY
ALTERNATIVE REGIMENS FOR INITIAL THERAPY: CNI THERAPY

7.4.2: We suggest that CNIs be discontinued in patients who do not achieve complete or partial remission after 6 months of treatment. (2C)

7.4.3: We suggest that the dosage of CNI be reduced at intervals of 4–8 weeks to a level of about 50% of the starting dosage, provided that remission is maintained and no treatment-limiting CNI-related nephrotoxicity occurs, and continued for at least 12 months. (2C)
MEMBRANOUS NEPHROPATHY
ALTERNATIVE REGIMENS FOR INITIAL THERAPY: CNI THERAPY

7.4.4: We suggest that CNI blood levels be monitored regularly during the initial treatment period, and whenever there is an unexplained rise in SCr ( > 20%) during therapy. (NOT GRADED)
WHY CNIs ARE NOT THE 1st OPTION

- Although EFFECTIVE IN INDUCING REMISSION, one limitation with CNIs is a HIGH RELAPSE RATE
  
  - Relapse may be decreased BY PROLONGING TREATMENT DURATION TO 1 YEAR
Cyclosporine in patients with steroid-resistant membranous nephropathy: A randomized trial


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

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.
Tacrolimus monotherapy in membranous nephropathy: A randomized controlled trial

M Praga¹, V Barrio², G Fernández Juárez² and J Luño³, For the GRUPO ESPAÑOL DE ESTUDIO DE LA NEFROPATÍA MEMBRANOSA (Members of the Group listed at the end of the paper)

¹Hospital 12 de Octubre, Madrid, Spain; ²Fundación Hospital Alcorcón, Alcorcón, Madrid, Spain and ³Hospital Gregorio Marañón, Madrid, Spain

Figure 3 | Percentage of complete (grey) and partial (white) remissions in the tacrolimus (T) and in the control (C) group. Numbers within columns indicate the total number of patients in CR or PR in both groups.
MEMBRANOUS NEPHROPATHY

**Treatment algorithm of IMN**

- **Low risk group**
  - Urine protein < 4g/day + normal RFT
  - Dietary protein restriction, BP control, and proteinuria reduction by ACEI/ARB, statins for hyperlipidemia

- **Medium risk group**
  - Urine protein 4–8g/day + normal RFT
  - Supportive treatment × 6 months
    - Dietary protein restriction, BP control, and proteinuria reduction by ACEI/ARB, statins for hyperlipidemia
    - Persistent proteinuria of nephrotic range and presence of poor prognostic factors
    - Steroid alternating with cytotoxics
    - Deteriorating RFT

- **High risk group**
  - Urine protein ≥ 8g/day + impaired RFT
  - Supportive treatment
    - Dietary protein restriction, BP control, and proteinuria reduction by ACEI/ARB, statins for hyperlipidemia
    - Combined steroids and cytotoxics
    - Persistent proteinuria of nephrotic range and deteriorating RFT
MEMBRANOUS NEPHROPATHY
REGIMENS NOT RECOMMENDED OR SUGGESTED FOR INITIAL THERAPY

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)*
Mycophenolate Mofetil in Idiopathic Membranous Nephropathy: A Clinical Trial With Comparison to a Historic Control Group Treated With Cyclophosphamide

Amanda J. Branten, MD, PhD,¹ Peggy W. du Buf-Vereijken, MD, PhD,¹,² Marc Vervloet, MD,³ and Jack F. Wetzels, MD, PhD¹

Figure 1. Cumulative incidence of partial remission of proteinuria in patients treated with mycophenolate mofetil (MMF) or cyclophosphamide (CP). Numbers of patients at risk are indicated.

Figure 2. Cumulative incidence of relapses in patients treated with mycophenolate mofetil (MMF) or cyclophosphamide (CP). Numbers of patients at risk are indicated.
MMF vs CYCLOPHOSPHAMIDE in IMN

- MMF reduced proteinuria
- MMF improved renal function
- Complication rates similar
- MMF had **HIGHER RELAPSE RATE**
- MMF was **NOT AS EFFECTIVE** as Cyclophosphamide
Rituximab Therapy in Idiopathic Membranous Nephropathy: A 2-Year Study

Fernando C. Fervenza,* Roshini S. Abraham,† Stephen B. Erickson,* Maria Valentina Irazabal,* Alfonso Eirin,* Ulrich Specks,‡ Patrick H. Nachman,§ Eric J. Bergstrahl,‖ Nelson Leung,* Fernando G. Cosio,* Marie C. Hogan,* John J. Dillon,* LaTonya J. Hickson,* Xujian Li,‖ and Daniel C. Cattran,‖ for the Mayo Nephrology Collaborative Group

*Division of Nephrology and Hypertension, †Division of Clinical Biochemistry and Immunology, Department of Laboratory Medicine and Pathology, ‡Division of Pulmonary and Critical Care, and §Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota; ‖Division of Nephrology and Hypertension, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and ‖Department of Nephrology, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada
Treatment of nephrotic syndrome with adrenocorticotropic hormone (ACTH) gel

Andrew S Bomback1
James A Tumlin2
Joel Baranski2
James E Bourdeau3
Anaolo Besarab1
Alice S Appel1
Jai Radhakrishnan1
Gerald B Appel1

Purpose: A synthetic adrenocorticoprotin (ACTH) analog has shown efficacy in Europe as primary and secondary therapy for nephrotic syndrome, but there is no published experience using the natural, highly purified ACTH gel formulation, available in the United States, for nephrotic syndrome. We therefore investigated the use of ACTH gel for nephrotic syndrome in the United States.

Patients and methods: Twenty-one patients with nephrotic syndrome treated with ACTH gel outside of research settings in the United States, with initiation of therapy by December 31, 2009, allowing a minimum 6 months follow-up. We defined complete remission as stable renal function with proteinuria falling to <500 mg/day, and partial remission as stable renal function with proteinuria >500 mg/day.

Figure 1 Changes in proteinuria with ACTH gel therapy in 11 patients with nephrotic syndrome due to membranous nephropathy.

Abbreviation: ACTH, adrenocorticotropic.
## Table 2: Drug-specific treatment

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Protocol</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid alone</td>
<td>A 3-day course of 1G methylprednisolone followed by prednisone (0.4–0.5 mg/kg/day) for 1 month alternating with 1 month of chlorambucil (0.2 mg/kg/day) for a total treatment period of 6 months</td>
<td>After 5 years of follow-up, renal function had deteriorated in about 50% of the control group, but only in 10% of the treated patients</td>
<td>Not beneficial. Not widely used in the United States because of bone marrow suppression</td>
<td>First-line treatment</td>
<td>[14,15]</td>
</tr>
<tr>
<td>Steroid with chlorambucil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>Cyclophosphamide, with low-dose prednisone</td>
<td>Cyclophosphamide (1.5–2.0 mg/kg/day) with prednisone (0.5 mg/kg/day) for 3–6 months</td>
<td>Comparable results to steroid with chlorambucil</td>
<td>Side effects leading to stop therapy in only 10% cases</td>
<td></td>
<td>[17,18]</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>3.5–5 mg/kg/day (trough levels of 150–225 mg)</td>
<td>70% of patients show occasional complete or partial remission</td>
<td>Prolonged courses (1–2 years) may produce more permanent remission</td>
<td>The best-studied alternative to steroid–cytotoxic drug therapy</td>
<td>[19,20]</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Tacrolimus (0.05 mg/kg/day) over 12 months with a 6-month taper</td>
<td>Decreases proteinuria in MN</td>
<td>Patients have significant relapse rate</td>
<td></td>
<td>[21,22]</td>
</tr>
<tr>
<td>Mycophenolate methotrexil</td>
<td>With steroids in a dose of 2 g/day for a year Four weekly infusions</td>
<td></td>
<td>Limited data</td>
<td>Third alternative in the treatment</td>
<td>[23]</td>
</tr>
<tr>
<td>Anti-B cell monoclonal antibody</td>
<td></td>
<td>Proteinuria was significantly reduced and renal function stabilized 1 year later Comparably to a combined regimen of steroids and alkylating agents</td>
<td>Limited data</td>
<td></td>
<td>[24]</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone</td>
<td></td>
<td></td>
<td>Limited data</td>
<td></td>
<td>[25]</td>
</tr>
</tbody>
</table>
7.6.1: We suggest that patients with IMN resistant to alkylation agent/steroid-based initial therapy be treated with a CNI. (2C)

7.6.2: We suggest that patients with IMN resistant to CNI-based initial therapy be treated with an ALKYLATING AGENT/ STEROID-based therapy. (2C)
7.7.1: We suggest that relapses of nephrotic syndrome in IMN be treated by **REINSTITUTION OF THE SAME THERAPY** that resulted in the initial remission. (2D)

7.7.2: We suggest that, if a 6-month cyclical corticosteroid/alkylating-agent regimen was used for initial therapy, the regimen be **REPEATED ONLY ONCE** for treatment of a relapse. (2B)
7.9.1: We suggest that patients with IMN and nephrotic syndrome, with marked reduction in serum albumin (< 2.5 g/dl) and additional risks for thrombosis, be considered for prophylactic anticoagulant therapy, using ORAL WARFARIN. (2C)
Venous Thromboembolism in Patients with Membranous Nephropathy


Table 4. Adjusted risk of VTE by the level of serum albumin in 732 patients with available data

<table>
<thead>
<tr>
<th>Serum Albumin (g/dl)</th>
<th>N</th>
<th>Patients with VTE</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference range ≥3.0</td>
<td>219</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.8 to &lt;3.0</td>
<td>66</td>
<td>1.41</td>
<td>0.34, 5.87</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>2.0 to &lt;2.8</td>
<td>74</td>
<td>2.17</td>
<td>0.66, 7.46</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>2.4 to &lt;2.6</td>
<td>72</td>
<td>2.05</td>
<td>0.59, 7.12</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>2.2 to &lt;2.4</td>
<td>77</td>
<td>1.31</td>
<td>0.31, 5.62</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>2.0 to &lt;2.2</td>
<td>82</td>
<td>4.32</td>
<td>1.46, 12.77</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>&lt;2.0</td>
<td>142</td>
<td>3.56</td>
<td>1.28, 9.88</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>&lt;2.8 versus ≥2.8</td>
<td>447/285</td>
<td>2.53</td>
<td>1.17, 5.47</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

aLogistic regression model with incremental values of serum albumin, adjusted for age at biopsy, sex, 24-hour proteinuria (g/dl), immunosuppressive therapy, and registry site.

bLogistic regression model with serum albumin as a dichotomous variable. The serum albumin cut-point of 2.8 g/dl was determined from the incremental model (by 0.2 g/dl) reported in this table, with threshold for effect noted for values <2.8 g/dl. Adjusted for age at biopsy, sex, 24-hour proteinuria (g/dl), immunosuppressive therapy, and registry site.

Figure 2. Distribution of venous thromboembolic event (VTE) during the observation time.
• There is very low–quality evidence to suggest the use of prophylactic anticoagulation with warfarin in patients with IMN and severe nephrotic syndrome.

• Based on Markov modeling of anticipated benefits and risks derived from observational studies, prophylactic anticoagulation might be considered when the serum albumin concentration is < 2.0–2.5 g/dl with one or more of the following:
  – proteinuria > 10 g/d
  – BMI > 35 kg/m²
  – prior history of thromboembolism
  – family history of thromboembolism with documented genetic predisposition
  – NYHA class III or IV congestive heart failure
  – recent abdominal or orthopedic surgery
  – prolonged immobilization.
IMMUNOGLOBULIN A NEPHROPATHY
IMMUNOGLOBULIN A NEPHROPATHY
IgA Nephropathy is the MOST COMMON GLOMERULONEPHRITIS in the world.
- RARE in African Americans
- COMMON in Native Americans
- EVEN WITH LOW PROGRESSION RATE, its HIGH PREVALENCE results in 10-20% contribution to ESKD.

<table>
<thead>
<tr>
<th></th>
<th>ALL BIOPSIES (%)</th>
<th>GN BIOPSIES (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>ASIA</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>EUROPE</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>
IgA Nephropathy is Morphologically Heterogeneous
Light Microscopic Morphology

Mesangioproliferative Glomerulopathy

Normal Glomeruli

Proliferative Glomerulonephritis

Chronic Glomerulonephritis

Crescentic Glomerulonephritis

End Stage Kidney

Asymptomatic Hematuria/Proteinuria

Acute Nephritis

Rapidly Progressive Nephritis

Chronic Nephritis

Kidney Disease: Improving Global Outcomes
Kidney Disease: Improving Global Outcomes
10.1.1: Assess all patients with biopsy-proven IgAN for **SECONDARY CAUSES** of IgAN. *(NOT GRADED)*
## Diseases Reported in Association with IgA Nephropathy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Common</th>
<th>Reported</th>
<th>Rare</th>
</tr>
</thead>
</table>
| Rheumatic and Autoimmune Disease        | - Ankylosing spondylitis  
- Rheumatoid arthritis  
- Reactive arthritis  
- Uveitis                                                             | - Behcet’s syndrome  
- Takayasu’s arthritis  
- Myasthenia gravis                                                           |                                                                                                       |
| Gastrointestinal Disease                | Celiac disease                                                                                                  | Ulcerative colitis                                                                                   |                                                                                                       |
| Hepatic Disease                         | - Alcoholic liver disease  
- Non-alcoholic cirrhosis  
- Schistosomal liver disease                                                   |                                                                                                       |                                                                                                       |
| Lung Disease                            | Sarcoid                                                                                                          |                                                                                                       |                                                                                                       |
| Skin Disease                            | Dermatitis herpetiformis                                                                                        |                                                                                                       |                                                                                                       |
| Malignancy                              |                                                                                                                 | IgA monoclonal gammopathy                                                                           |                                                                                                       |
| Infection                               | - HIV  
- HBV                                                                                                          | Brucellosis                                                                                           |                                                                                                       |
| Miscellaneous                           |                                                                                                                 | Wiskott-Aldrich syndrome                                                                             |                                                                                                       |
10.1.2: Assess the **risk of progression** in all cases by evaluation of **proteinuria, blood pressure, and eGFR** at the time of diagnosis and during follow-up. *(NOT GRADED)*
IMMUNOGLOBULIN A NEPHROPATHY
PROGNOSTIC IMPLICATIONS (?)

- DEGREE OF PROTEINURIA: 1.0 vs 0.5 g/d
- DEGREE OF BP CONTROL
  - 130/80 for proteinuria 0.3 g/d
  - 125/75 mm Hg for proteinuria 1 g/d
- OXFORD Pathology Classification
10.1.3: Pathological features may be used to assess prognosis. (NOT GRADED)
The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification


Table 7 | Definitions of pathological variables used in the classification of IgA nephropathy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial hypercellularity</td>
<td>&lt;4 Mesangial cells/mesangial area=0</td>
<td>M0 ≤ 0.5</td>
</tr>
<tr>
<td></td>
<td>4-5 Mesangial cells/mesangial area=1</td>
<td>M1 &gt; 0.5^a</td>
</tr>
<tr>
<td></td>
<td>6-7 Mesangial cells/mesangial area=2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;8 Mesangial cells/mesangial area=3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The mesangial hypercellularity score is the mean score for all glomeruli</td>
<td></td>
</tr>
<tr>
<td>Segmental glomerulosclerosis</td>
<td>Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion</td>
<td>S0 – absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S1 – present</td>
</tr>
<tr>
<td>Endocapillary hypercellularity</td>
<td>Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina</td>
<td>E0 – absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E1 – present</td>
</tr>
<tr>
<td>Tubular atrophy/interstitial fibrosis</td>
<td>Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater</td>
<td>0-25% – T0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26-50% – T1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 50% – T2</td>
</tr>
</tbody>
</table>

^Mesangial score should be assessed in periodic acid-Schiff-stained sections. If more than half the glomeruli have more than three cells in a mesangial area, this is categorized as M1. Therefore, a formal mesangial cell count is not always necessary to derive the mesangial score.
Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy

James V. Donadio¹, Erik J. Bergstralh², Joseph P. Grande³ and Diana M. Rademacher²

¹Division of Nephrology, Department of Internal Medicine, ²Section of Biostatistics and ³Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology, Mayo Clinic and Foundation, Rochester, MN, USA

Fig. 1. 24-h UP levels at 1 year were significantly associated with subsequent ESRD after 1 year on study in (A) IgAN 1 (\(P < 0.001\), linear trend) and (B) IgAN 2 (\(P < 0.001\), linear trend).
Remission of Proteinuria Improves Prognosis in IgA Nephropathy

Heather N. Reich,* Stéphan Troyanov,† James W. Scholey,* and Daniel C. Cattran,* for the Toronto Glomerulonephritis Registry

*Division of Nephrology, University Health Network, University of Toronto, Toronto, Ontario, and †Department of Medicine, Division of Nephrology, Hôpital du Sacré-Coeur de Montréal, Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada

- Rate of decline of function increased with the amount of proteinuria.
- Those with sustained proteinuria ≥ 3 gms/day lost renal function 25-FOLD FASTER than those with < 1 gm/day.
- Those who presented with ≥ 3 gms/day who achieved proteinuria < 1 gm/day had a SIMILAR COURSE to those who had < 1gm/day throughout and fared far better than those who never achieved it.
- NO EVIDENCE in IgAN that decreasing proteinuria < 1 gm/day in adults gives additional benefit.
# IMMUNOGLOBULIN A NEPHROPATHY PROGNOSTIC MARKERS AT PRESENTATION

<table>
<thead>
<tr>
<th>CLINICAL</th>
<th>HISTOPATHOLOGIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POOR PROGNOSIS</strong></td>
<td></td>
</tr>
<tr>
<td>• HYPERTENSION</td>
<td>• Mesangial hypercellularity</td>
</tr>
<tr>
<td>• RENAL IMPAIRMENT</td>
<td>• Endocapillary proliferation</td>
</tr>
<tr>
<td>• SEVERITY OF PROTEINURIA</td>
<td>• Segmental glomerulosclerosis</td>
</tr>
<tr>
<td>• Hyperuricemia</td>
<td>• Tubular atrophy</td>
</tr>
<tr>
<td>• Gross Obesity</td>
<td>• Interstitial fibrosis</td>
</tr>
<tr>
<td>• Duration of preceding symptoms</td>
<td>• CAPILLARY LOOP IgA DEPOSITS</td>
</tr>
<tr>
<td>• Increasing age</td>
<td>- <em>Specific to IgA Nephropathy</em></td>
</tr>
<tr>
<td></td>
<td>• Crescents <em>(Controversial)</em></td>
</tr>
<tr>
<td><strong>GOOD PROGNOSIS</strong></td>
<td></td>
</tr>
<tr>
<td>Recurrent macroscopic hematuria</td>
<td></td>
</tr>
<tr>
<td><strong>NO IMPACT ON PROGNOSIS</strong></td>
<td></td>
</tr>
<tr>
<td>• Gender</td>
<td>• Intensity of IgA deposits</td>
</tr>
<tr>
<td>• Serum IgA level</td>
<td></td>
</tr>
</tbody>
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Kidney Disease: Improving Global Outcomes

**RECURRENT MACROSCOPIC HEMATURIA IN IgAN**

- Most frequent in **CHILDREN**
- Associated with URT or GIT infection; flank or loin pain is common
- Nephrotic syndrome and Hypertension are **UNCOMMON**
- **PROLONGED REMISSIONS OF CLINICAL SIGNS**
- Associated with **GOOD PROGNOSIS**

**ASYMPTOMATIC HEMATURIA/ PROTEINURIA**

- **PERSISTENT MICROSCOPIC HEMATURIA**
- **HYPERTENSION MORE COMMON**
- Impairment of renal function may be apparent on presentation
- Remission is **UNCOMMON**
10.2.1: We recommend long-term ACE-I or ARB treatment when proteinuria is > 1 g/d, with up-titration of the drug depending on blood pressure. (1B)

10.2.3: We suggest the ACE-I or ARB be titrated upwards as far as tolerated to achieve proteinuria < 1 g/d. (2C)

10.2.4: In IgAN, use blood pressure treatment goals of < 130/80 mmHg in patients with proteinuria < 1 g/d, and < 125/75 mmHg when initial proteinuria is > 1 g/d. (NOT GRADED)
IgACE: A Placebo-Controlled, Randomized Trial of Angiotensin-Converting Enzyme Inhibitors in Children and Young People with IgA Nephropathy and Moderate Proteinuria

Rosanna Coppo,* Licia Peruzzi,* Alessandro Amore,* Antonio Piccoli,† Pierre Cochat,‡ Rosario Stone,§ Martin Kirschstein,‖ and Tommy Linné;¶ on behalf of the EC Biomed Concerted Action Project BMH4-97-2487(DG 12-SSMI) and IgACE European Collaborative Group

*Nephrology, Dialysis and Transplantation, Pediatric Nephrology School, Regina Margherita University Hospital, Turin, Italy; †Department of Medical and Surgical Sciences, Nephrology Clinic, University of Padua, Padua, Italy; ‡Département de Pédiatrie, Hôpital Edouard-Herriot, Lyon, France; §Unidade de Nefrologia, Servico de Pediatria, Hospital de Santa Maria, Lisboa, Portugal; ‖Klinik für Kinder- und Jugendmedizin des Allgemeines Krankenhauses, Celle, Germany; and ¶Department of Women and Child Health, Karolinska Universitetaket, Stockholm, Sweden

- Placebo-controlled, double blind RCT of ACE-I
- 66 patients randomly assigned
- **Primary outcome** was progression of kidney disease, i.e., > 30% decrease in CrCl
- **Secondary outcomes**: endpoint > 30% decrease in CrCl, worsening of proteinuria, proteinuria partial/total remission
Combination Therapy of Prednisone and ACE Inhibitor Versus ACE-Inhibitor Therapy Alone in Patients With IgA Nephropathy: A Randomized Controlled Trial

Jicheng Lv, MD,¹,² Hong Zhang, MD, PhD,¹,² Yuqing Chen, MD,¹,² Guangtao Li, MD,¹,² Lei Jiang, MD,¹,² Ajay K. Singh, MB, FRCP,³ and Haiyan Wang, MD¹,²

Figure 2. Kidney survival estimated on the basis of an increase up to 50% greater than baseline serum creatinine level and a decrease of 25% in estimated glomerular filtration rate (eGFR). Abbreviation: ACE, angiotensin-converting enzyme.

Conclusions: Our results suggest that the addition of steroid to ACE-inhibitor therapy provided additional benefit compared with an ACE inhibitor alone. However, this was a pilot study with a small number of participants achieving the end points, and thus further validation is necessary.

Combined treatment with renin–angiotensin system blockers and polyunsaturated fatty acids in proteinuric IgA nephropathy: a randomized controlled trial

Pietro Manuel Ferraro¹, Gian Franco Ferraccioli², Giovanni Gambaro³, Pierluigi Fulignati¹ and Stefano Costanzi¹

¹Department of Nephrology, ²Department of Rheumatology, Catholic University of the Sacred Heart, Rome and ³Department of Nephrology, University Hospital of Verona, Verona, Italy

• PUFA associated with RASB reduced proteinuria in patients with IgAN more than RASB alone.

• It appears that ACE-I enhance the effects of PUFA.

Fig. 1. Proteinuria at 6 months. UPE, urinary protein excretion; PUFA, polyunsaturated fatty acids.
10.3.1: We suggest that patients with persistent proteinuria > 1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR > 50 ml/min per 1.73 m², receive a 6-month course of CORTICOSTEROID therapy. (2C)

A 6-month course of steroid treatment protected against deterioration in renal function in IgA nephropathy with no notable adverse effects during follow-up. An increase in urinary protein excretion could be a marker indicating the need for a second course of steroid therapy.
Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy

Carlo Manno, Diletta Domenica Torres, Michele Rossini, Francesco Pesce and Francesco Paolo Schena

Renal, Dialysis and Transplant Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy

- The combination of CORTICOSTEROIDS and RAMIPRIL may provide ADDITIONAL BENEFITS compared with Ramipril alone in PREVENTING THE PROGRESSION OF RENAL DISEASE in proteinuric IgAN patients in the long-term follow up.
MAIN LIMITATION: Subjects with IgAN and eGFR < 50 mL/min were EXCLUDED from these trials
Low dose corticosteroids (20 mgs/day tapered to 5 mgs/day by 2 years) **HAD ANTIPROTEINURIC EFFECT** but **COULD NOT IMPROVE KIDNEY SURVIVAL.**
Corticosteroid Therapy in IgA Nephropathy

Jicheng Lv,* Damin Xu,* Vlado Perkovic,† Xinxin Ma,* David W. Johnson,‡§ Mark Woodward,¶ Adeera Levin,‖ Hong Zhang,* and Haiyan Wang,* for the TESTING Study Group

*Renal Division, Department of Medicine, Peking University First Hospital, Peking University Institute of Nephrology, Key Laboratory of Renal Disease, Ministry of Health of China, Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Beijing, China; †George Institute for Global Health, University of Sydney, Sydney, Australia; ‡Department of Renal Medicine, Princess Alexandra Hospital, Brisbane, Australia; ¶School of Medicine, University of Queensland, Brisbane, Australia; ‖Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland; and "Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada

Figure 2. Effect of steroids on composite renal endpoint (ESRD or doubling of serum creatinine or halving of GFR) in patients with IgA nephropathy. Boxes and horizontal lines represent relative risk and 95% CI, respectively, for each trial. Size of boxes is proportional to weight of that trial result. Diamonds represent the 95% CI for pooled estimates of effect and are centered on pooled relative risk. Dotted lines on the center of the diamonds represent pooled relative risk. Solid lines represent that the relative risk is 1.

Figure 5. Meta-regression for the association of RR for composite renal endpoint and proteinuria reduction.
Corticosteroid Therapy in IgA Nephropathy

Jicheng Lv,* Damin Xu,* Vlad Perkovic,† Xinxin Ma,* David W. Johnson,‡§ Mark Woodward,¶ Adeera Levin,¶ Hong Zhang,* and Haiyan Wang,* for the TESTING Study Group

*Renal Division, Department of Medicine, Peking University First Hospital, Peking University Institute of Nephrology, Key Laboratory of Renal Disease, Ministry of Health of China, Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Beijing, China; †George Institute for Global Health, University of Sydney, Sydney, Australia; ‡Department of Renal Medicine, Princess Alexandra Hospital, Brisbane, Australia; §School of Medicine, University of Queensland, Brisbane, Australia; ¶Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland; and *Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada

• Relatively HIGH-DOSE and SHORT-TERM STEROID THERAPY (prednisone 30 mg/d or high-dose pulse IV methylprednisolone for 1 year) produced SIGNIFICANT RENAL PROTECTION, whereas low-dose, long-term steroid use did not.

• Steroid therapy was associated with a 55% HIGHER RISK FOR ADVERSE EVENTS.

• The quality of included studies was low, thereby limiting the generalizability of the results.

• The authors concluded that although steroids appeared to provide renal protection in patients with IgAN there was a significant increased risk for adverse events. They also recommended that defining the efficacy and safety of steroids in IgAN requires a high-quality trial with a large sample size.
CORTICOSTEROIDS REDUCED DOUBLING OF SERUM CREATININE (Strippoli et al, Am J Kidney Dis 2009)

85% of the weight was contributed by 2 studies: Pozzi et al, Lancet 1999 and Kobayashi et al, Nephron 1996, both of which lacked optimal antiproteinuric and antihypertensive therapy based on contemporary studies.
IMMUNOGLOBULIN A NEPHROPATHY
IMMUNOSUPPRESSIVE AGENTS

• Cyclophosphamide
• Azathioprine
• MMF
• Cyclosporine
10.4.1: We suggest NOT TREATING with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients (unless there is crescentic IgAN with rapidly deteriorating kidney function). (2D)
10.4.2: We suggest **NOT USING** immunosuppressive therapy in patients with GFR < 30 ml/min per 1.73 m² unless there is crescentic IgAN with rapidly deteriorating kidney function. (2C)

10.4.3: We suggest **NOT USING MMF** in IgAN. (2C)
Patients selected for moderately progressive IgAN benefit from treatment with prednisolone and cytotoxic agents.

Kidney Disease: Improving Global Outcomes
Corticosteroids combined with cyclophosphamide followed by several years of azathioprine in patients with serum creatinine 2-3 mgs/dL plus a 15% rise within the previous year.

The active treatment group had a much greater renal survival (72% 5-year survival vs 6% in control group).

- There was NO steroid monotherapy arm
- Use of RASB was NOT detailed but these agents could not be initiated after the start of the trial
- The follow-up BP was higher than recommended by current guidelines.

- Early treatment with prednisolone and azathioprine appears to be beneficial in preventing the progression of immunologic renal injury and in improving histopathological features in IgAN patients with isolated hematuria.

However, the patients enrolled have an excellent prognosis and there is consensus that they should not have received immunosuppression.
Treatment significantly decreased proteinuria from 2.00 to 1.07 gms/day during follow up (p < 0.001) on average, with no difference between groups.

- Treatment related adverse events were more frequent among those receiving azathioprine.
- **ADDING LOW-DOSE AZATHIOPRINE TO CORTICOSTEROIDS for 6 months** **DOES NOT PROVIDE ADDITIONAL BENEFIT** to patients with IgAN and may **INCREASE THE RISK FOR ADVERSE EVENTS**.
2 YEAR COMBINATION OF PREDNISOLONE/ AZATHIOPRINE/ WARFARIN/ DIPYRIDAMOLE vs PREDNISOLONE alone

- There was COMPLETE REMISSION OF PROTEINURIA in 92% in the combination group (vs 74% in the prednisolone alone group)
- GFR remained normal in all children
- It may be difficult to justify an intense immunosuppression in children on the basis of a relatively soft endpoint.
Mycophenolate mofetil in IgA nephropathy: Results of a 3-year prospective placebo-controlled randomized study

BART D. MAES, RAYMOND OYEN, KATHLEEN CLAES, PIETER EVENEPOEL, DIRK KUYPERS, JOHAN VANWALLEGHEM, BOUDEWIJN VAN DAMME, and YVES F. CH. VANRENTERGHEM

Department of Medicine, Division of Nephrology, University Hospital Gasthuisberg, Leuven, Belgium; Department of Radiology and Department of Pathology, University Hospital Gasthuisberg, Leuven, Belgium

**MMF 2 gms/day for 3 years vs. Placebo (34 patients with average initial inulin clearance 70 mL/min/1.73 m2 and proteinuria 1.8 gms/day)**

- **NO DIFFERENCE IN PROTEINURIA REDUCTION or PRESERVATION OF GFR** was observed.
Long-term study of mycophenolate mofetil treatment in IgA nephropathy

Sydney C.W. Tang\textsuperscript{1,2}, Anthony W.C. Tang\textsuperscript{2}, Sunny S.H. Wong\textsuperscript{2}, Joseph C.K. Leung\textsuperscript{1}, Yiu Wing Ho\textsuperscript{2} and Kar Neng Lai\textsuperscript{1}

\textsuperscript{1}Nephrology Division, Department of Medicine, The University of Hong Kong and Queen Mary Hospital, Hong Kong, China and \textsuperscript{2}Department of Medicine and Geriatrics, United Christian Hospital, Hong Kong, China

\textbf{Figure 1} | Kaplan–Meier analysis of overall renal survival of 40 IgAN subjects over the 6-year follow-up period. Ctrl, control; MMF, mycophenolate mofetil.
40 patients with mean initial GFR 72 mL/min/1.73 m2 and mean proteinuria 1.8 gms/day

• **SIGNIFICANT REDUCTION IN PROTEINURIA** at 18 months with MMF given for 6 months vs controls (2005 study)

• 6 year follow-up: **RENAL SURVIVAL BENEFIT** (2010 study)

*The ANTI-PROTEINURIC EFFECT DISAPPEARED after nearly 2 years.*
Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial

Gershon Frisch, Julie Lin, Jordan Rosenstock, Glen Markowitz, Vivette D’Agati, Jai Radhakrishnan, Dean Preddie, John Crew, Anthony Valeri and Gerald Appel

Division of Clinical Nephrology, New York Presbyterian Hospital, Columbia University, New York, NY, USA

**Fig. 1.** Kaplan–Meier survival to outcomes. Log rank significance for a 50% increase in SCr = 0.31 (a), a 0.5 mg/dl increase in SCr = 0.19 (b) and for ESRD = 0.26 (c).
Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial

Gershon Frisch, Julie Lin, Jordan Rosenstock, Glen Markowitz, Vivette D’Agati, Jai Radhakrishnan, Dean Preddie, John Crew, Anthony Valeri and Gerald Appel

Division of Clinical Nephrology, New York Presbyterian Hospital, Columbia University, New York, NY, USA

1 year regimen of MMF 2 gms/day vs Placebo (32 patients with initial GFR 40 mL/min/1.73 m² and proteinuria 2.7 gms/day)

• NO BENEFITS over 24 months was seen in patients who received MMF in this high-risk group probably reflecting the advanced stage of disease in the population studied.

• MMF IS PROBABLY NOT EFFECTIVE in patients with IgAN who already have moderate renal insufficiency.
10.5.1.1: We suggest using fish oil in the treatment of IgAN with persistent proteinuria > 1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control). (2D)
In patients with IgAN, treatment with fish oil for 2 years retards the rate at which renal function is lost.
ANTIPLATELET AGENTS

10.5.2.1: We suggest NOT using antiplatelet agents to treat IgAN. (2C)

DIPYRIDAMOLE, Trimetazidine and Dilazep were the 3 moist commonly used antiplatelet agents in studies.

- **SUBOPTIMAL QUALITY** of individual controlled trials
- **Most studies** DID NOT ASSESS the true outcome of renal death
- **Long-term follow up studies** yielded DIFFERENT RESULTS

The EFFECT OF ANTIPLATELET AGENTS ALONE could not be discerned because patient received other concomitant therapies.

This study supports the observation that treatment of IgA nephropathy with cyclophosphamide, dipyridamole and warfarin is associated with a reduction of urinary protein excretion but a significant effect on preservation of renal function, at least as determined by serum creatinine values, could not be confirmed over this two-year study.


While we agree that cyclophosphamide cannot be recommended, we suggest that there is available evidence to support the use of dipyridamole and low-dose warfarin. This regimen has been shown to be safe and its use as long-term therapy in patients with IgA nephropathy with poor prognostic indices can slow the rate of decline in renal function and progression to ESRD.
TONSILLECTOMY

10.5.3.1: We suggest that tonsillectomy NOT BE PERFORMED for IgAN. (2C)
• Tonsillar lymphocytes from patients with IgAN synthesize excessive amounts of under-glycosylated IgA₁, some of which “spills” into the circulation
• IgA in glomerular deposits resemble IgA synthesized in the tonsils
• Tonsillar stimulation (ultra short wave) causes deterioration of urinary findings in IgAN
• Tonsillectomy possibly decreases hematuria and proteinuria
  ? effect on ESKD
TONSILLECTOMY FOR IgAN
WHAT DOES THE LITERATURE SAY?

Tonsillectomy and Steroid Pulse Therapy Significantly Impact on Clinical Remission in Patients With IgA Nephropathy

Osamu Hotta, MD, Mariko Miyazaki, MD, Takashi Furuta, MD, Sachiko Tomioka, MD, Shigemi Chiba, MD, Ikuo Horigome, MD, Keishi Abe, MD, and Yoshio Taguma, MD

We conducted a retrospective investigation of renal outcome in 329 patients with immunoglobulin A (IgA) nephropathy with an observation period longer than 36 months (82.3 ± 38.2 months) in our renal unit between 1977 and 1995. Clinical remission, renal progression, and the impact of covariates were estimated by Kaplan-Meier analysis and a Cox regression model. In 157 of 329 patients (48%), disappearance of urinary abnormalities (clinical remission) was obtained. None of these 157 patients showed progressive deterioration, defined as a 50% increase in serum creatinine (Scr) level from baseline, during the observation period. Conversely, in patients without clinical remission, the Kaplan-Meier estimate of probability of progressive deterioration was 21% ± 5% at 10 years. In the multivariate Cox regression model with 13 independent covariates, initial Scr level, histological score, tonsillectomy, and high-dose methylprednisolone therapy had a significant impact on clinical remission, whereas proteinuria, age, sex, levels of hematuria, blood pressure, conventional steroid therapy, angiotensin-converting enzyme inhibitor therapy, and cyclophosphamide therapy had no significant effect. These findings indicate that interventions aimed at achieving clinical remission have provided encouraging results applicable to managing patients with IgA nephropathy.

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• Improved urinary protein excretion and hematuria, BUT NO EFFECT ON LONG-TERM SURVIVAL

Kidney Disease: Improving Global Outcomes
The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy

Yuansheng Xie, Shinichi Nishi, Mitsuhiro Ueno, Naofumi Imai, Minoru Sakatsume, Ichiei Narita, Yasushi Suzuki, Kouhei Akazawa, Hisaki Shimada, Masaaki Arakawa, and Fumitake Gejyo

Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; Saiseikai Niigata Daini Hospital, Niigata, Japan; Department of Medical Informatics, Niigata University Medical Hospital, Niigata, Japan; Internal Medicine, Niigata Prefectural Central Hospital, Jyoetsu, Japan; and Department of Health & Social Welfare and Bureau of Hospital Administration, Niigata Prefectural Government, Niigata, Japan

- Improved 20-year outcome in treatment group (90%) vs non-treatment group (64%)

• Improved (in 2 years) in all but 5 patients: hematuria improved; proteinuria decreased (65% of pre-treatment values)

• But IS THE EFFECT DUE TO CONCOMITANT GLUCOCORTICOIDs or is it a POPULATION-SPECIFIC ISSUE?
MCD with MESANGIAL IgA DEPOSITS

10.6.1.1: We recommend treatment as for MCD in nephrotic patients showing pathological findings of MCD with mesangial IgA deposits on kidney biopsy. (2B)
AKI ASSOCIATED WITH MACROSCOPIC HEMATURIA

10.6.2.1: Perform a **REPEAT KIDNEY BIOPSY** in IgAN patients with AKI associated with macroscopic hematuria if, after 5 days from the onset of kidney function worsening, there is no improvement. (NOT GRADED)

10.6.2.2: We suggest general supportive care for AKI in IgAN, with a kidney biopsy performed during an episode of macroscopic hematuria showing **only ATN** and intratubular erythrocyte casts. (2C)
Define crescentic IgAN as IgAN with crescents in more than 50% of glomeruli in the renal biopsy with rapidly progressive renal deterioration. *(NOT GRADED)*

We suggest the use of **STEROIDS** and **CYCLOPHOSPHAMIDE** in patients with IgAN and rapidly progressive crescentic IgAN, analogous to the treatment of ANCA vasculitis. *(2D)*

3 observational studies conclude that **IMMUNOSUPPRESSION IS POTENTIALLY USEFUL.**

• The patients with crescentic IgAN mostly show rapidly progressive nephritis associated with more severe pathological changes including glomerular, tubular interstitial and vascular lesions than in patients with general IgAN.

• The infiltrates in glomeruli may contribute to the crescentic formation, and the intensive immune suppressing treatment is useful to improve renal damage in patients with diffuse crescentic IgAN.
Crescentic, proliferative IgA nephropathy: clinical and histological response to methylprednisolone and intravenous cyclophosphamide

James A. Tumlin¹, Verachai Lohavichan¹ and Randy Hennigar²

¹Division of Nephrology and ²Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA

**Fig. 1.** Steroids and cyclophosphamide stabilize renal function in patients with crescentic/proliferative IgA nephropathy. Serum creatinine and 24-h proteinuria levels were averaged for all patients at baseline and after 6 and 36 months of follow-up. Serum Cr increased significantly ($P<0.03$) to a maximum of 2.65 mg/dl, falling to 1.51 mg/dl after 6 months of cyclophosphamide. After 36 months, serum creatinine was 1.72 mg/dl and significantly ($P<0.04$) lower than peak levels. Proteinuria at baseline was 3.70 g/24 h, increasing to a peak of 4.25 g/24 h. After 6 and 36 months of follow-up, proteinuria was reduced to 1.35 and 1.46 g of protein per 24 h. Data are presented as means ± SD.

**Fig. 4.** Steroids and cyclophosphamide reduce glomerular activity and minimize cortical scarring. A modified NIH SLE histological activity/chronicity index was applied to baseline renal biopsies in the treatment group and historical controls. There were no significant differences in the average activity and chronicity scores between the two groups. After 6 months of cyclophosphamide, the mean activity score in the treatment group was significantly lower than pre-treatment levels ($P<0.004$). Mean chronicity scores were not significantly different between baseline levels in the treatment group or baseline levels among the historical controls. Data are presented as means ± SD.

**Fig. 5.** Progressive renal insufficiency and nephrotic-range proteinuria in untreated crescentic/proliferative IgA nephropathy. Serum creatinine and 24-h proteinuria levels were averaged for 12 patients with crescentic proliferative IgA nephropathy who did not receive immunosuppressive therapy at baseline and after 6 and 36 months of follow-up. Serum Cr increased significantly ($P<0.03$) from 1.72 to a maximum of 5.18 mg/dl, falling to 4.31 mg/dl after 36 months of follow-up. Proteinuria was 4.73 g/24 h at baseline, remaining in the nephrotic range (4.33 g/24 h) after 36 months of follow-up. Data are presented as means ± SD.
CRESCENTIC IgAN

- N = 12 with CRESCENTIC, PROLIFERATIVE IgA
- Pulse Methylprednisolone x 3 days, then monthly IV Cylophosphamide x 6 months
- **REPEAT KIDNEY BIOPSY:** Elimination of endocapillary proliferation, cellular crescents and karyorrhexis in all patients after 6 months

- **Presenting renal function, blood pressure and chronic damage in the biopsy** are important **prognostic factors** in vasculitic IgA nephropathy.

- **Immunosuppression is advocated** in some patients.
HENOCH-SCHÖNLEIN PURPURA NEPHRITIS
HENOCH-SCHÖNLEIN PURPURA NEPHRITIS
HENOCH-SCHÖNLEIN PURPURA NEPHRITIS TREATMENT

11.4.1: We suggest that HSP nephritis in adults be treated the same as in children. (2D)

11.1.1: We suggest that children with HSP nephritis and persistent proteinuria $> 0.5–1$ g/d per 1.73 m$^2$, are treated with ACE-I or ARBs. (2D)

11.1.2: We suggest that children with persistent proteinuria $> 1$ g/d per 1.73 m$^2$, after a trial of ACE-I or ARBs, and GFR $> 50$ ml/min per 1.73 m$^2$, be treated the same as for IgAN with a 6-month course of CORTICOSTEROID therapy. (2D)

11.2.1: We suggest that children with crescentic HSP with nephrotic syndrome and/or deteriorating kidney function are treated the same as for crescentic IgAN. (2D)

11.3.1: We recommend NOT USING CORTICOSTEROIDS to prevent HSP nephritis. (1B)

Compared with placebo, **EARLY PREDNISONE THERAPY** controlled extra-renal symptoms more effectively and reduced the severity of nephritis, although **IT DID NOT PREVENT THE DEVELOPMENT OF RENAL INVOLVEMENT**
LUPUS NEPHRITIS
LUPUS NEPHRITIS

Class I

Class II

Class III

Class IV

Class V

[Diagrams of kidney sections for each class]
### ISN/ RPS 2002 Consensus Conference on the Classification of Lupus Glomerulonephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Minimal mesangial lupus nephritis</td>
</tr>
<tr>
<td>II</td>
<td>Mesangial proliferative lupus nephritis</td>
</tr>
<tr>
<td>III</td>
<td>Focal lupus nephritis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse segmental (IV-S) or global (IV-G) lupus nephritis&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>V</td>
<td>Membranous lupus nephritis&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>VI</td>
<td>Advanced sclerosing lupus nephritis</td>
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</tbody>
</table>

Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis and other vascular lesions

<sup>a</sup> Indicate the proportion of glomeruli with active and with sclerotic lesions

<sup>b</sup> Indicate the proportion of glomeruli with fibrinoid necrosis and cellular crescents

<sup>c</sup> Class V may occur in combination with class III or IV, in which case both will be diagnosed
12.1.1: We suggest that patients with class I LN be treated as dictated by the extra-renal clinical manifestations of lupus. (2D)
# LUPUS NEPHRITIS
## CLASS I LN (MINIMAL-MESANGIAL LN)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Malar rash</td>
<td>A “butterfly rash” of flat or raised fixed erythema tending to spare the nasolabial folds</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging associated with scarring</td>
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<tr>
<td>Photosensitivity</td>
<td>A reaction to sunlight causing rash that may last for several weeks after brief sun exposure</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Often painless oral or nasopharyngeal ulceration</td>
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<tr>
<td>Arthritis</td>
<td>Nonerosive arthritis tenderness, swelling, or effusion involving 2 or more peripheral joints</td>
</tr>
<tr>
<td>Serositis</td>
<td>Pleuritis (chest pain on inspiration) or pericarditis; note that premature coronary artery disease is associated with inflammatory conditions like SLE</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Persistent proteinuria</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>Seizures or psychosis in the absence of offending drugs or known metabolic derangements</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>Leucopenia (often an early sign), hemolytic anemia, lymphopenia, thrombocytopenia in the absence of offending drugs</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>Positive LE cell preparation, anti-DNA, anti-Sm, or false positive serologic test for syphilis</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>An abnormal titer of antinuclear antibody at any point in time and in the absence of drugs known to be associated with “drug-induced lupus” syndrome</td>
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ACR = American College of Rheumatology; LE = lupus erythematosus; SLE = systemic lupus erythematosus. Adapted from references 3, 4, and 7.
# LUPUS NEPHRITIS

## CLASS II LN (MESANGIAL-PROLIFERATIVE LN)

<table>
<thead>
<tr>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
<th>Class V</th>
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<tbody>
<tr>
<td>Mesangial proliferative LN</td>
<td>Focal LN</td>
<td>Diffuse LN</td>
<td>Membranous LN</td>
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**Class II LN**

The glomeruli show mesangial proliferation with mesangial immune deposits by IF (lower panel) and EM. Isolated subepithelial or subendothelial deposits may be present by IF or EM.

**Class III LN**

Active or inactive segmental or global endocapillary or crescentic GN involving less than 50% of all glomeruli. The glomerular lesions are classified as global (G) when > 50% of the involved glomeruli have global lesions (upper panel), and as segmental (S) when > 50% of the involved glomeruli have segmental lesions (lower panel).

**Class IV LN**

Global or segmental subepithelial immune deposits, usually with mesangial alterations. Class V LN may occur in combination with Class III or IV LN.

*LN = Lupus Nephritis; IF = Immunofluorescence; EM = Electron Microscopy*
LUPUS NEPHRITIS

CLASS II LN (MESANGIAL-PROLIFERATIVE LN)
12.2.1: Treat patients with class II LN and proteinuria $< 1\, \text{g/d}$ as dictated by the extra-renal clinical manifestations of lupus. (2D)

12.2.2: We suggest that class II LN with proteinuria $> 3\, \text{g/d}$ be treated with CORTICOSTEROIDS or CNIs as described for MCD. (2D)
LUPUS NEPHRITIS
CLASS III LN (FOCAL LN)
LUPUS NEPHRITIS
CLASS IV LN (DIFFUSE LN)

CAMERON J S JASN 1999;10:413-424

Kidney Disease: Improving Global Outcomes
Survival (not doubling serum creatinine, ESRD or death) of 122 Lupus Nephritis Patients as a Function of the WHO Classification

- WHO II and $V_A$
  - $P = .048$

- WHO III, IV and $V_B$

Graph showing survival probability over months.
Lupus Nephritis: Indices of Activity and Chronicity

Activity *

Glomeruli
- Hypercellularity
- Karyorrhesis or fibrinoid necrosis
- Cellular crescents **
- Wire loops **
- Leukocyte infiltration

Tubule/Interstitium
- Mononuclear cell infiltration

Chronicity *

Glomerulosclerosis
- Segmental
- Mesangial
- Global
- Fibrous crescent
- Interstitial fibrosis
- Tubule atrophy

* Score 0-3 for each item, ** Multiply by 2 Activity Index

Multivariate Analyses: Factors Associated with Increased Risk of Chronic Renal Failure

Not Amenable to Change

- Male gender
- Black race
- Age < 24 years
- Crescents ≥ 50%
- Chronicity index ≥ 1

Amenable to change

- Rx with prednisone only
- Initial high SCr (> 1.2 - 2.0 mg/dL
- Nephrotic syndrome
- Hypertension
- Noncompliant patient
- Hematocrit ≤ 26%

Treatment options for Lupus Nephritis

**Controlled Studies**
- Plasmapheresis
- Steroids
- Cyclophosphamide
- Azathioprine
- Mycophenolate mofetil

**Uncontrolled Studies**
- Chlorambucil
- Nitrogen mustard
- Methotrexate
- Adenosine analogues
- Total lymphoid irradiation
- Monoclonal antibodies
- Cyclosporine A
- Thromboxane inhibitors
- Ancrod venom
- IV gamma globulin
- Marrow ablation/reconstitution
LUPUS NEPHRITIS
CLASS III LN (FOCAL LN) and CLASS IV LN (DIFFUSE LN)

INITIAL THERAPY

12.3.1: We recommend initial therapy with CORTICOSTEROIDS (1A), combined with either CYCLOPHOSPHAMIDE (1B) or MMF (1B).

12.3.2: We suggest that, if patients have WORSENING LN (rising SCr, worsening proteinuria) during the first 3 months of treatment, a change be made to an alternative recommended initial therapy, or a repeat kidney biopsy be performed to guide further treatment. (2D)
Long term preservation of renal function in 111 patients with Lupus Nephritis

Steinberg and Steinberg. Arthritis Rheum. 1991;34:945.
# LUPUS NEPHRITIS

## CLASS III LN (FOCAL LN) and CLASS IV LN (DIFFUSE LN)

### INITIAL THERAPY

<table>
<thead>
<tr>
<th>Regimen</th>
<th>A. NIH</th>
<th>B. Euro-Lupus</th>
<th>C. Oral cyclophosphamide</th>
<th>D. MMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>i.v. cyclophosphamide 0.5–1 g/m²; monthly for 6 months</td>
<td>i.v. cyclophosphamide 500 mg; every 2 weeks for 3 months</td>
<td>Oral cyclophosphamide 1.0–1.5 mg/kg/d (maximum dose 150 mg/d) for 2–4 months</td>
<td>—</td>
</tr>
<tr>
<td>MMF</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>MMF up to 3 g/d for 6 months</td>
</tr>
<tr>
<td>Benefit shown by RCT in proliferative LN</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Benefit shown by RCT in severe proliferative LN</td>
<td>Yes</td>
<td>Untested</td>
<td>Untested</td>
<td>Untested</td>
</tr>
<tr>
<td>Comments</td>
<td>Effective in whites, blacks, Hispanics, Chinese</td>
<td>Effective in whites. Untested in blacks, Hispanics, Chinese</td>
<td>Effective in whites, blacks, Chinese; easy to administer and lower cost than i.v. cyclophosphamide</td>
<td>Effective in whites, blacks, Hispanics, Chinese; high cost</td>
</tr>
</tbody>
</table>

LN, lupus nephritis; MMF, mycophenolate mofetil; RCT, randomized controlled trial.

All regimens include corticosteroids:

- Oral prednisone, initial dose up to 0.5–1 mg/kg/d, tapering over 6–12 months according to clinical response.
- i.v. methylprednisolone is sometimes added initially for severe disease.
Mycophenolate Mofetil versus Cyclophosphamide for Induction Treatment of Lupus Nephritis

Gerald B. Appel,* Gabriel Contreras,† Mary Anne Dooley,‡ Ellen M. Ginzel,§ David Isenberg,‖ David Jayne,¶ Lei-Shi Li,** Eduardo Mysler,†† Jorge Sánchez-Guerrero,‡‡ Neil Solomons,§§ David Wofsy,¶¶ and the Aspreva Lupus Management Study Group

Figure 2. Response rates of study population and by racial group.
12.4.1: We recommend that, after initial therapy is complete, patients with class III and IV LN receive maintenance therapy with AZATHIOPRINE (1.5–2.5 mg/kg/d) or MMF (1–2 g/d in divided doses), and low-dose ORAL CORTICOSTEROIDS (≤ 10 mg/d prednisone equivalent). (1B)
Sequential Therapies for Proliferative Lupus Nephritis

Gabriel Contreras, M.D., M.P.H., Victoriano Pardo, M.D., Baudouin Leclercq, M.D., Oliver Lenz, M.D., Flaine Trzman, M.D., Patricia O'Nan, R.N., and David Roth, M.D.

**Figure 1.** Kaplan–Meier Estimates of Patient Survival.

- Azathioprine
- Mycophenolate mofetil
- Intravenous cyclophosphamide

For patients with proliferative lupus nephritis, short-term therapy with intravenous cyclophosphamide followed by maintenance therapy with mycophenolate mofetil or azathioprine appears to be more efficacious and safer than long-term therapy with intravenous cyclophosphamide.
Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis

Ellen M. Ginzier, M.D., M.P.H., Mary Anne Dooley, M.D., M.P.H., Cynthia Aranow, M.D., Mimi Y. Kim, Sc.D., Jill Buyon, M.D., Joan T. Merrill, M.D., Michelle Petri, M.D., M.P.H., Gary S. Gilkeson, M.D., Daniel J. Wallace, M.D., Michael H. Weisman, M.D., and Gerald B. Appel, M.D.

- Open label RCT between IV Cyclophosphamide vs MMF
- Adults and children from age 13
- 140 patients entered

**Remission rates: MMF vs IVC**

**Intent-to-Treat analysis**

In this 24-week trial, mycophenolate mofetil was more effective than intravenous cyclophosphamide in inducing remission of lupus nephritis and had a more favorable safety profile.
Evidence supporting the use of AZA as maintenance therapy is from this trial, in which AZA was comparable to MMF after induction therapy with Euro-Lupus dosing of IV cyclophosphamide.

Preferential use of AZA over MMF as maintenance therapy should be limited to whites with less severe renal disease at presentation who have been continued on prednisone, akin to the patients treated in the Euro-Lupus trials.
Mycophenolate versus Azathioprine as Maintenance Therapy for Lupus Nephritis

Mary Anne Dooley, M.D., M.P.H., David Jayne, M.D., Ellen M. Ginzler, M.D., M.P.H., David Isenberg, M.D., Nancy J. Olsen, M.D., David Wofsy, M.D., Frank Eitner, M.D., Gerald B. Appel, M.D., Gabriel Contreras, M.D., M.P.H., Laura Lisk, B.Sc., and Neil Solomons, M.D., for the ALMS Group*

CONCLUSIONS

Mycophenolate mofetil was superior to azathioprine in maintaining a renal response to treatment and in preventing relapse in patients with lupus nephritis who had a response to induction therapy. (Funded by Vifor Pharma [formerly Aspreva]; ALMS ClinicalTrials.gov number, NCT00377637)
• The ALMS (Aspreva Lupus Management Study) extension phase results lend strong support to using MMF rather than azathioprine for maintenance therapy, particularly if steroids are to be tapered and stopped during the maintenance phase.

Indeed, the ACR guideline explicitly spells out this difference by recommending as maintenance options **MMF alone or azathioprine with steroids.**
• MMF is SUPERIOR to AZA in MAINTAINING RENAL RESPONSE and PREVENTING RELAPSE in subjects with active LN who responded to induction therapy with either MMF or IV Cyclophosphamide.

• **FAILURE RATE** was 32% in the AZA Group vs 16% in the MMF Group ($p = 0.005$).

• **COMPLETION RATE** at 3 years was 49% for AZA and 63% for MMF.

• SUPERIORITY OF MMF WAS CONSISTENT regardless of induction treatment, race or region.

• SUPERIORITY OF MMF WAS CONFIRMED by consistent results in secondary endpoints.
LUPUS NEPHRITIS
CLASS III LN (FOCAL LN) and CLASS IV LN (DIFFUSE LN)
MAINTENANCE THERAPY

12.4.2: We suggest that CNIs with low-dose CORTICOSTEROIDS be used for maintenance therapy in patients who are intolerant of MMF and azathioprine. (2C)

12.4.3: We suggest that, after complete remission is achieved, maintenance therapy be CONTINUED FOR AT LEAST 1 YEAR before consideration is given to tapering the immunosuppression. (2D)
LUPUS NEPHRITIS
CLASS III LN (FOCAL LN) and CLASS IV LN (DIFFUSE LN)
MAINTENANCE THERAPY

12.4.4: If complete remission has not been achieved after 12 months of maintenance therapy, consider performing a repeat kidney biopsy before determining if a change in therapy is indicated. (NOT GRADED)

12.4.5: While maintenance therapy is being tapered, if kidney function deteriorates and/or proteinuria worsens, we suggest that treatment be increased to the previous level of immunosuppression that controlled the LN. (2D)
LUPUS NEPHRITIS
CLASS V LN (MEMBRANOUS LN)
LUPUS NEPHRITIS
CLASS V LN (MEMBRANOUS LN)

WHY IS IT IMPORTANT TO TREAT CLASS V LN (MEMBRANOUS LN)?

• CKD occurs in up to 20% of patients
• ESKD in 12% of these patients after 7-10 years
• Composite endpoint of death or ESKD
  – 14% at 5 years
  – 28% at 10 years
• Unlike IMN, **spontaneous remission of heavy proteinuria DOES NOT OCCUR often**
• Complications of heavy proteinuria
  – Atherosclerosis and CVD
  – Predisposition to clotting
12.5.1: We recommend that patients with class V LN, normal kidney function, and non-nephrotic-range proteinuria be treated with antiproteinuric and antihypertensive medications, and only receive corticosteroids and immunosuppressives as dictated by the extrarenal manifestations of systemic lupus. (2D)
12.5.2: We suggest that patients with pure class V LN and persistent nephrotic proteinuria be treated with CORTICOSTEROIDS plus an additional immunosuppressive agent: CYCLOPHOSPHAMIDE (2C), or CNI (2C), or MMF (2D), or AZATHIOPRINE (2D).
Randomized, Controlled Trial of Prednisone, Cyclophosphamide, and Cyclosporine in Lupus Membranous Nephropathy

Howard A. Austin, III,* Gabor G. Illei,†‡ Michelle J. Braun,* and James E. Balow*

*National Institute of Diabetes and Digestive and Kidney Diseases, †National Institute of Arthritis and Musculoskeletal and Skin Diseases, and ‡National Institute of Dental and Craniofacial Disorders, National Institutes of Health, Bethesda, Maryland

Figure 1. Cumulative probability of remission of proteinuria during the 12-mo protocol treatment period by treatment group. No patients were lost to follow-up or censored during this period. PRED, prednisone alone.

Figure 3. Cumulative probability of relapse of nephrotic syndrome after completion of protocol treatment with IVCY versus CSA. Follow-up begins at the end of the 12-mo protocol treatment period. Patients were censored when they were lost to follow-up.
BIOLOGICS (?)

- No decrease in proportion of patients with LN progressing to ESKD
- ≈ 50% of LN patients achieve Complete/Partial remission with treatment over 6 months
  - Many patients do not achieve Complete remission following induction therapy.
- No decrease in death rates in LN patients in the last decade
Biologic Therapy for Lupus Nephritis: The time has come.
• **DIRECT B CELL TARGETING** treatments (B cell depletion)
  - Anti-CD20: **Rituximab (EXPLORER 2010/ LUNAR 2012)**, Ocreluzimab
  - Anti-CD22: Epratuzumab

• **INDIRECT B CELL TARGETING** treatments (Targeting C-cell survival molecule Blys)
  - ANTI-BLys: Belimumumab
  - Anti-Blys/April: Atacicept

• **BLOCK CO-STIMULATION INTERACTIONS** between T and B cells
  - Anti-CD40L: BG9566, IDEC-131
12.6.1: We suggest that all patients with LN of any class are treated with HYDROXYCHLOROQUINE (maximum daily dose of 6–6.5 mg/kg ideal body weight), unless they have a specific contraindication to this drug. (2C)
12.7.1: We recommend that patients with class VI LN be treated with CORTICOSTEROIDS and IMMUNOSUPPRESSIVES only as dictated by the extra-renal manifestations of systemic lupus. (2D)
Table 29 | Criteria for the diagnosis and classification of relapses of LN

<table>
<thead>
<tr>
<th>Mild kidney relapse</th>
<th>Moderate kidney relapse</th>
<th>Severe kidney relapse</th>
</tr>
</thead>
</table>
| Increase in glomerular hematuria from <5 to >15 RBC/hpf, with ≥2 acanthocytes/hpf | If baseline creatinine is:  
<2.0 mg/dl [<177 μmol/l], an increase of 0.20–1.0 mg/dl [17.7–88.4 μmol/l]  
≥2.0 mg/dl [≥177 μmol/l], an increase of 0.40–1.5 mg/dl [35.4–132.6 μmol/l] | If baseline creatinine is:  
<2 mg/dl [<177 μmol/l], an increase of >1.0 mg/dl [≥88.4 μmol/l]  
≥2 mg/dl [≥177 μmol/l], an increase of >1.5 mg/dl [≥132.6 μmol/l] |
| and/or recurrence of ≥1 RBC cast, WBC cast (no infection), or both | and/or  
If baseline uPCR is:  
<500 mg/g [<50 mg/mmol], an increase to ≥1000 mg/g [≥100 mg/mmol]  
500–1000 mg/g [50–100 mg/mmol], an increase to ≥2000 mg/g [≥200 mg/mmol], but less than absolute increase of <5000 mg/g [<500 mg/mmol]  
>1000 mg/g [≥100 mg/mmol], an increase of ≥2-fold with absolute uPCR <5000 mg/g [<500 mg/mmol] | and/or  
an absolute increase of uPCR >5000 mg/g [>500 mg/mmol] |

hpf, high-power field; LN, lupus nephritis; RBC, red blood cell; uPCR, urine protein:creatinine ratio; WBC, white blood cell.

12.8.1: We suggest that a relapse of LN after complete or partial remission be treated with the initial therapy followed by the maintenance therapy that was effective in inducing the original remission. (2B)
12.8.1.1: If resuming the original therapy would put the patient at risk for excessive lifetime cyclophosphamide exposure, then we suggest a non–cyclophosphamide-based initial regimen be used. (2B)
12.8.2: Consider a REPEAT KIDNEY BIOPSY during relapse if there is suspicion that the histologic class of LN has changed, or there is uncertainty whether a rising SCr and/or worsening proteinuria represents disease activity or chronicity. (NOT GRADED)
12.9.1: In patients with worsening SCr and/or proteinuria after completing one of the initial treatment regimens, consider performing a repeat kidney biopsy to distinguish active LN from scarring. (NOT GRADED)

12.9.2: Treat patients with worsening SCr and/or proteinuria who continue to have active LN on biopsy with one of the alternative initial treatment regimens. (NOT GRADED)
12.9.3: We suggest that **NON-RESPONDERS** who have failed more than one of the recommended initial regimens may be considered for treatment with **RITUXIMAB, IV IMMUNOGLOBULIN**, or CNIs. (2D)
SYSTEMIC LUPUS and THROMBOTIC MICROANGIOPATHY

12.10.1: We suggest that the ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS) involving the kidney in systemic lupus patients, with or without LN, be treated by ANTICOAGULATION (target [INR] 2–3). (2D)

12.10.2: We suggest that patients with systemic lupus and THROMBOTIC THROMBOCYTOPENIC PURPUR (TTP) receive PLASMA EXCHANGE as for patients with TTP without systemic lupus. (2D)
12.11.1: We suggest that women be counseled TO DELAY PREGNANCY until a complete remission of LN has been achieved. (2D)

12.11.2: We recommend that cyclophosphamide, MMF, ACE-I, and ARBs NOT BE USED during pregnancy. (1A)

12.11.3: We suggest that HYDROXYCHLOROQUINE be continued during pregnancy. (2B)
12.11.4: We recommend that LN patients who become pregnant while being treated with MMF be switched to AZATHIOPRINE. (1B)

12.11.5: We recommend that, if LN patients relapse during pregnancy, they receive treatment with CORTICOSTEROIDS and, depending on the severity of the relapse, AZATHIOPRINE. (1B)
12.11.6: If pregnant patients are receiving corticosteroids or azathioprine, we suggest that these drugs not be tapered during pregnancy or for at least 3 months after delivery. (2D)

12.11.7: We suggest administration of low-dose ASPIRIN during pregnancy to decrease the risk of fetal loss. (2C)
• If you would like a copy of my unabridged slide presentation (KDIGO Glomerulonephritis) kindly Email me at nephron0@gmail.com

• Twitter @edgarvlermammd
Thank You