Lupus Nephritis for PMK Resident

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Organ Involvement in the Course of SLE

- Systemic (fatigue, malaise, fever) 95%
- Musculoskeletal 95%
- Cutaneous 80%
- Hematologic 85%
- Neurological 60%
- Cardiopulmonary 60%
- **Kidney 30-50%**
- Gastrointestinal 40%
- Thrombosis 15%
- Ocular 15%
- Vasculitis 5%

Harrison's Principle of Internal Medicine 20th edition

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

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SPECIAL ARTICLE

2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus

Martin Aringer,[1] Karen Costenbader,[2] David Daikh,[3] Ralph Brinks,[4] Marta Mosca,[5] Rosalind Ramsey-Goldman,[6]

Entry criterion Anti-nuclear antibodies at a titre of ≥1:80* on HEp-2 cells or an equivalent positive test
Additive criteria Do not count a criterion if an explanation other than systemic lupus erythematosus is more likely Occurrence of a criterion on at least one occasion is sufficient At least one clinical criterion is required Criteria need not occur simultaneously Within each domain, only the highest weighted criterion is counted toward the total score

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Cutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis	
Either synovitis characterised by swelling or effusion in ≥two joints or tenderness in ≥two joints plus ≥30 min of morning stiffness	6
Neurological	
Delirium	2
Psychosis	3
Seizure	5
Serositis	
Pleural or pericardial effusion	5
Acute pericarditis	6
Haematological	
Leucopenia	3
Thrombocytopenia	4
Autoimmune haemolysis	4
Renal	
Proteinuria >0·5 g/24 h	4
Renal biopsy class II or V lupus nephritis	8
Renal biopsy class III or IV lupus nephritis	10

Immunological domains and criteria	Weight
Anti-phospholipid antibodies	
Anti-cardiolipin antibodies or anti-β2GP1 antibodies or lupus anticoagulant	2
Complement proteins	
Low C3 or low C4	3
Low C3 and low C4	4
Highly specific antibodies	
Anti-dsDNA antibody†	6
Anti-Smith antibody	6

Classify as SLE with a score of 10 or more if entry criterion fulfilled

Aringer M, et al. Arthritis Rheumatol. 2019; 71(9):1400-1412.

New classification criteria compared with the ACR 1997 and SLICC 2012 classification criteria in the derivation and the validation cohorts

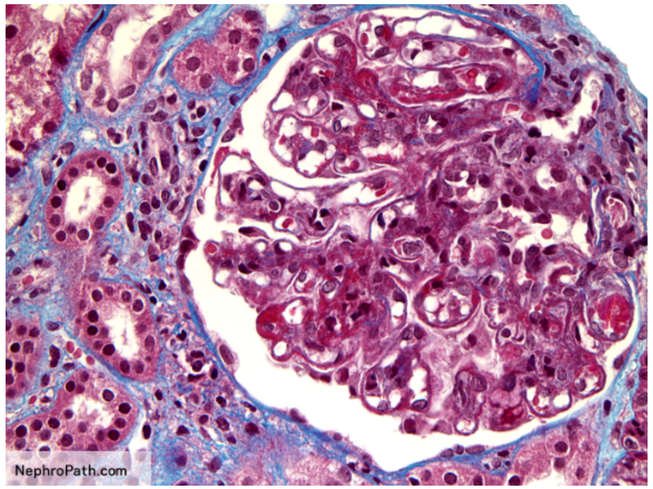
	ACR 1997 criteria	SLICC 2012 criteria	EULAR/ACR 2019 criteria
Derivation			
Sensitivity (95% CI)	0.85 (0.81–0.88)	0.97 (0.95–0.98)	0.98 (0.97–0.99)
Specificity (95% CI)	0.95 (0.93–0.97)	0.90 (0.87–0.92)	0.96 (0.95–0.98)
Combined (95% CI)	1.80 (1.76–1.83)	1.87 (1.84–1.90)	1.94 (1.92–1.96)
Validation			
Sensitivity (95% CI)	0.83 (0.80–0.85)	0.97 (0.95–0.98)	0.96 (0.95–0.98)
Specificity (95% CI)	0.93 (0.91–0.95)	0.84 (0.80–0.87)	0.93 (0.91–0.95)
Combined (95% CI)	1.76 (1.73–1.80)	1.80 (1.77–1.84)	1.90 (1.87–1.92)

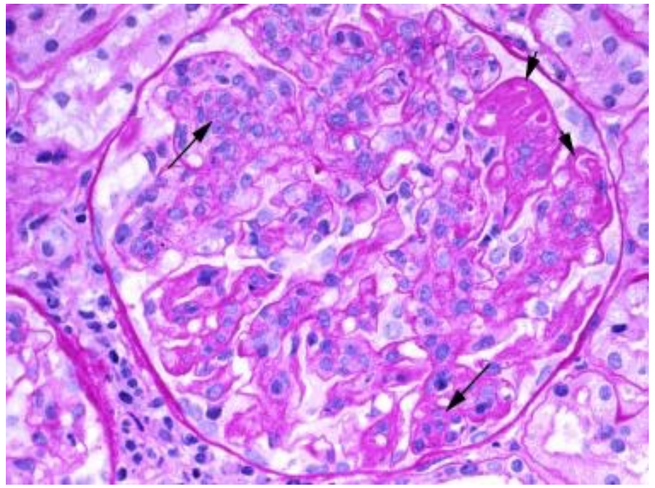
* ACR = American College of Rheumatology; SLICC = Systemic Lupus International Collaborating Clinics; EULAR = European League Against Rheumatism; 95% CI = 95% confidence interval.

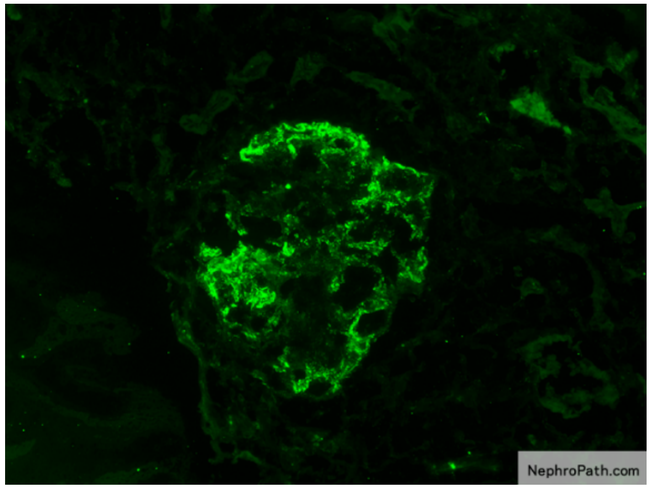
Aringer M, et al. Arthritis Rheumatol. 2019; 71(9):1400-1412.

2019 ACR criteria for lupus nephritis

- Proteinuria >0.5 g/24 hours by 24-hour urine or equivalent spot urine protein-to- creatinine ratio
- Class II, III, IV or V lupus nephritis on renal biopsy according to ISN/RPS 2003 classification







Aringer M, et al. Arthritis Rheumatol. 2019; 71(9):1400-1412.

Systemic lupus erythematosus (SLE)

PREDISPOSING FACTORS

GENES

High Hazard Ratios (≥6);

Deficiencies of C1q,C2,C4 (rare)
TREX1 mutations affecting DNA degradation (rare)

Affecting Ag presentation or persistence, e.g., phagocytosis of immune complexes

HLA-DRB1 (*1501,*0301), DR3, DQA2
CR2, FCGR2A/B

Enhance Innate Immunity, including production of IFNs

TNFAIP3, IRF5/TNPO3, IRF7/PHRF1, ITGAM, ICAMs

Alter Adaptive Immunity B and/or T Cell Signaling

BANK1, STAT4, MSHS, IZKF3, TCF7

GENES FOR LUPUS NEPHRITIS

HLA-DR3, STAT4, APOL1 (African Americans), FCGR3A, ITGAM, IRF5, IRF7, TNFSF4 (Ox40L), DNAse1

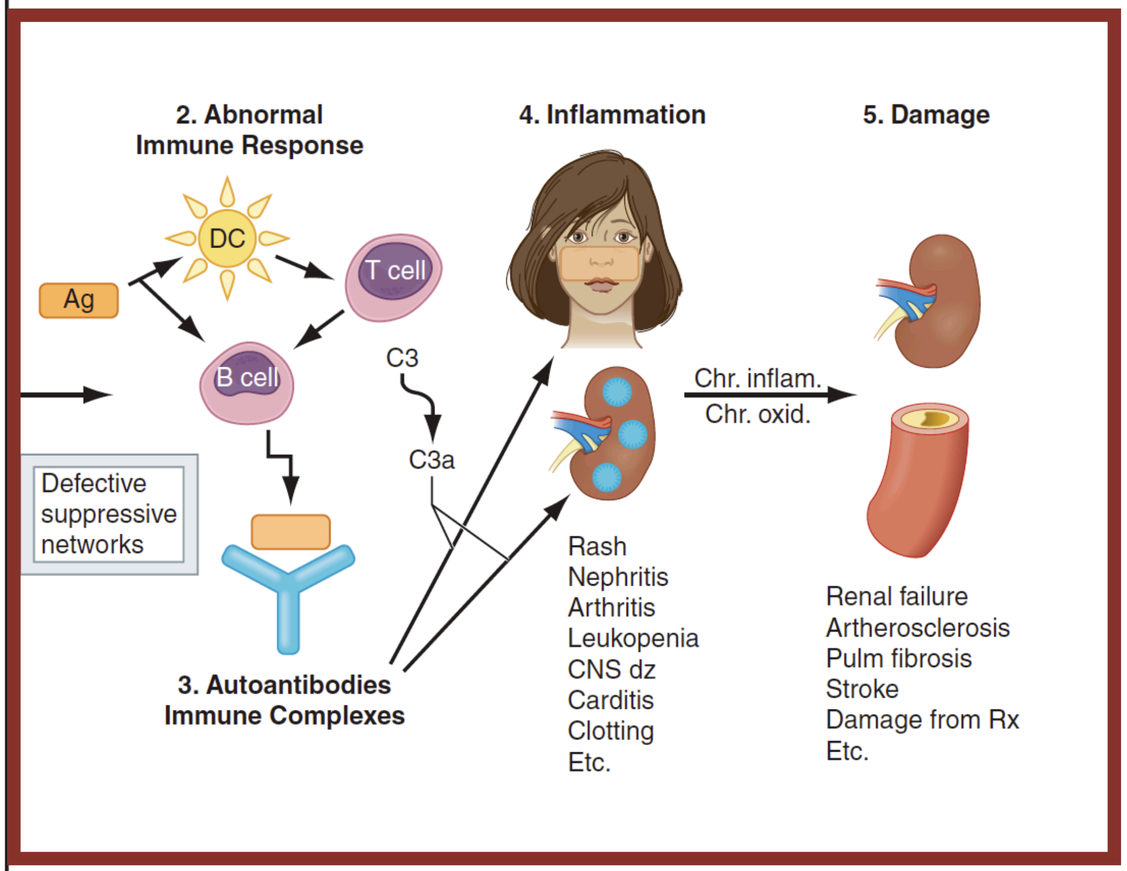
ENVIRONMENT/MICROENVIRONMENT

Ultraviolet Light, Smoking, Crystalline Silica, ?EBV infection
Femaleness

EPIGENETICS

Hypomethylation of DNA: In CD4+T, B and monocytes
Some affect IFN production
Histone modifications: Some increase expression of predisposing genes and/or IFN production
MicroRNA affecting gene expression

Mir-21, -146A, -155, -569, -30A, Let-7a



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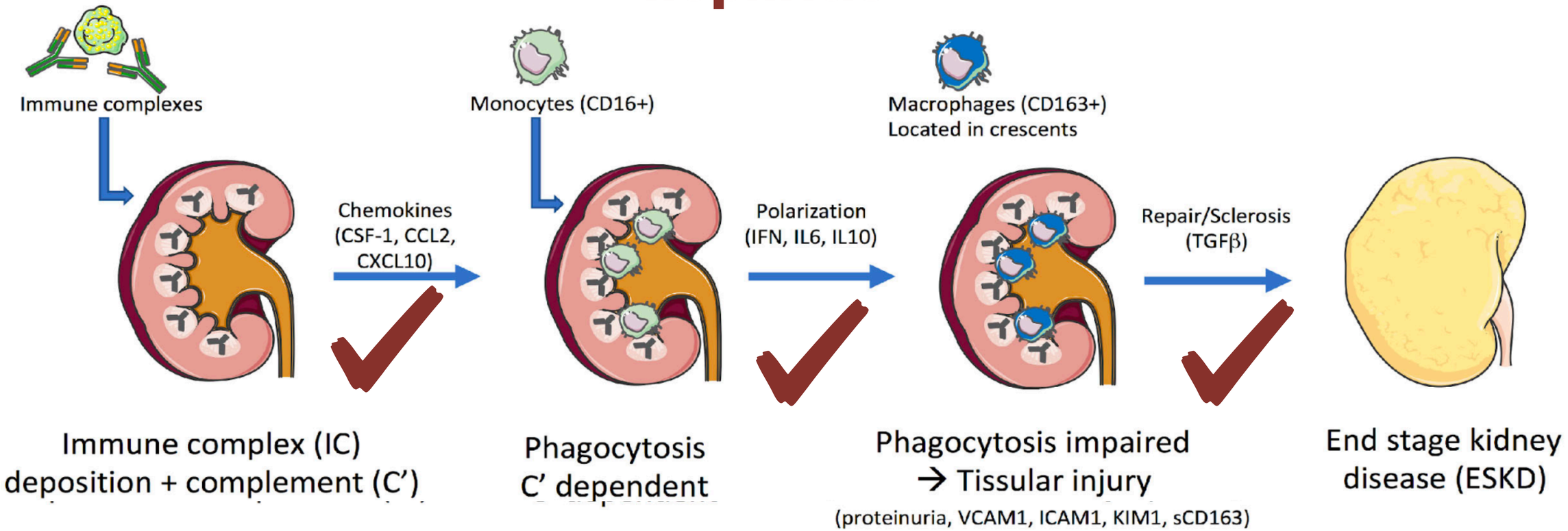
Pathogenic mechanisms and related biomarkers in lupus nephritis



Anti-dsDNA/chromatin Abs (anti-Sm Abs, anti-PL Abs)

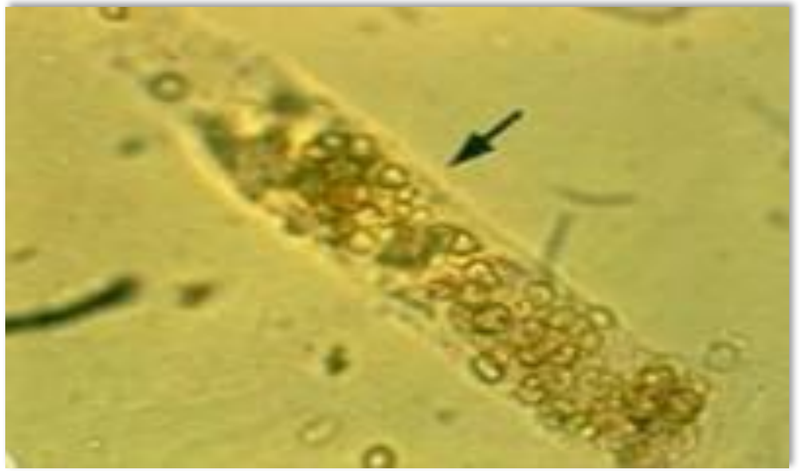
Complement consumption +/- anti-C1q Abs (amplification)

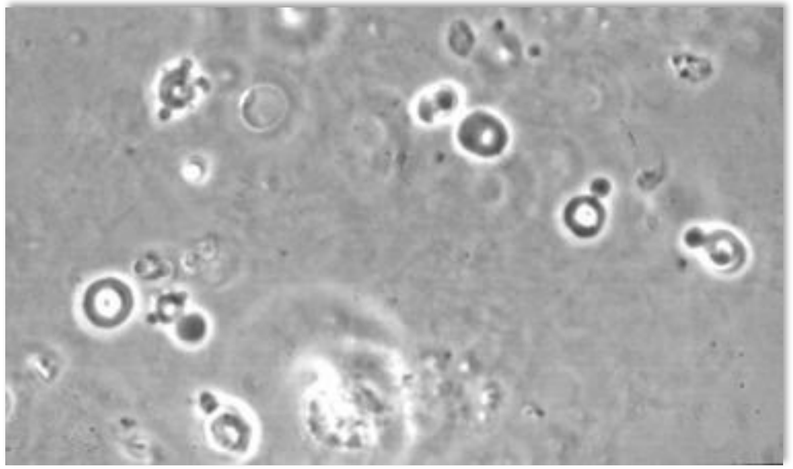
Proteinuria / urinary biomarkers

Renaudineau, Y, et al. Int. J. Mol. Sci. 2023, 24, 14526.

Glomerular syndrome

- Proteinuria (100%)
- Nephrotic syndrome (45-65%)
- Microhematuria (80%)
- Macrohematuria (1-2%)
- Impaired renal function (40-80%)
- RPGN (30%)
- Hypertension (15-50%)





Renal Manifestation

- Vascular syndrome
  - Renal vein or artery thrombosis
- Tubular abnormalities (60-80%)
  - Renal tubular acidosis (RTA)
  - Hyperkalemia (15%)

Investigation for active lupus nephritis

- Systemic symptoms and signs
- Initial laboratory:
  - CBC, BUN, serum creatinine
  - Urinalysis: active sediment and proteinuria
  - Serum albumin, cholesterol
- Complements: CH50, C3, C4
- Anti-ds DNA and anti-C1q antibody titer
- Kidney biopsy

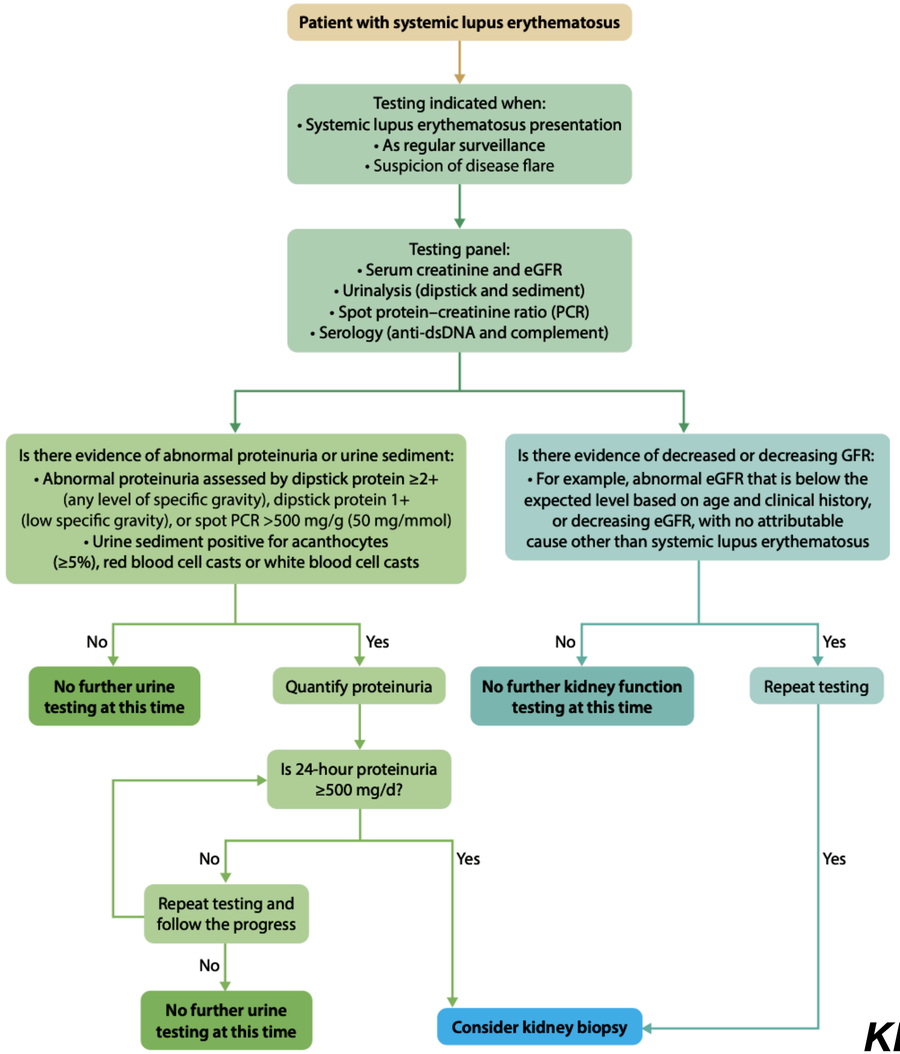
Kidney biopsy

- First attack
  - Verify diagnosis
  - Assessment of activity & severity
  - Assessment of chronicity
- Repeat attack
  - Distinguish active and chronic forms

KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF LUPUS NEPHRITIS

KDIGO The management of lupus nephritis . Kidney Int. 2024: 105 (Suppl 1S), S1–S69.

Diagnosis of kidney involvement in SLE



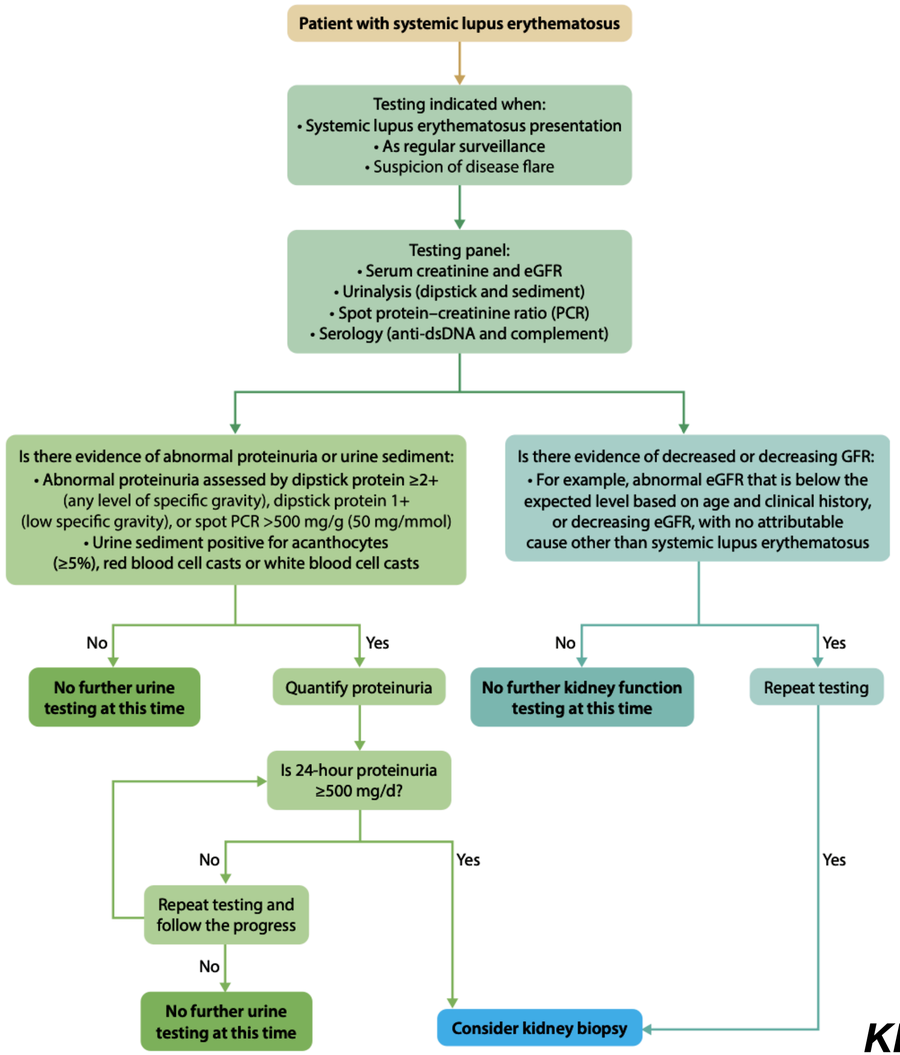
Patient with systemic lupus erythematosus

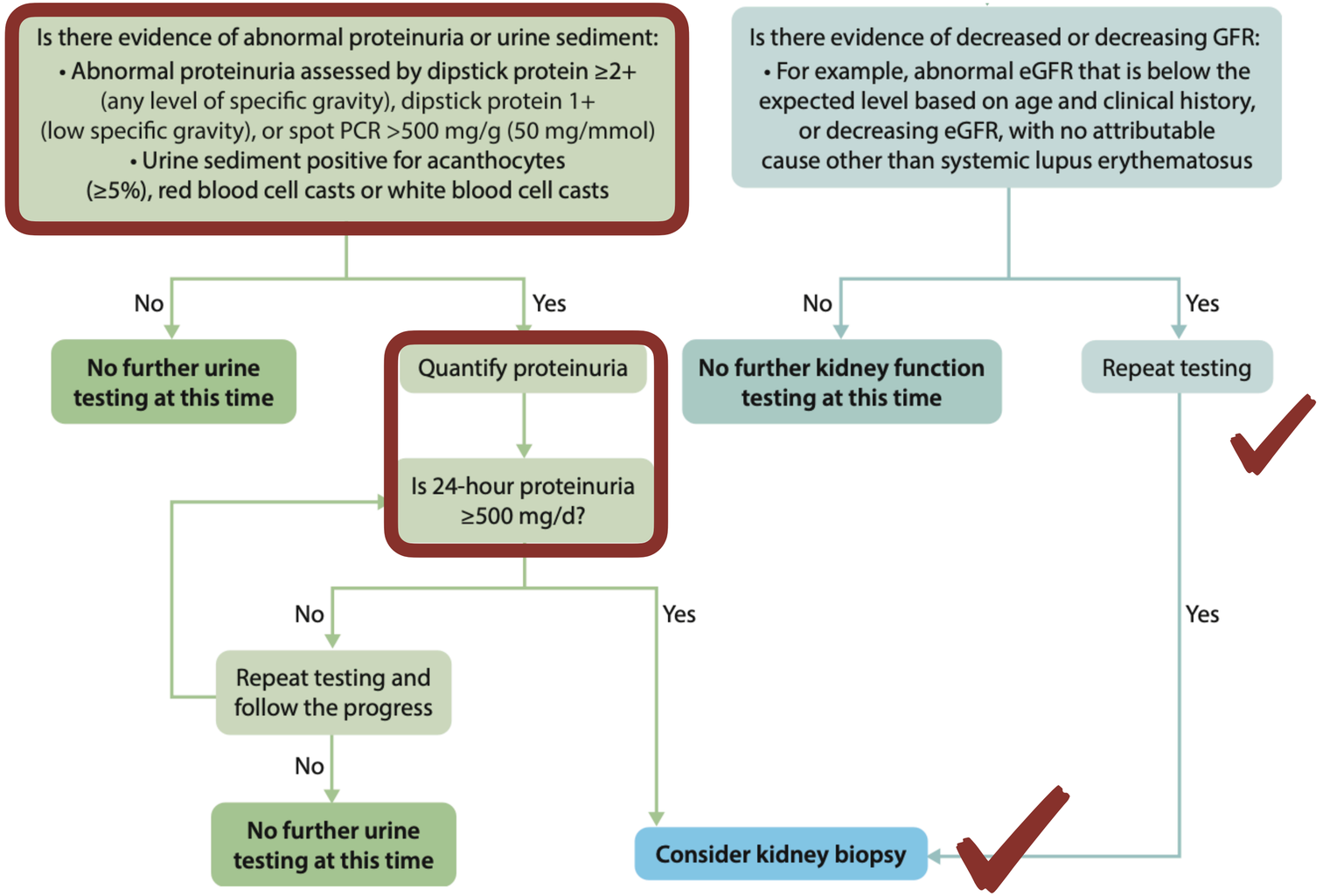
Testing indicated when:
• Systemic lupus erythematosus presentation
• As regular surveillance
• Suspicion of disease flare

Testing panel:
• Serum creatinine and eGFR
• Urinalysis (dipstick and sediment)
• Spot protein–creatinine ratio (PCR)
• Serology (anti-dsDNA and complement)

KDIGO The management of lupus nephritis . Kidney Int. 2024: 105 (Suppl 1S), S1–S69.

Diagnosis of kidney involvement in SLE





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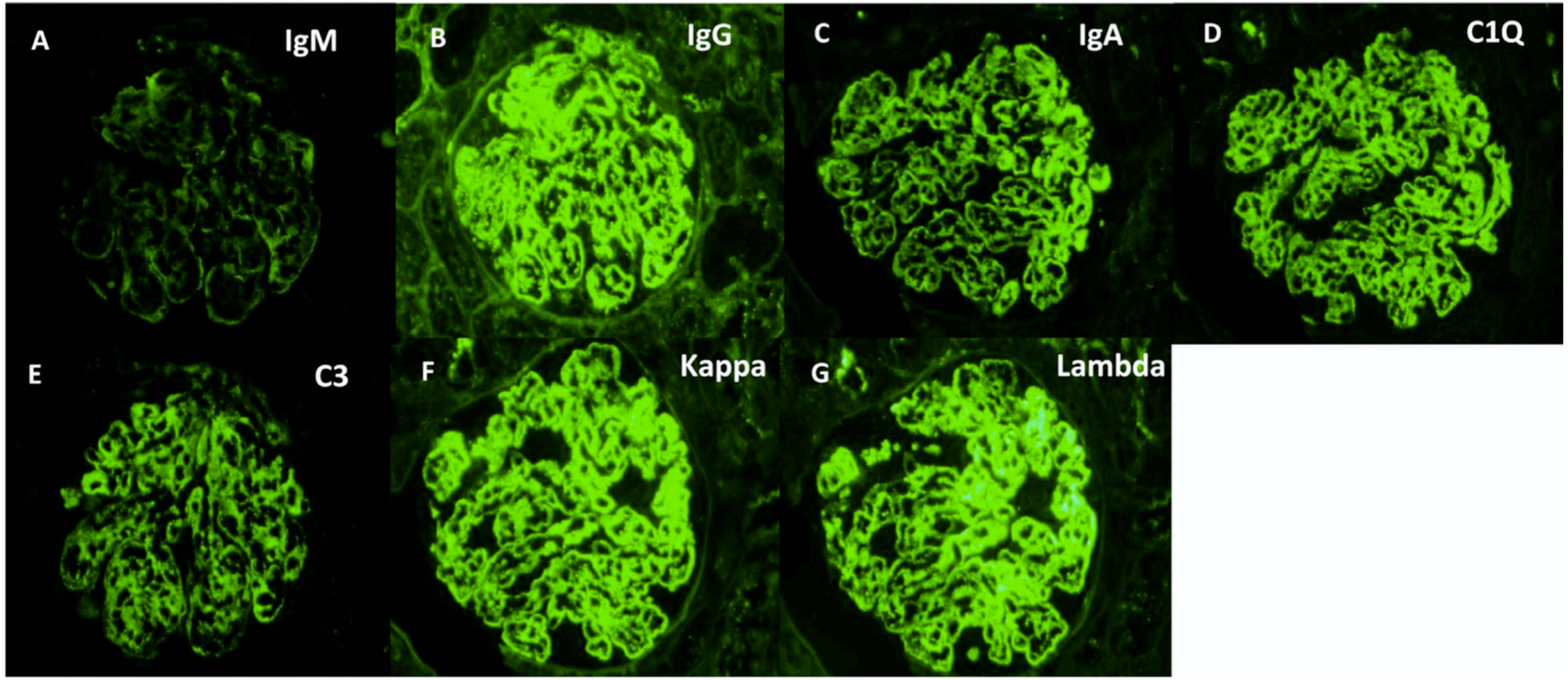
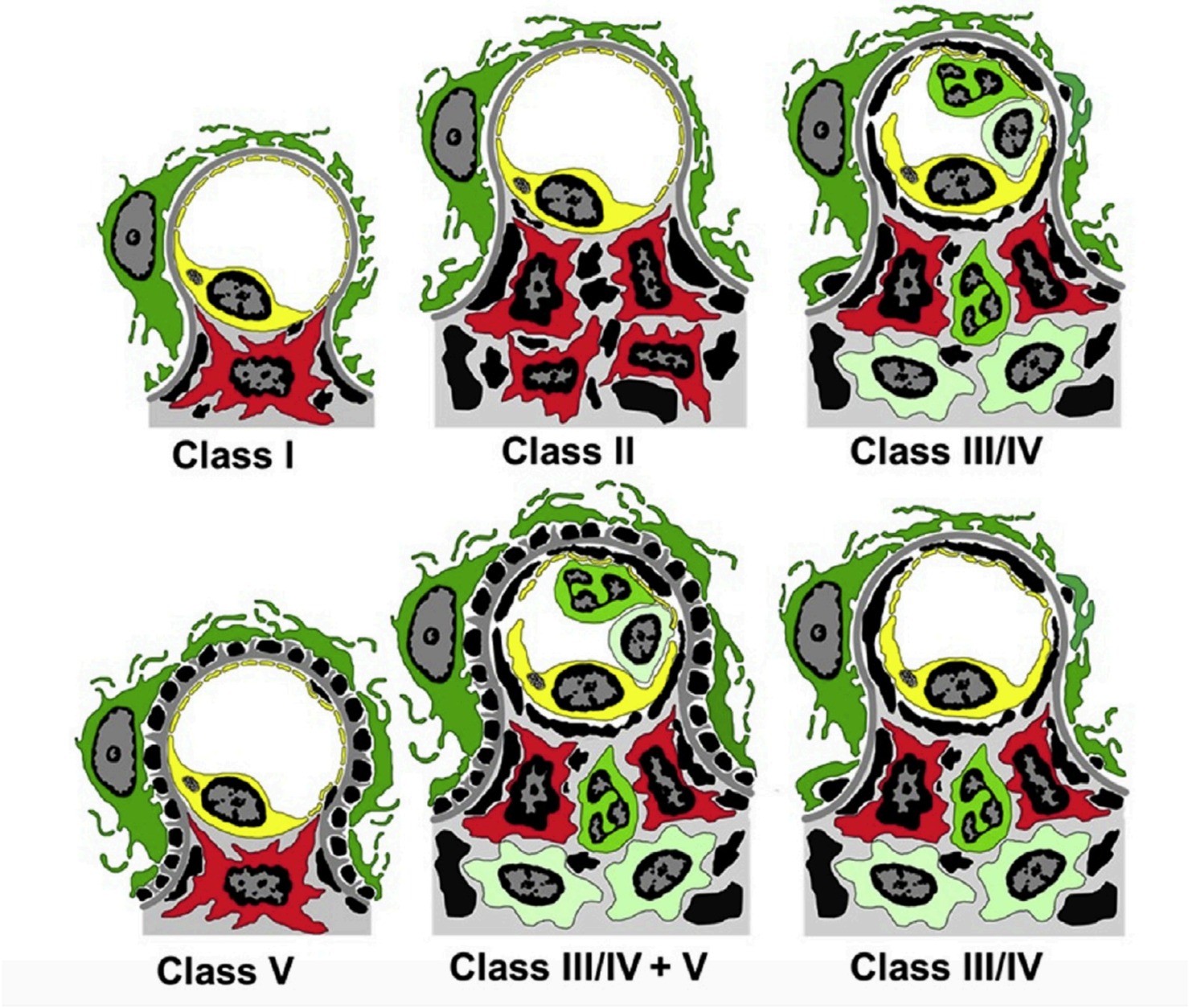
Immunofluorescence (IF) staining in lupus nephritis



Full house staining

Minimum 10 glomeruli , Diagnosis of LN dominant IgG, C3 and C1q deposits are absolutely required.

Parikh SV, et al. Am J Kidney Dis. 2020; DOI: 10.1053/j.ajkd.2019.10.017



Bajema IM, et al Kidney Int 2018; 93(4): 789-96.

Lupus nephritis biopsy ISN/RPS 2013 Classification

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis[a]
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis[b]
Class V	Membranous lupus nephritis[c]
Class VI	Advanced sclerosing lupus nephritis

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

[a]Indicate the proportion of glomeruli with active and with sclerotic lesions.

[b]Indicate the proportion of glomeruli with fibrinoid necrosis and cellular crescents.

[c]Class V may occur in combination with class III or IV, in which case both will be diagnosed.

% active/sclerotic glomeruli

Fibrnoid necrosis/cellular crescents

Weening JJ, et al. Kidney Int, 2004: 65: 521–530.

CLINICAL MANIFESTRATION RELATED RENAL PATHOLOGICAL CLASSIFICATION

Class	Urine sediment active	Proteinuria	Nephrotic syndrome	Renal insuff	5-year renal survival
I	0	0	0	0	100%
II	<25%	25-50%	0	<15%	>90%
III	50%	67%	25-33%	10-25%	70-80%
IV	75%	>95%	50%	>50%	60-80%
V	30%	>95%	90%	10%	80-90%

Satirapoj B, Essentials of Glomerular Disease. 2018

General management of patients with lupus nephritis

- **We recommend that patients with SLE, including those with lupus nephritis (LN), be treated with hydroxychloroquine or an equivalent antimalarial unless contraindicated (1C).**

- **This recommendation places a relatively higher value on the various benefits associated with hydroxychloroquine use reported in observational studies and on the generally favorable safety profile of hydroxychloroquine treatment**
- **The recommended starting dose of hydroxychloroquine is around 5 mg/kg/d (≤2.3 mg/kg/d for chloroquine)**
- **In patients with eGFR <30 ml/min per 1.73 m^2, the dose of hydroxychloroquine should be reduced by ≥25%**

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Measures to minimize the risk of complications related to lupus nephritis or its treatment

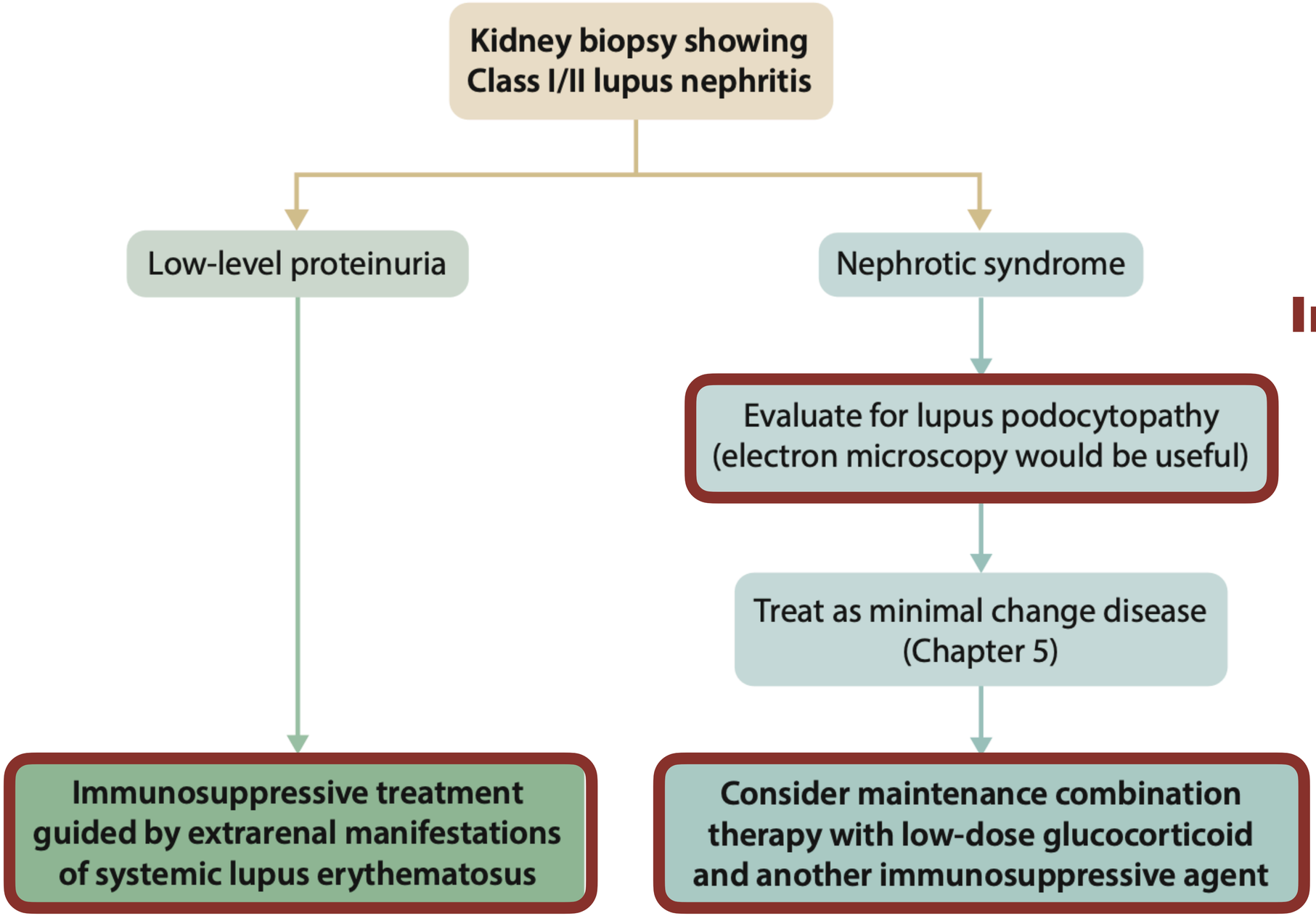
1	**Cardiovascular risk**	• Lifestyle modifications – smoking cessation, body weight optimization, exercise • Dyslipidemia management • Low-dose aspirin during pregnancy • Blood pressure control
2	**Proteinuria and CKD progression (refer to Chapter 1)**	• Avoid high-sodium diet • Optimize blood pressure • Renoprotective medications, such as RAAS blockade, SGLT2 inhibitor, etc., in stable patients without AKI • Avoid nephrotoxic insult • Prevent AKI
3	**Infection risk**	• Assess medical history of herpes zoster and tuberculosis • Screening for HBV, HCV, HIV, and HBV vaccination • *Pneumocystis jirovecii* prophylaxis (issue of potential adverse drug reaction discussed below) • Influenza and pneumococcal vaccination • Individualized consideration for recombinant zoster vaccine • Individualized consideration for other infectious organisms as dictated by public health concerns at the time of treatment

KDIGO The management of lupus nephritis . Kidney Int. 2024: 105 (Suppl 1S), S1–S69.

Measures to minimize the risk of complications related to lupus nephritis or its treatment

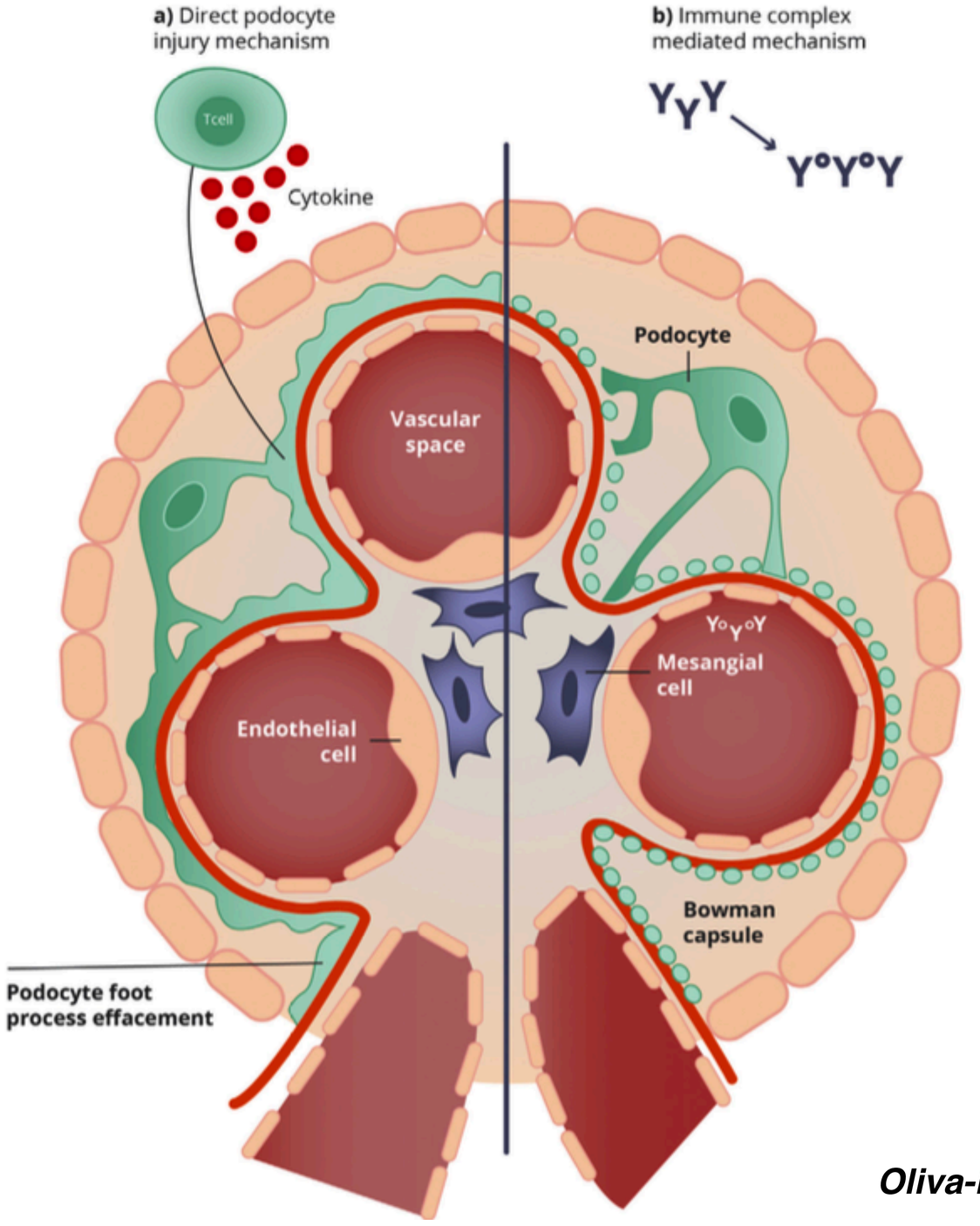
4	**Bone injury**	• Bone mineral density and fracture risk assessment • Calcium and vitamin D supplementation • Bisphosphonates when appropriate
5	**Ultraviolet light exposure**	• Broad-spectrum sunscreen • Limit ultraviolet light exposure
6	**Premature ovarian failure**	• Gonadotropin-releasing hormone agonists (i.e. leuprolide) • Sperm/oocyte cryopreservation
7	**Unplanned pregnancy**	• Individual evaluation and counselling for contraception type (preference, thrombosis risk, age)
8	**Cancer**	• Evaluate individual risk factors for malignancies • Age-specific malignancy screening • Minimize lifetime cyclophosphamide exposure to <36 g

KDIGO The management of lupus nephritis . Kidney Int. 2024: 105 (Suppl 1S), S1–S69.



Immunosuppressive treatment for patients with Class I or Class II lupus nephritis

KDIGO The management of lupus nephritis . Kidney Int. 2024: 105 (Suppl 1S), S1–S69.

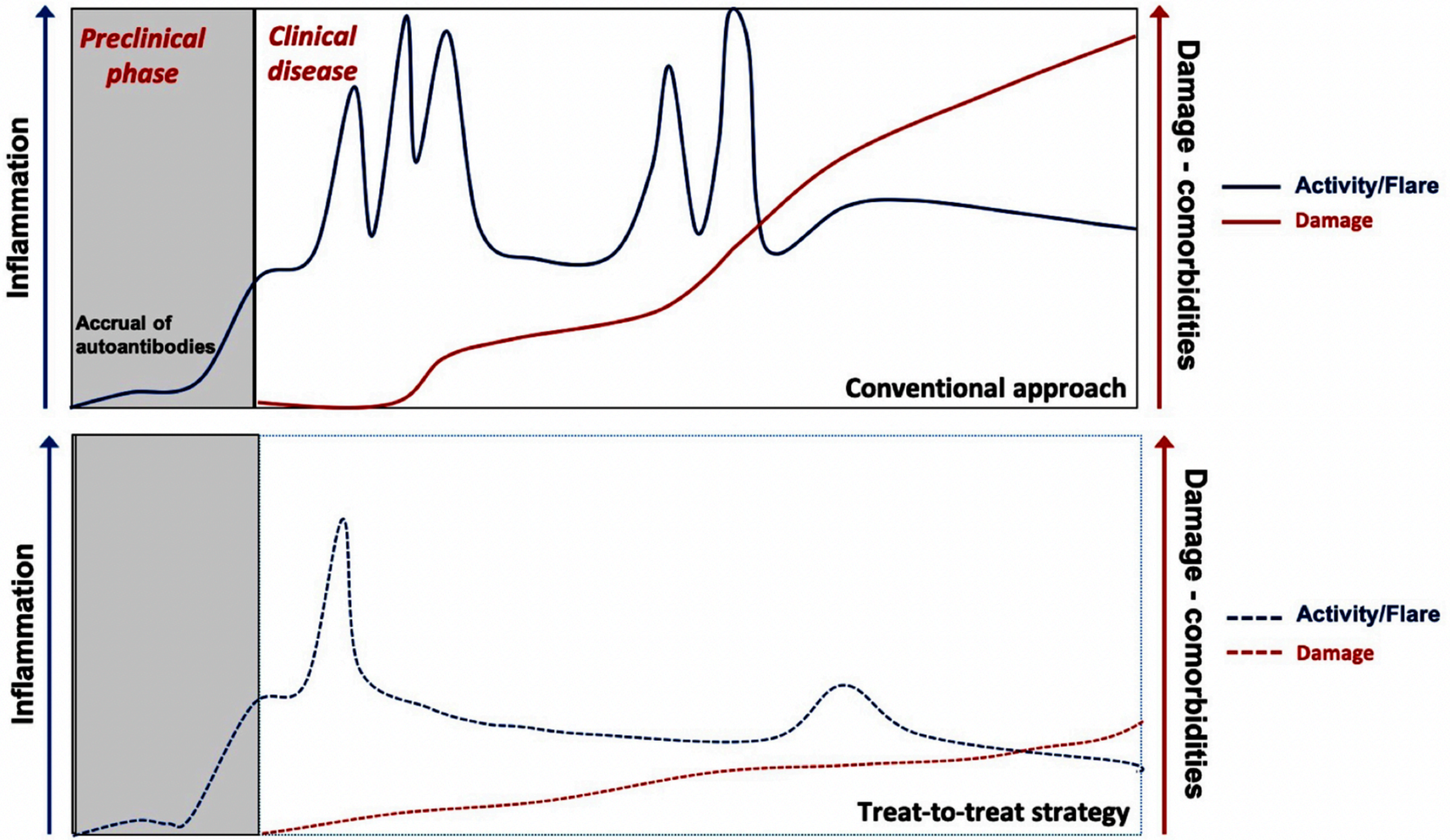


Lupus podocytopathy

Foot process effacement explained by a direct injury associated with T cell dysfunction, cytokines, or lymphokines that damage the podocyte.

Oliva-Damaso N, et al. Adv Chronic Kidney Dis. 2019; 26(5):369-375.

Natural history of SLE and the potential impact of a treat-to-target strategy



Fanouriakis A, et al. Ann Rheum Dis. 2021; 80(1):14-25.

Treatment of Proliferative Lupus Nephritis (Class III-IV)

- Induction phase
  - Renal remission at presentation and during follow up
- Maintenance phase
  - Prevent relapse and minimizing the side effects of treatment

Oral corticosteroids for induction

- Need for high doses (1.5-2.0 MKD of prednisolone)
- Little efficacy in severe case
- Frequent relapses of activity
- High toxicity

Flanc RS; et al. Cochrane Database Syst Rev 2004;(1):CD002922.

NIH study

Therapy	Pts	10 yrs Renal survival
Prednisolone	30	40%
Azathioprine	20	72%
Cyclophosphamide	18	80%
AZA+CYC	23	88%
IV CYC	20	91%

Prednisolone vs IV CYC p = 0.014

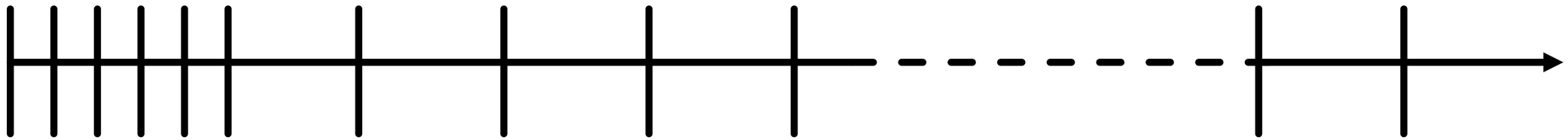
Austin H, et al. NEJM 1984; 314: 614

Regimens for initial therapy in class III/class IV LN

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

KDIGO. Kidney International Supplements (2012) 2, 143–153

IV Pulse Cyclophosphamide: NIH regimen



Induction IVCY q 1 mo x 6

Maintenance IVCY q 3 mo x 6

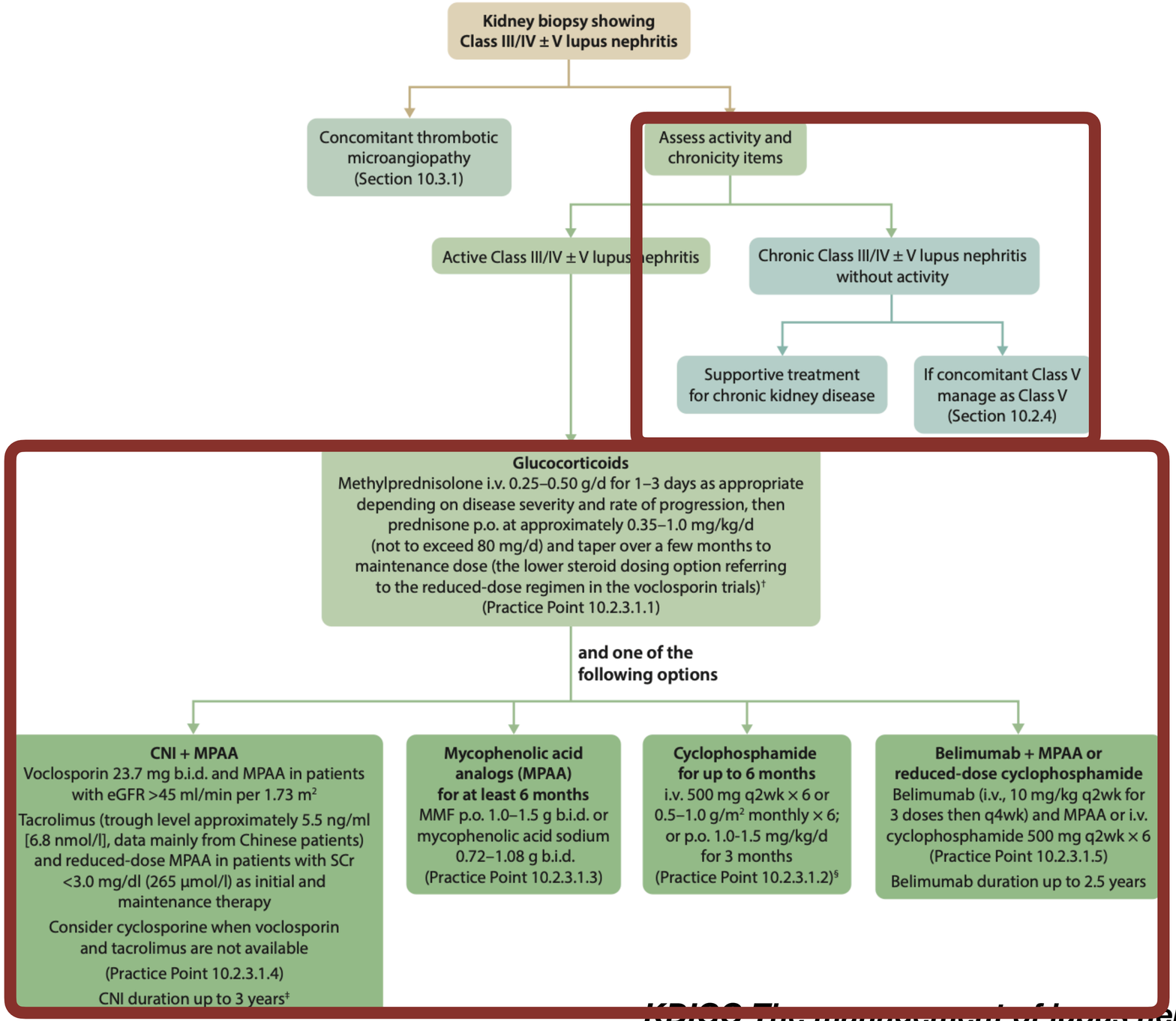
- **Initial IVCY 0.5-1.0 g/m^2 (0.5 g/m^2 if GFR 1/3 normal)**
- **Adjust subsequent IVCY to maximum dose of 1 g/m^2 unless WBC nadir at 10-14 days after ICVY falls below 1,500/mm^3**
- **Prednisolone 0.5-1 mg/kg/day for 4-8 weeks, which is subsequently tapered to low dose maintenance therapy**

Boumpas DT, Austin HA, et al. Lancet 1992: 340.

Cochrane Renal Group: 50 RCTs involving 2846 participants

- MMF was as effective as IVCY in complete remission of proteinuria (RR 1.16, 95% CI 0.85 to 1.58)
  - No differences in mortality (RR 1.02, 95% CI 0.52 to 1.98)
  - No differences in major infection (RR 1.11, 95% CI 0.74 to 1.68) were observed.
- MMF: A significant reduction
  - Ovarian failure (RR 0.15, 95% CI 0.03 to 0.80)
  - Alopecia (RR 0.22, 95% CI 0.06 to 0.86)

Cochrane Database Syst Rev. 2012 Dec 12;12:CD002922.
Am J Kidney Dis. 2013 Jan;61(1):74-87.



Recommended approach for initial therapy of active Class III/IV lupus nephritis

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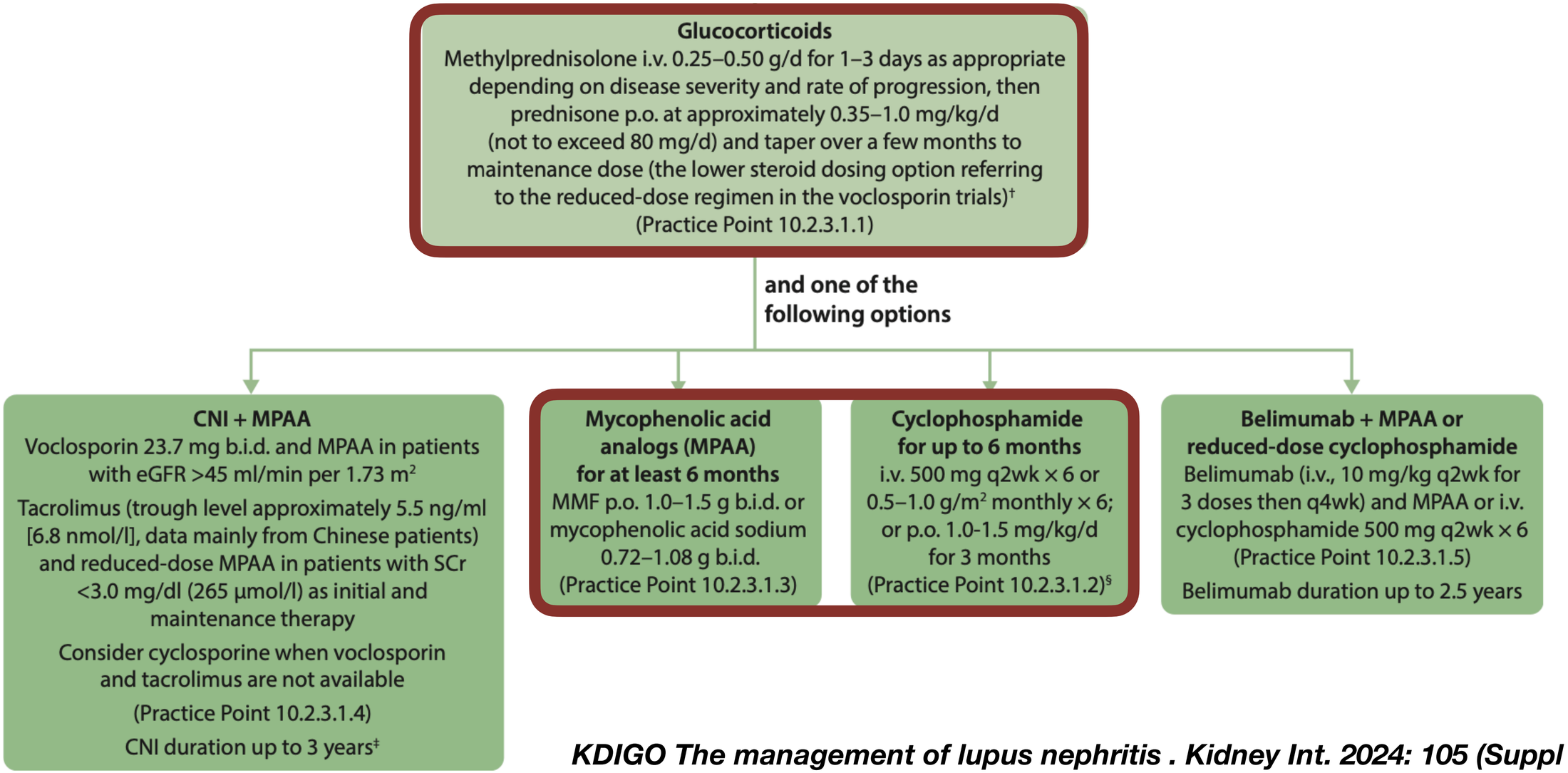
Recommended approach for initial therapy of active Class III/IV lupus nephritis



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Cyclophosphamide dosing regimens

	High-dose intravenous cyclophosphamide (NIH regimen)	Low-dose intravenous cyclophosphamide (Euro-Lupus regimen)	Oral cyclophosphamide
Cyclophosphamide	i.v. 0.5–1 g/m^2 monthly for 6 months	i.v. 500 mg every 2 weeks for 3 months	p.o. 1.0–1.5 mg/kg/d (max 150 mg/d) for 2–6 months
Comments	Efficacy data included patients of different races/ethnicities	Efficacy data mainly in Caucasian patients, with some data from patients of African or Caribbean descent, Hispanic descent, Indian patients, and other Asian countries	Efficacy data included patients of different races/ethnicities

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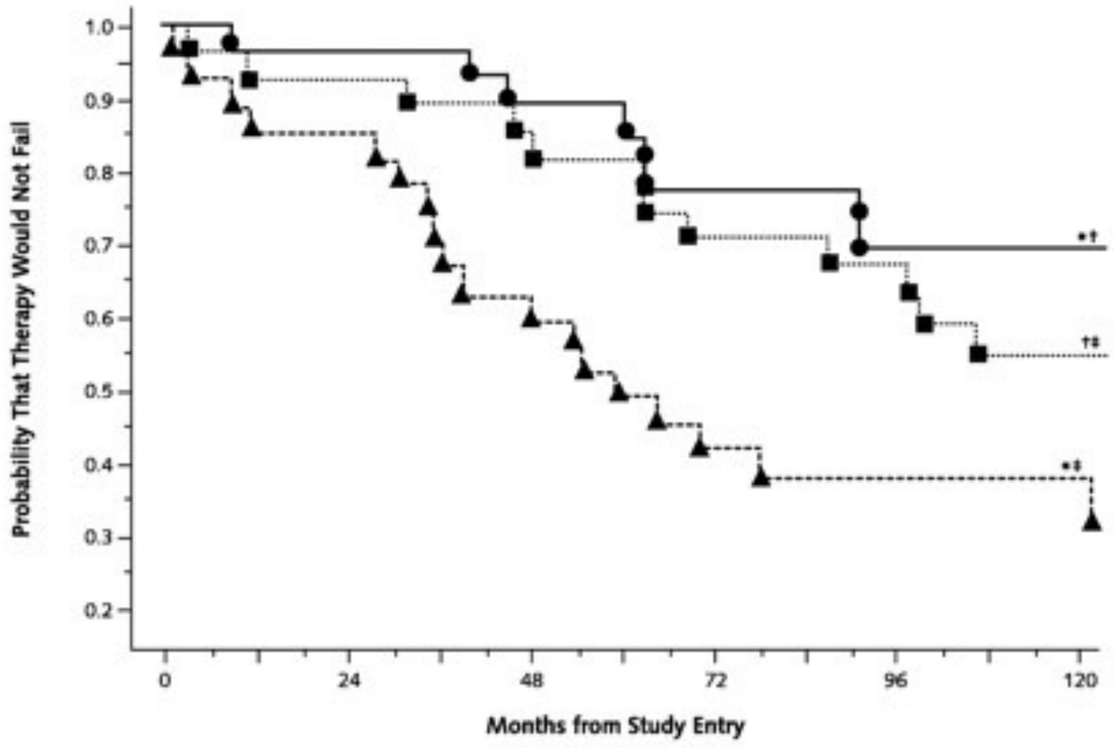
Treatment of Active Lupus Nephritis (Class III-IV)

Practice Point

- IV cyclophosphamide should be used as the initial therapy for active Class III and Class IV LN in patients who may have difficulty adhering to an oral regimen
  - Total lifetime exposure
    - The risk of future hematologic malignancy is related to total lifetime exposure (>36 g), as is myelofibrosis (>80 g)
    - Total lifetime exposure plus age constitutes a significant risk factor for premature ovarian failure (>7.5–15 g/m^2 for young to older pediatric patients, respectively; 300 mg/kg for adults)
- EULAR: In patients at high-risk for renal failure (defined as reduced GFR, histological presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation), high-dose IV cyclophosphamide in combination with pulse IV methylprednisolone, can be considered.

EULAR recommendations for the management of SLE: 2023 update. Ann Rheum Dis. 2023: ard-2023-224762.
KDIGO The management of lupus nephritis . Kidney Int. 2024: 105 (Suppl 1S), S1–S69.

Controlled Trial in Lupus Nephritis: IVCY vs IVMP vs Combination



Patients at Risk

Treatment											
Cyclophosphamide											
Cyclophosphamide pl											
methylprednisolone	28	27	27	26	23	23	20	20	17	15	12
Methylprednisolone	27	23	23	19	17	13	11	10	10	8	6

Combination

IVCY

IVMP

“ Adding pulse methylprednisolone during the initial phase may be advantage for pt with severe proliferative LN ”

Illei GG, et al. Ann Intern Med 2001; 135: 248-57.

Cochrane Library

Cochrane Database of Systematic Reviews

Immunosuppressive treatment for proliferative lupus nephritis (Review)

Tunnicliffe DJ, Palmer SC, Henderson L, Masson P, Craig JC, Tong A, Singh-Grewal D, Flanc RS, Roberts MA, Webster AC, Strippoli GFM

- **67 studies (4791 participants; median 12 months duration)**
- **Induction Rx: MMF vs IV cyclophosphamide**

Cochrane Database Syst Rev. 2018 Jun 29;6:CD002922. doi: 10.1002/14651858.CD002922.pub4.

Induction Rx: MMF vs IVCY

- No differences in complete remission [RR 1.17 (95% CI 0.97 to 1.42)]
- No differences in ESRD [RR 0.,74 (95% CI 0.27 to 1.84)]
- No differences in major infection [RR 1.02 (95% CI 0.67 to 1.54)]

- MMF: Significant reduction in alopecia [RR 0.29. (95%CI 0.19. to 0.46)]
- MMF: Significant increase in diarrhea [RR 2.42. (95%CI 1.64. to 3.58)]

Cochrane Database Syst Rev. 2018 Jun 29;6:CD002922. doi: 10.1002/14651858.CD002922.pub4.

Treatment of Active Lupus Nephritis (Class III-IV)

Practice Point

- An MPAA-based regimen is the preferred initial therapy of proliferative LN for patients at high risk of infertility, such as patients who have a moderate-to-high prior cyclophosphamide exposure

  - MPA pharmacokinetics varies considerably among patients, especially in the context of hypoalbuminemia and impaired kidney function.
  - MPA area under the concentration-versus-time curve of 35–45 mg h/l or a trough level of 3.0–4.5 mg/l may serve to ensure adequate exposure during initial therapy

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Glucocorticoids dosing regimens

	High-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

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Definitions of response commonly used in clinical trials of lupus nephritis

Criteria	Definition
Complete response*	• Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy, but could take more than 12 mo
Primary efficacy renal response	• PCR ≤0.7 g/g (70 mg/mmol) • eGFR that was no worse than 20% below the pre-flare value or ≥60 ml/min per 1.73 m^2 • No use of rescue therapy for treatment failure
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6–12 mo of starting therapy

KDIGO The management of lupus nephritis . Kidney Int. 2024: 105 (Suppl 1S), S1–S69.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 4, 2004 VOL. 350 NO. 10

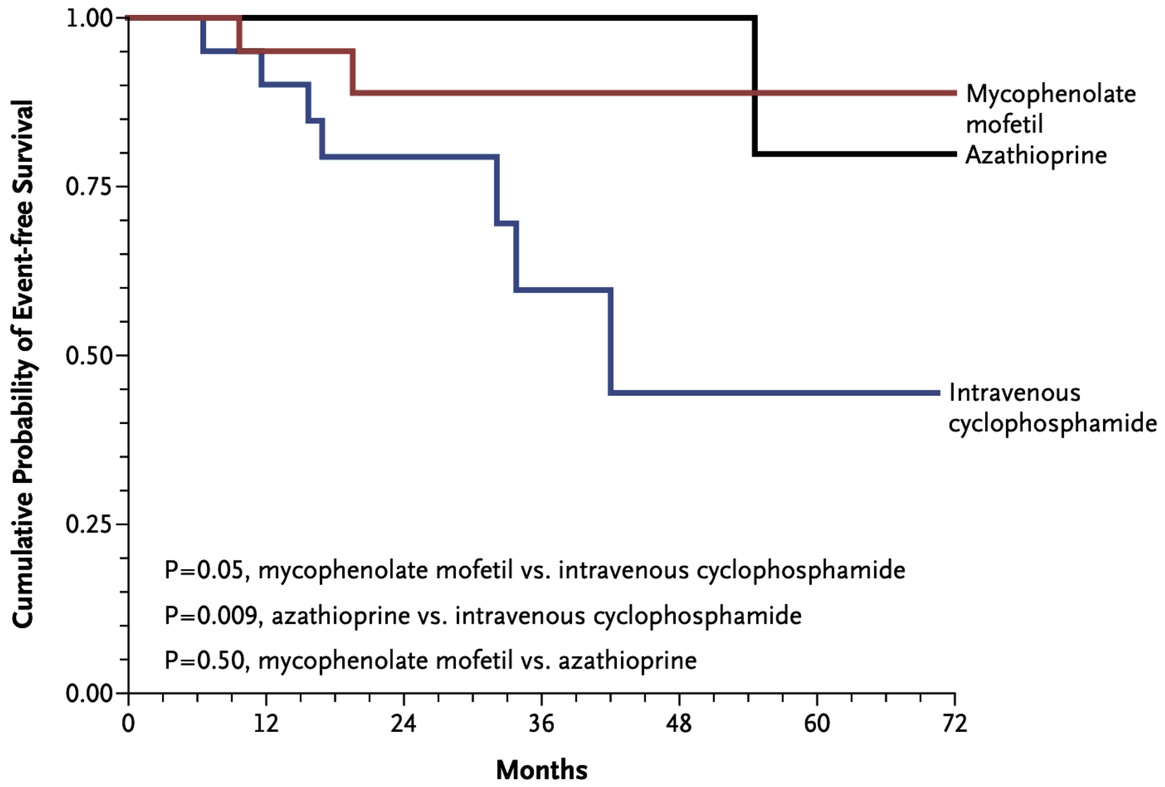
Sequential Therapies for Proliferative Lupus Nephritis

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

Contreras G. et al. NEJM 2004; 350: 971-980.

Maintenance therapy with MMF/AZA/IVCY

The 72-month event-free survival rate for the composite end point of death or chronic renal failure



No. at Risk							
Azathioprine	19	19	15	10	9	4	2
Intravenous cyclophosphamide	20	19	12	6	3	2	1
Mycophenolate mofetil	20	20	14	11	6	2	2

Contreras G. et al. NEJM 2004; 350: 971-980.

Cochrane Library

Cochrane Database of Systematic Reviews

Immunosuppressive treatment for proliferative lupus nephritis (Review)

Tunnicliffe DJ, Palmer SC, Henderson L, Masson P, Craig JC, Tong A, Singh-Grewal D, Flanc RS, Roberts MA, Webster AC, Strippoli GFM

- **Maintenance therapy**
- **Nine studies (767 participants; median 30 months duration (range 6 to 63 months)**

Cochrane Database Syst Rev. 2018 Jun 29;6:CD002922. doi: 10.1002/14651858.CD002922.pub4.

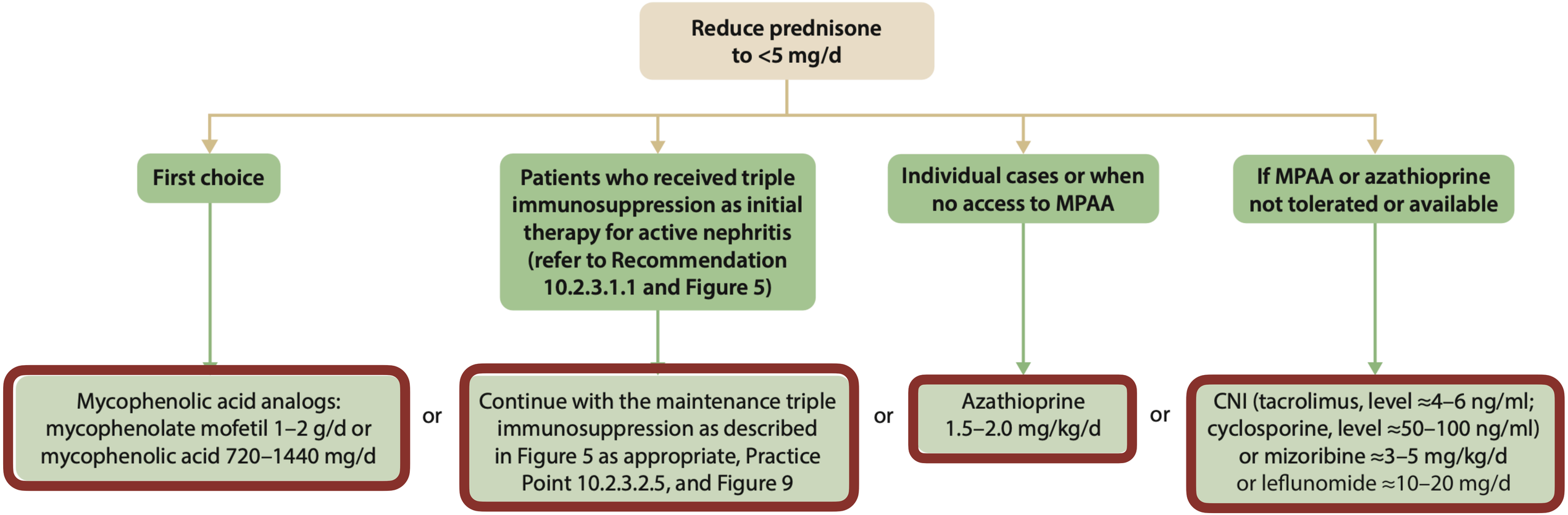
Maintenance therapy: AZA vs MMF

- No differences in death [RR 1.15(95%CI 0.34 to 3.87)]
- No differences in ESRD [RR 1.70 (95% CI 0.52 to 5.54)]
- No differences in major infection [RR 1.08 (95% CI 0.69 to 1.96)]

- AZA: Significant increase in relapse [RR 1.75 (95%CI 1.20 to 2.55)]
- AZA: Significant increase in leukopenia [RR 5.61 (95%CI 1.68. to 18.72)]

Cochrane Database Syst Rev. 2018 Jun 29;6:CD002922. doi: 10.1002/14651858.CD002922.pub4.

Recommended maintenance therapy for Class III and Class IV lupus nephritis



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Recommended maintenance therapy for Class III and Class IV lupus nephritis

Maintenance immuno-suppressive regimens	Low-dose glucocorticoids AND					
	Mycophenolic acid analogs	Azathioprine	Belimumab and mycophenolic acid analogs or azathioprine	CNI and mycophenolic acid analogs	CNI (such as voclosporin, tacrolimus or cyclosporine)	Mizoribine
Comments	Preferred treatment based on high-certainty evidence; lower flare rate than azathioprine maintenance	Low medication cost; safe in pregnancy	Efficacy and safety of belimumab demonstrated in BLISS-LN (104-wk) and open-label extension trials (28-wk) [Practice Point 10.2.3.2.5]	Efficacy and safety of voclosporin demonstrated in AURORA 1 (52-wk) and AURORA 2 continuation trials (2-yr); efficacy and safety of tacrolimus demonstrated in 'Multitarget Therapy' trial in Chinese patients in which tacrolimus and reduced-dose MPAA were given for 24 months [Practice Point 10.2.3.2.5]	Tacrolimus and cyclosporine safe in pregnancy; insufficient pregnancy data on voclosporin	Experience mostly in Japanese patients

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Maintenance therapy for Class III and Class IV lupus nephritis

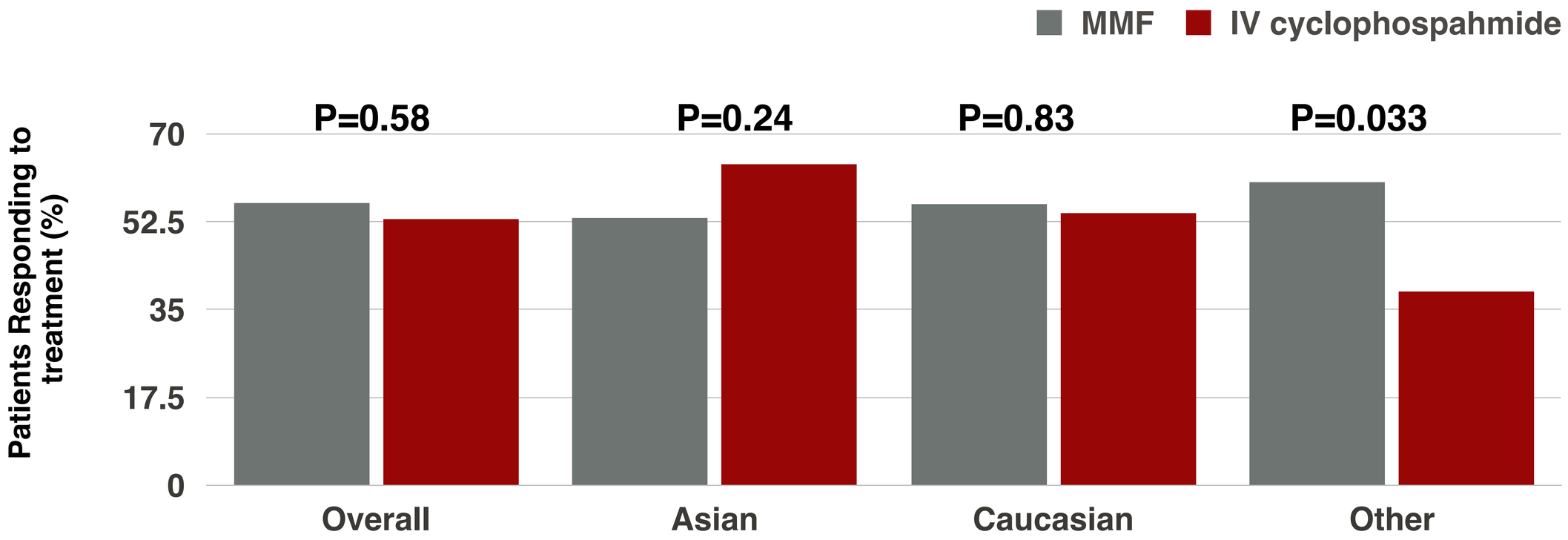
Practical point

- Glucocorticoids should be tapered to the lowest possible dose during maintenance, except when glucocorticoids are required for extrarenal lupus manifestations
- Discontinuation of glucocorticoids can be considered after patients have maintained a complete clinical renal response for ≥12 months.
- The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should be ≥36 months.

KDIGO The management of lupus nephritis . Kidney Int. 2024: 105 (Suppl 1S), S1–S69.

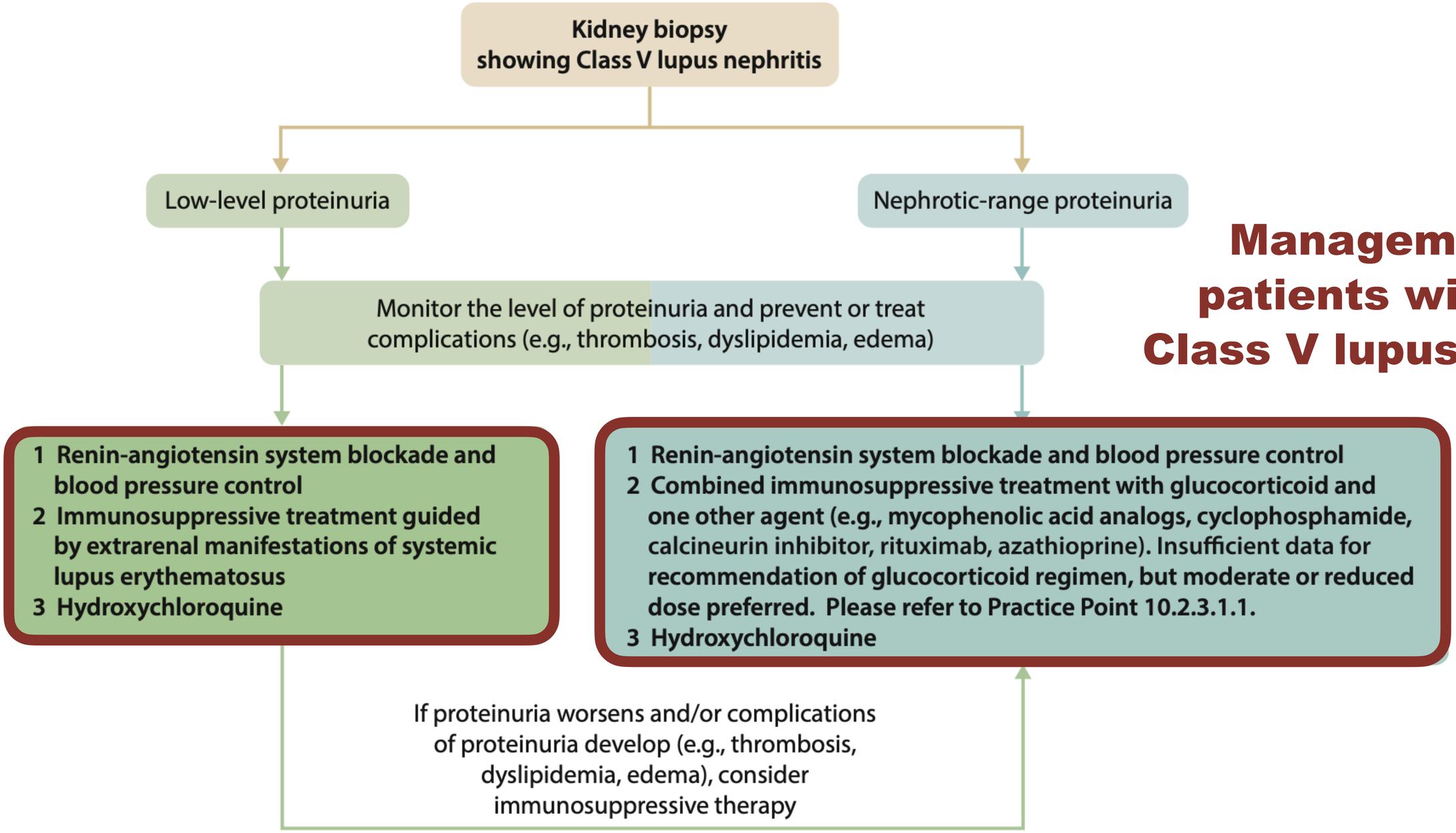
Post-hoc analyses of ASPREVA study

MMF with cyclophosphamide in 60 with pure membranous LN
Response rates were similar between patients with renal biopsy class V



Appel GB; et al. J Am Soc Nephrol. 2009;20(5):1103-12

Management of patients with pure Class V lupus nephritis



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Resistant lupus nephritis

- Steroid and cyclophosphamide/MMF appear to be the most effective
- Up to 15%: refractory to standard treatment
- 30%-50% still develop ESRD
- Infection and gonadal toxicity

Management of unsatisfactory response to treatment

1	Verify adherence to treatment
2	Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)
3	Repeat biopsy if concern for chronicity or other diagnosis (e.g., thrombotic microangiopathy)
4	Consider switching to an alternative recommended treatment regimen when there is persistent active disease
5	Consider the following in patients refractory to first-line treatment regimens: • Addition of rituximab or other biologic therapies • Extended course of i.v. pulse cyclophosphamide • Enrollment in clinical trials if eligible

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Emerging treatment regimens for proliferative LN

LN Induction: Emerging Therapies		
Rituximab	IV rituximab	1,000 mg on d 1 and 14 × 2 doses
Multitarget regimen	Tacrolimus or cyclosporine plus MMF	0.05 mg/kg/d tacrolimus (target trough level 4-6 ng/mL) *or* 3-5 mg/kg/d cyclosporine (level is not well established) *plus* MMF 500-1,000 mg 2×/d × 6 mo

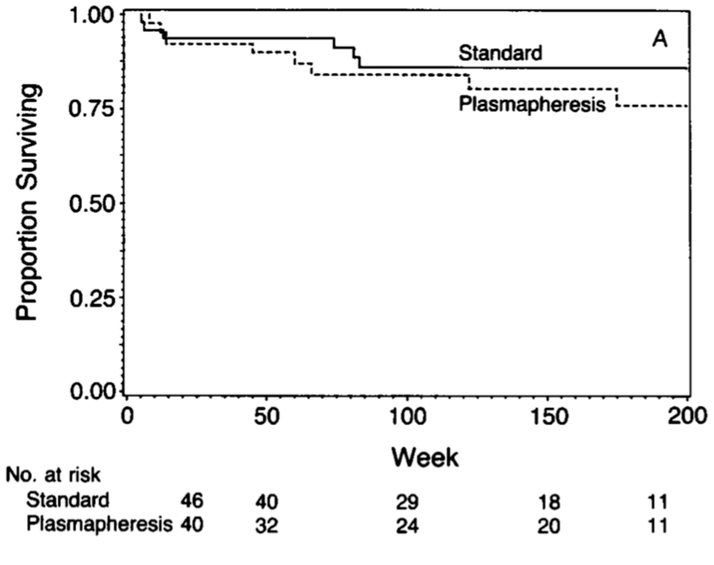
Parikh SV, et al. Am J Kidney Dis. 2020; 76(2):265-281.

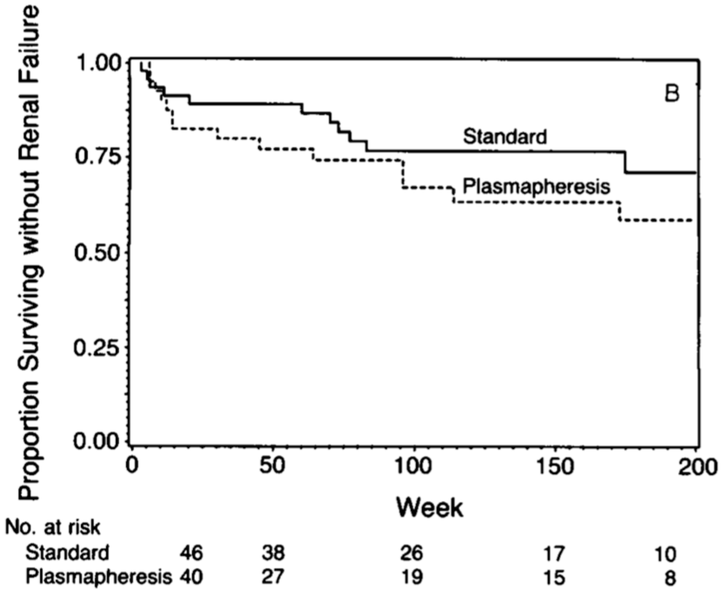
The New England
Journal of Medicine

Volume 326 MAY 21, 1992 Number 21

A CONTROLLED TRIAL OF PLASMAPHERESIS THERAPY IN SEVERE LUPUS NEPHRITIS

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., SHU-PING LAN, M.A., M.P.H.,
RICHARD D. ROHDE, B.S., AND JOHN M. LACHIN, SC.D., FOR THE LUPUS NEPHRITIS
COLLABORATIVE STUDY GROUP*





Treatment with plasmapheresis plus a standard regimen of prednisone and cyclophosphamide therapy does not improve the clinical outcome in patients with severe nephritis

Lewis E, et al. N Engl J Med 1992;326:1373–9.

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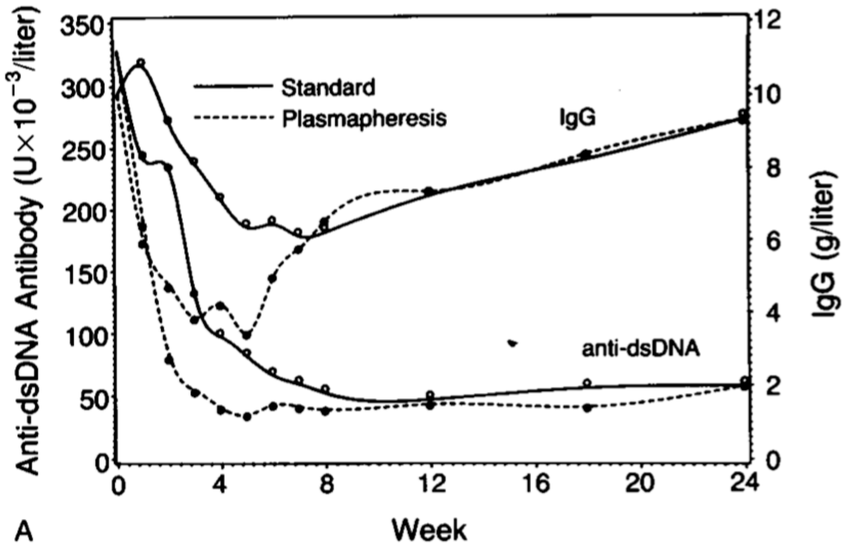

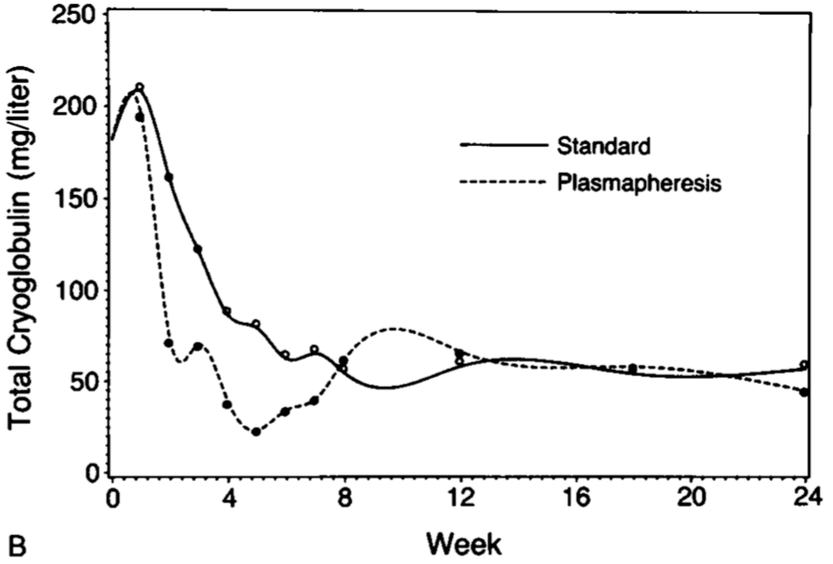

Patients treated with plasmapheresis had a significantly more rapid reduction of serum concentrations of antibodies against double-stranded DNA and cryoglobulins

Lewis E, et al. N Engl J Med 1992;326:1373–9.

American Society for Apheresis 2019 indications for therapeutic apheresis

	Category	Evidence
Systemic lupus erythematosus (SLE): Severe complications	II	2C
Catastrophic antiphospholipid syndrome (CAPS)	I	2C
Thrombotic thrombocytopenic purpura (TTP; severe ADAMTS13 deficiency)	I	1A
Microscopic polyangiitis (MPA)/granulomatous polyangiitis (GPA)/renal limited vasculitis (RLV): RPGN, Cr ≥5.7	I	1A
MPA/GPA/RLV: DAH	I	1C

Connelly-Smith L, Dunbar NM Curr Opin Hematol. 2019;26(6):461.

Treatment of LN relapse

Practice Point

- After a complete or partial remission has been achieved, LN relapse should be treated with the same initial therapy used to achieve the original response, or an alternative recommended therapy.
  - Ovarian failure has been associated with age and cumulative dose, with sustained amenorrhea occurring in up to 50% of patients aged >32 years with a cumulative exposure of 8 g/m^2
  - The chance of future malignancy increases after a total exposure of 36 g, so if a patient is approaching this level, cyclophosphamide is better avoided

KDIGO The management of lupus nephritis . Kidney Int. 2024: 105 (Suppl 1S), S1–S69.

Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review

G Ruiz-Irastorza,[1] M Ramos-Casals,[2] P Brito-Zeron,[2] M A Khamashta[3]

HCQ should be given to most patients with SLE during the whole course of the disease and be continued during pregnancy

Quality of evidence	AM
High:	
Reduction of SLE activity (also in pregnancy)	CQ/HCQ
Reduction of mortality	CQ/HCQ
Moderate:	
Increase in BMD	HCQ
Protective effect on thrombotic events	CQ/HCQ
Protective effect on irreversible organ damage	HCQ
Low:	
Reduction of severe flares	HCQ
Adjuvant effect for achieving LN remission	HCQ
Beneficial effect on serum lipid levels	CQ/HCQ
Protective effect on osteonecrosis	HCQ
Delaying the evolution to SLE	HCQ
Protective effect on cancer	CQ/HCQ

Ruiz-Irastorza G, et al. Ann Rheum Dis 2010; 69: 20-28.

General management

- **We recommend that patients with SLE, including those with lupus nephritis (LN), be treated with hydroxychloroquine or an equivalent antimalarial unless contra-indicated (1C)**

- Lower flare including kidney
- Higher response rates to therapy
- Lower incidence of CV and thrombotic events in APS patients
- Less organ damage
- Improved lipid profiles
- Preservation of bone mass

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FDA Pharmaceutical Pregnancy categories

Category A	Adequate and well-controlled studies show no risk
Category B	No evidence of risk in humans; the chance of fatal harm is remote
Category C	Animal studies show a risk, but no human studies have been performed. Potential benefits may outweigh the risks.
Category D	Human studies show a risk Potential benefits may outweigh the risks.
Category X	Animal or human studies show a risk. The risk outweigh the potential benefits.

Immunosuppressive agents

Drug	Teratogenicity	Fetal/neonatal effects	FDA
Prednisone	Possible increase in oral cleft palate	Rare except at large doses (cataracts, infection and adrenal insufficiency)	B
Azathioprine	Possible sporadic congenital abnormalities	Transient immune alterations in neonates	D
Tacrolimus and cyclosporine	No	Hyperkalemia and renal impairment	C
Intravenous immunoglobulin	No	None reported	C

Adapted from Hladunewich MA, et al. Kidney Int: 2016: 89, 995–1007.

Immunosuppressive agents

Drug	Teratogenicity	Fetal/neonatal effects	FDA
Mycophenolate mofetil	Congenital abnormalities in 22.9%: absent auditory canal, hypertelorism, microtia, cleft lip and palate, brachydactyly of the fifth finger, limb abnormalities, and hypoplastic toenails	No	D
Cyclophosphamide	Yes	Chromosomal abnormalities and cytopenia	D
Sirolimus and Everolimus	Unknown	Toxicity in animal studies, but not teratogenicity	C

Adapted from Hladunewich MA, et al. Kidney Int: 2016: 89, 995–1007.

Pregnancy in patients with LN

Practice Point

- Patients with active LN should be counseled to avoid pregnancy while the disease is active or when treatment with potentially teratogenic drugs is ongoing, and for ≥6 months after LN becomes inactive.
- To reduce the risk of pregnancy complications, hydroxychloroquine should be continued during pregnancy, and low-dose aspirin should be started before 16 weeks of gestation.
- Glucocorticoids, hydroxychloroquine, azathioprine, tacrolimus, and cyclosporine are considered safe immunosuppressive treatments during pregnancy.

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Lupus nephritis patients at high risk for poor renal outcome

Patient characteristics	Serologic characteristics
• African or Hispanic ancestry • Male • Pediatric onset • Frequent relapses • Incomplete remission • Neuropsychiatric lupus • Proteinuria >4 g/d at diagnosis	• Antiphospholipid antibodies or antiphospholipid syndrome • Persistent hypocomplementemia • High titer dsDNA antibodies • High titer C1q antibodies

dsDNA, double-stranded DNA.

Kidney International (2019) 95, 281–295.

High risk for poor renal outcome

Serologic characteristics	Histologic characteristics
• Antiphospholipid antibodies or antiphospholipid syndrome • Persistent hypocomplementemia • High titer dsDNA antibodies • High titer C1q antibodies	• Crescentic glomerulonephritis • Thrombotic microangiopathy • Extensive tubulointerstitial damage

Kidney International (2019) 95, 281–295.

DEPARTMENT OF MEDICINE
PHRAMONGKUTKLAO HOSPITAL

NEPHROLOGY
PHRAMONGKUTKLAO HOSPITAL

Intelligence Dialysis Center
Nephrology Unit
Phramongkutklao Hospital and College of Medicine