Lupus Nephritis for PMK Resident

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Disclosure information

- **Prof. Bancha Satirapoj, M.D.**
- **Scientific Advisor/Honoraria:**
  - **Astra Zeneca, Boehringer Ingelheim, LG Life Sciences, Janssen-Cilag, MSD, Novo Nordisk, Osotspa Taisho, Sanofi Aventis and Abbott Laboratories**
- **DISCLAIMER**
  - **This presentation is intended for educational purpose for HCPs only. It may contain new science data which is currently not in approved package insert information and is not intended for off-label promotion.**

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

ACR criteria for the diagnosis of lupus

The presence of four or more of the following criteria gives 96% sensitivity and specificity for the diagnosis of lupus:

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Nonerosive arthritis
6. Pleuropericarditis
7. Renal disease (proteinuria and/or cellular casts)
8. Neurologic disorder (seizures or psychosis in the absence of precipitating circumstances)
9. Hematologic disorder (hemolytic anemia, leukopenia/lymphopenia, thrombocytopenia)
10. Positive LE cell preparation, raised anti-DNA antibody, anti-Sm present, false-positive antitreponemal test
11. Positive fluorescent antinuclear antibody test

Sensitivity 86% and specificity 93%
4/11 item

SLICC Classification Criteria for SLE

At least one Clinical criteria

- Acute cutaneous lupus
- Chronic cutaneous lupus
- Oral ulcers
- Non-scarring alopecia
- Synovitis
- Serositis
- Renal
- Neurologic
- Hemolytic anemia
- Leukopenia <4,000/mm3
- Thrombocytopenia <100,000/mm3

At least one Immunologic criteria

- ANA level
- Anti-dsDNA antibody
- Anti-Sm antibody
- Antiphospholipid antibody
- Low complement
- Direct Coombs' test in the absence of hemolytic anemia

> 4 criterion OR Biopsy-proven lupus nephritis and ANA or anti-dsDNA Ab

Sensitivity 94% and specificity 92%, 4 item

Petri M, et al. ARTHRITIS & RHEUMATISM, 2012, 2677–268

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Arthritis & Rheumatology
Vol. 71, No. 9, September 2019, pp 1400–1412
DOI 10.1002/art.40930

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

Arthritis & Rheumatology 2019, 71: 1400-12.

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

Arthritis & Rheumatology 2019, 71: 1400-12.

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

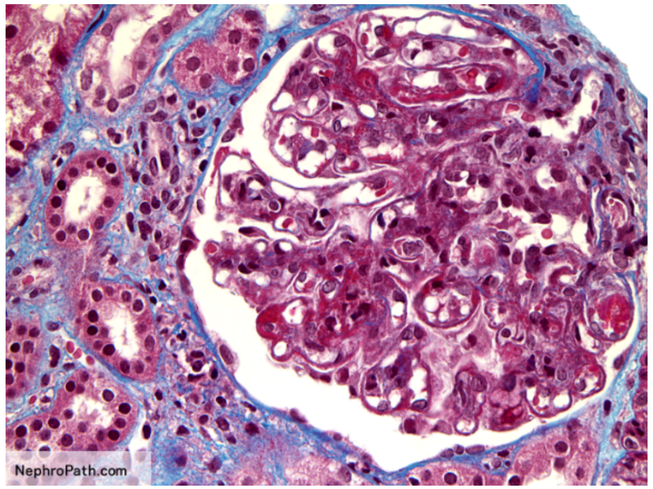
	ACR 1997 criteria	SLICC 2012 criteria	EULAR/ACR 2019 criteria
Derivation			
Sensitivity (95% CI)	0.85 (0.81–0.88)	0.97 (0.95–0.98)	0.98 (0.97–0.99)
Specificity (95% CI)	0.95 (0.93–0.97)	0.90 (0.87–0.92)	0.96 (0.95–0.98)
Combined (95% CI)	1.80 (1.76–1.83)	1.87 (1.84–1.90)	1.94 (1.92–1.96)
Validation	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

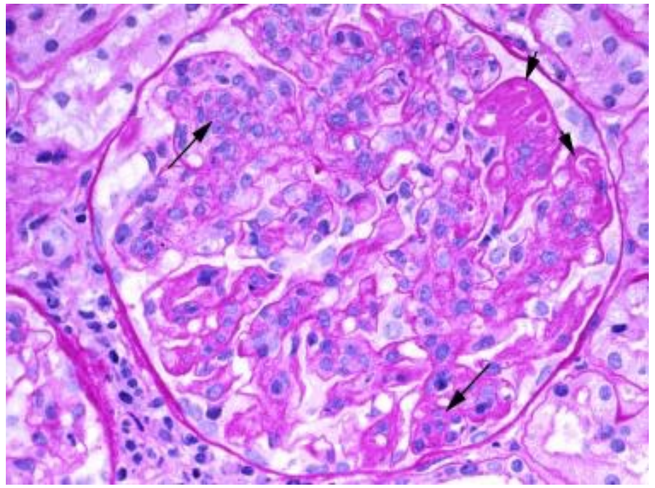
* ACR = American College of Rheumatology; SLICC = Systemic Lupus International Collaborating Clinics; EULAR = European League Against Rheumatism; 95% CI = 95% confidence interval.

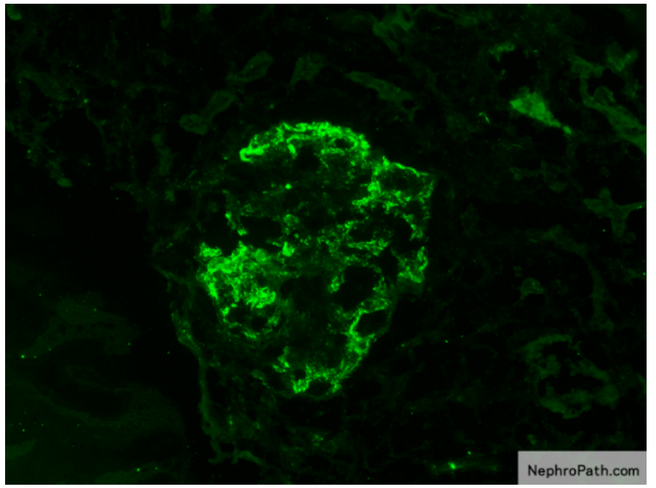
Arthritis & Rheumatology 2019, 71: 1400-12.

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







Arthritis & Rheumatology 2019, 71: 1400-12.

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

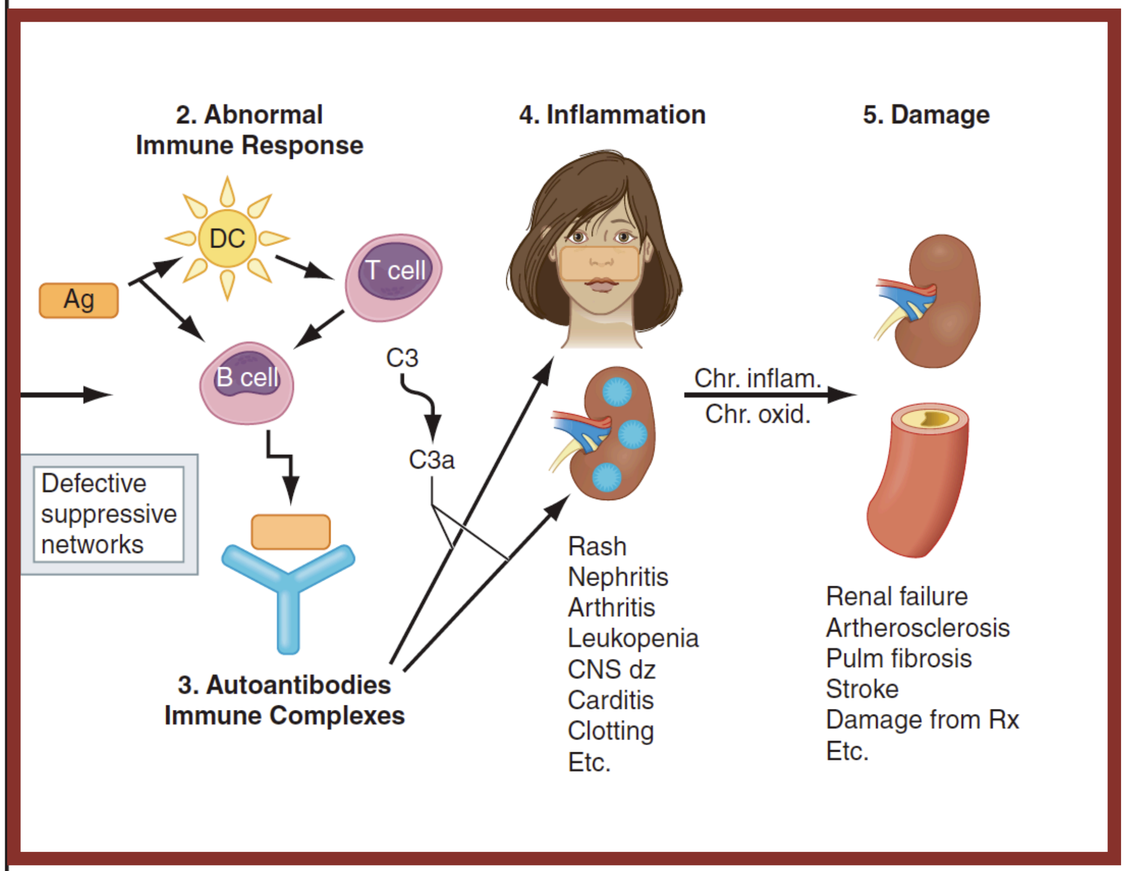
ENVIRONMENT/MICROENVIRONMENT

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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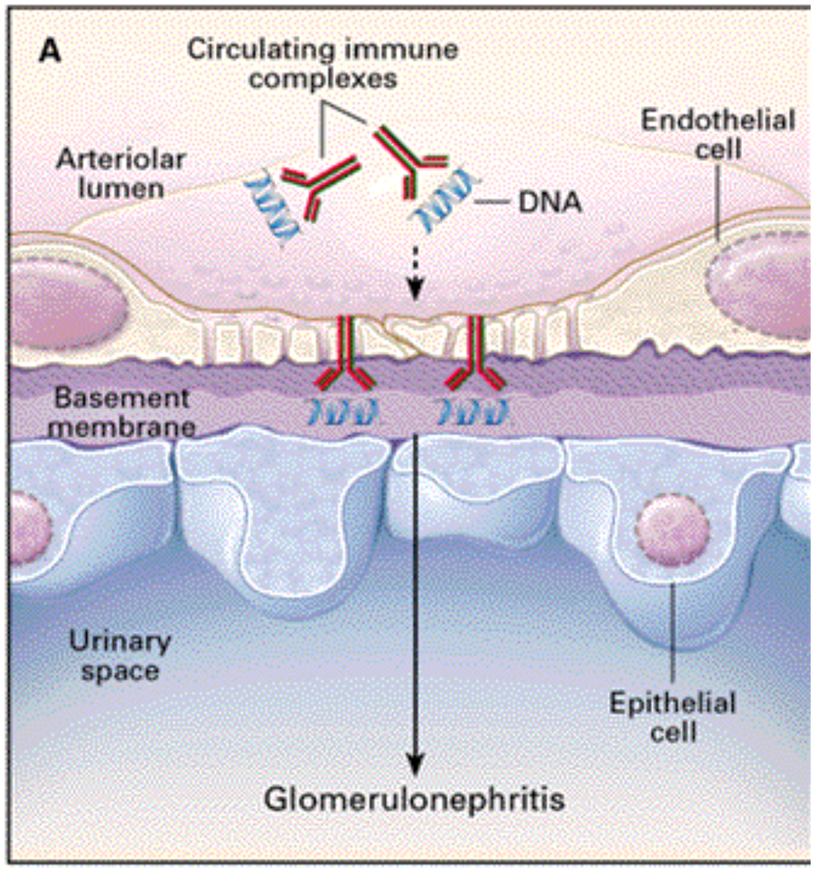
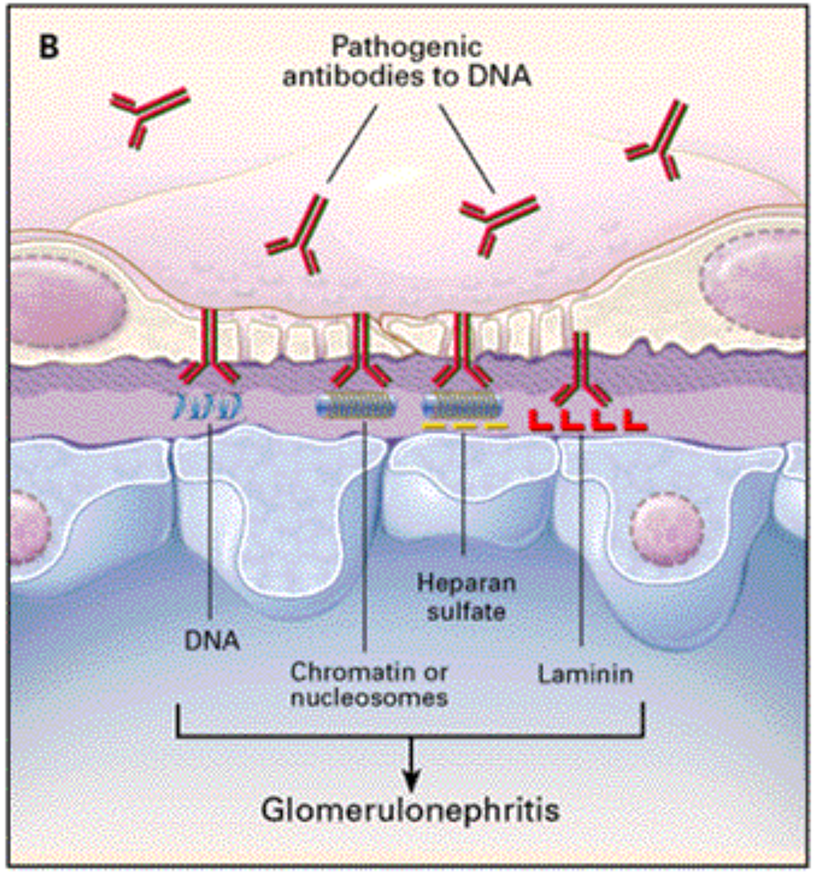
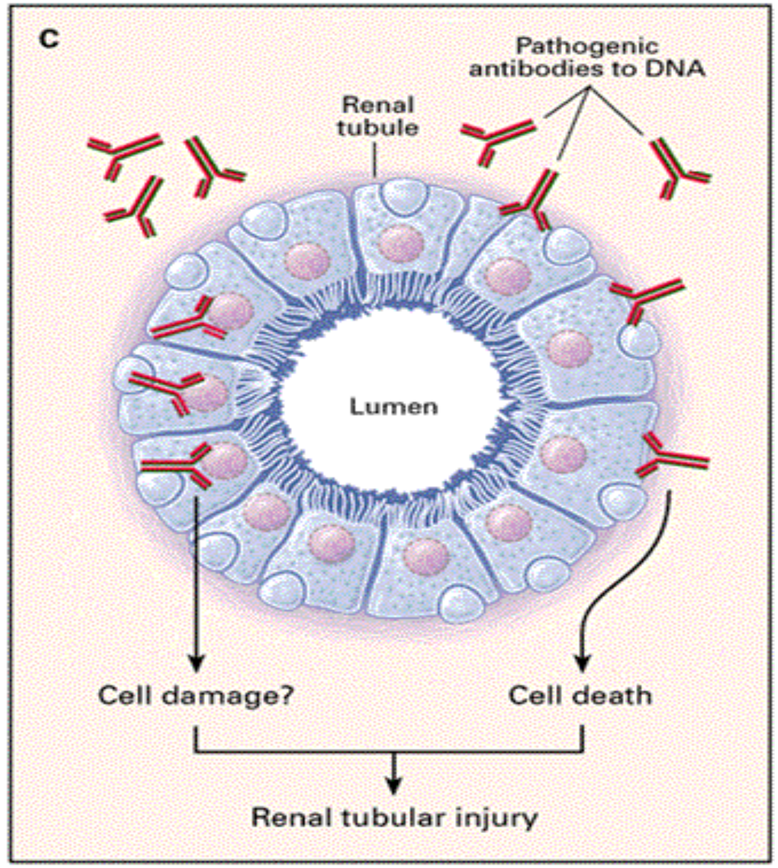
Mechanisms of renal damages

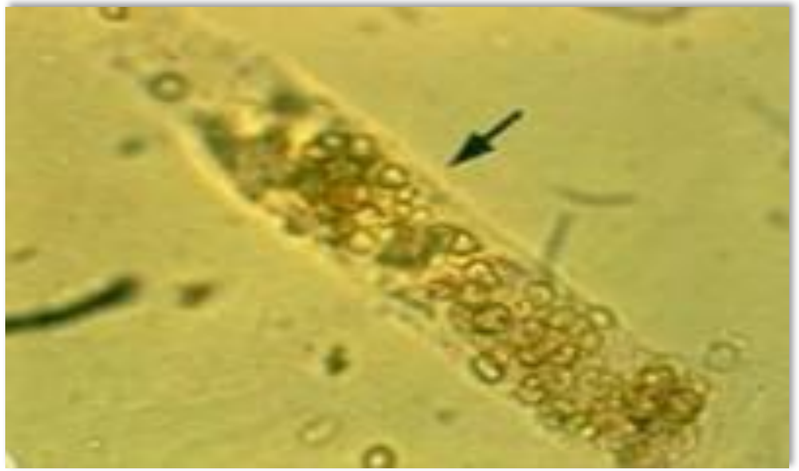


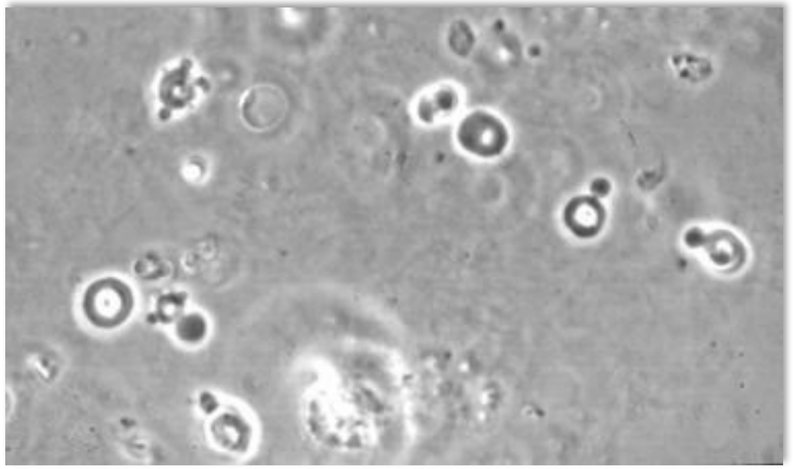




Glomerular syndrome

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





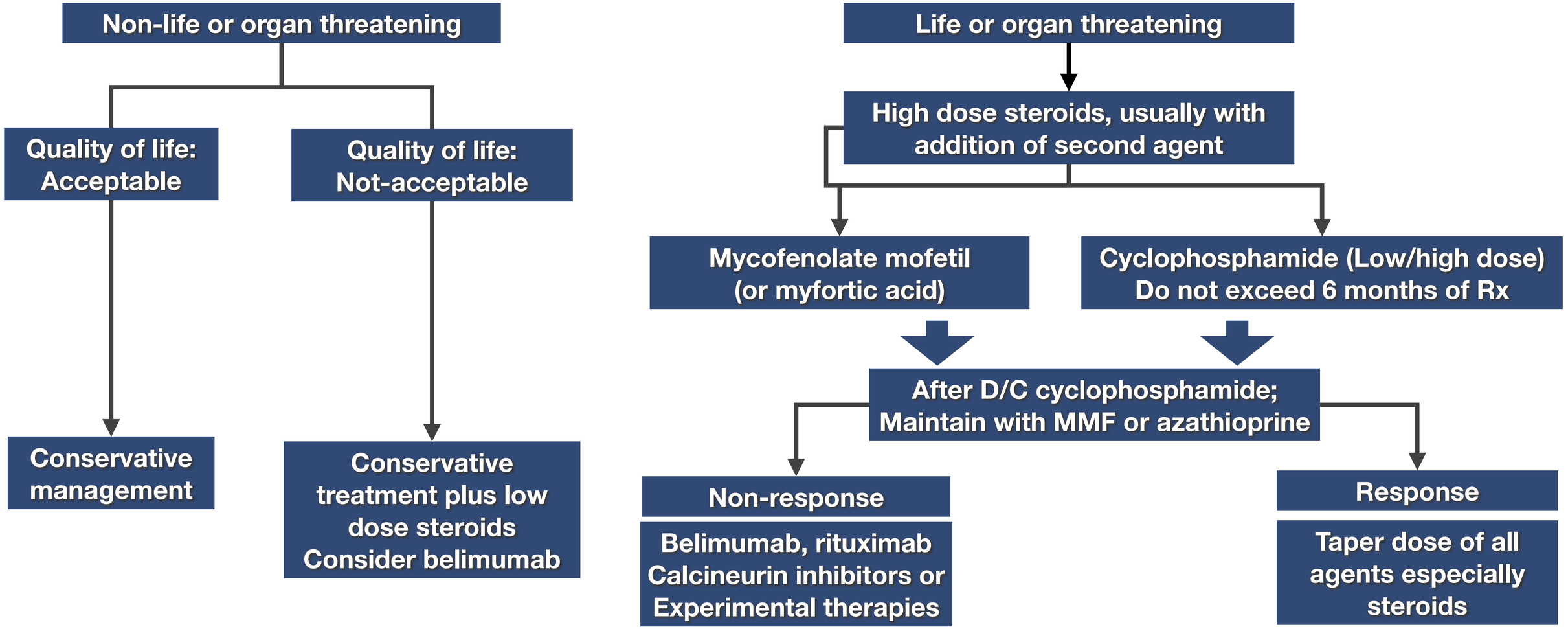
Renal Manifestation

- 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

Initial therapy of SLE



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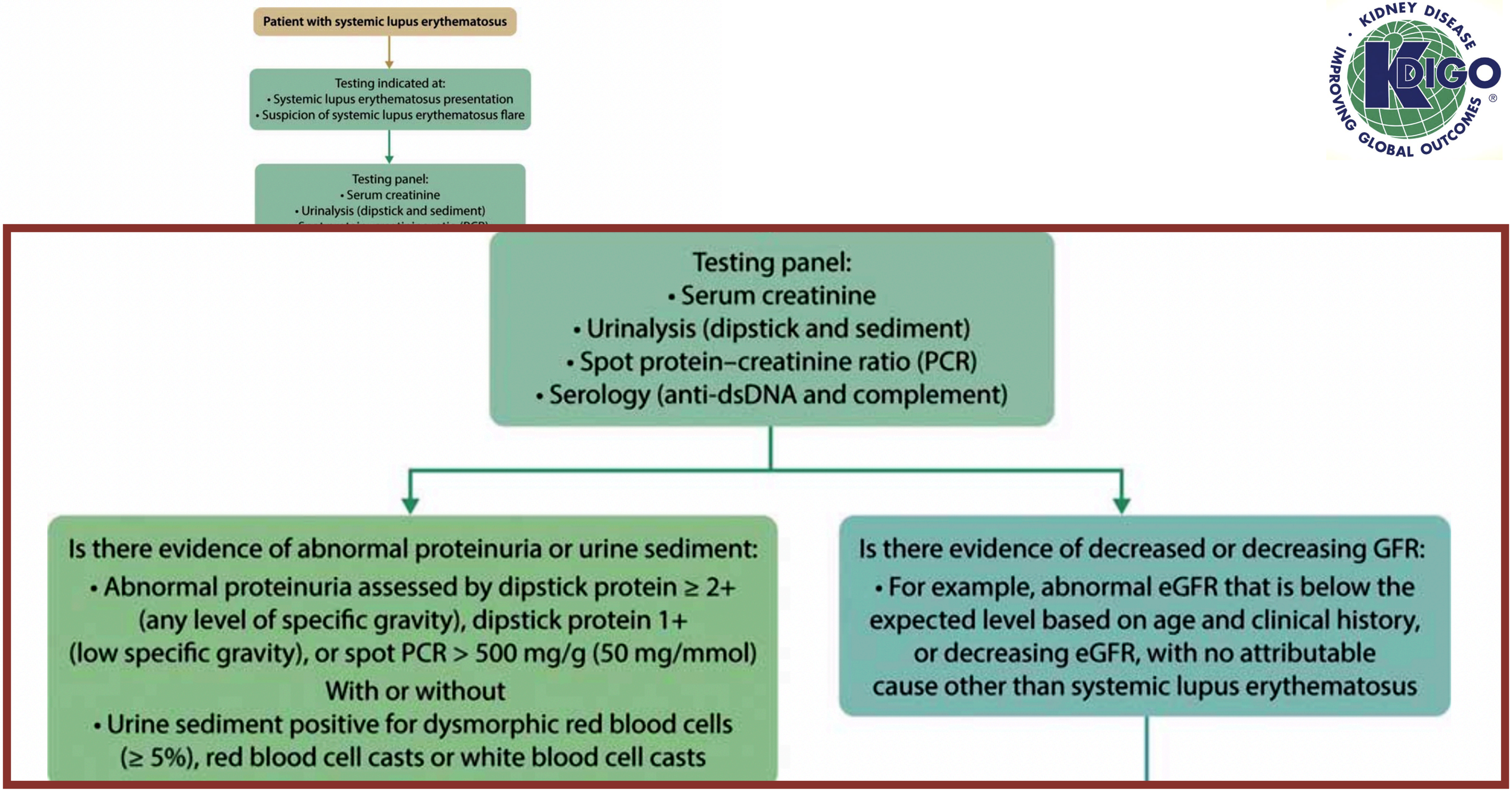
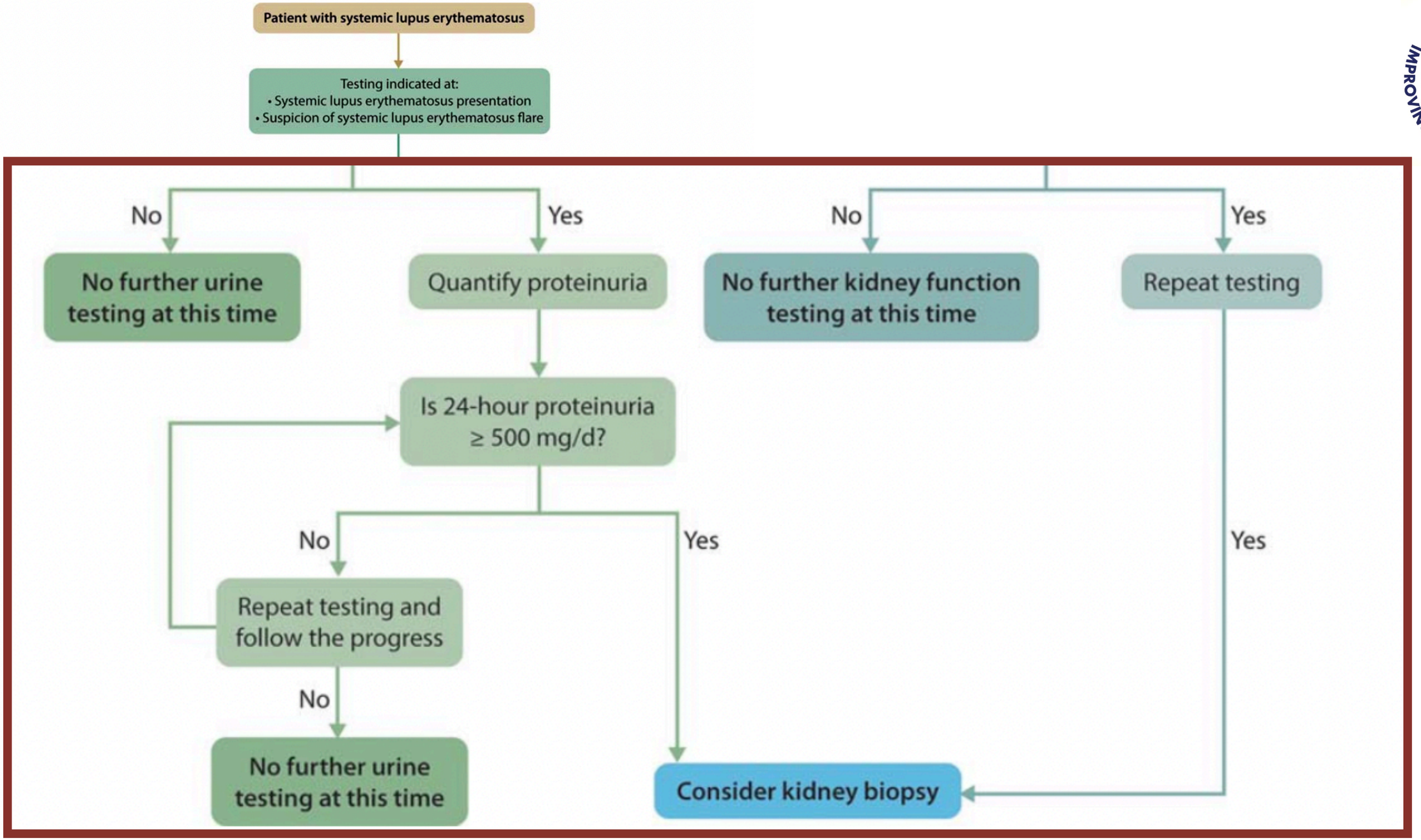
Kidney biopsy

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



KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES. Kidney Int 2021: 100, S1–S276



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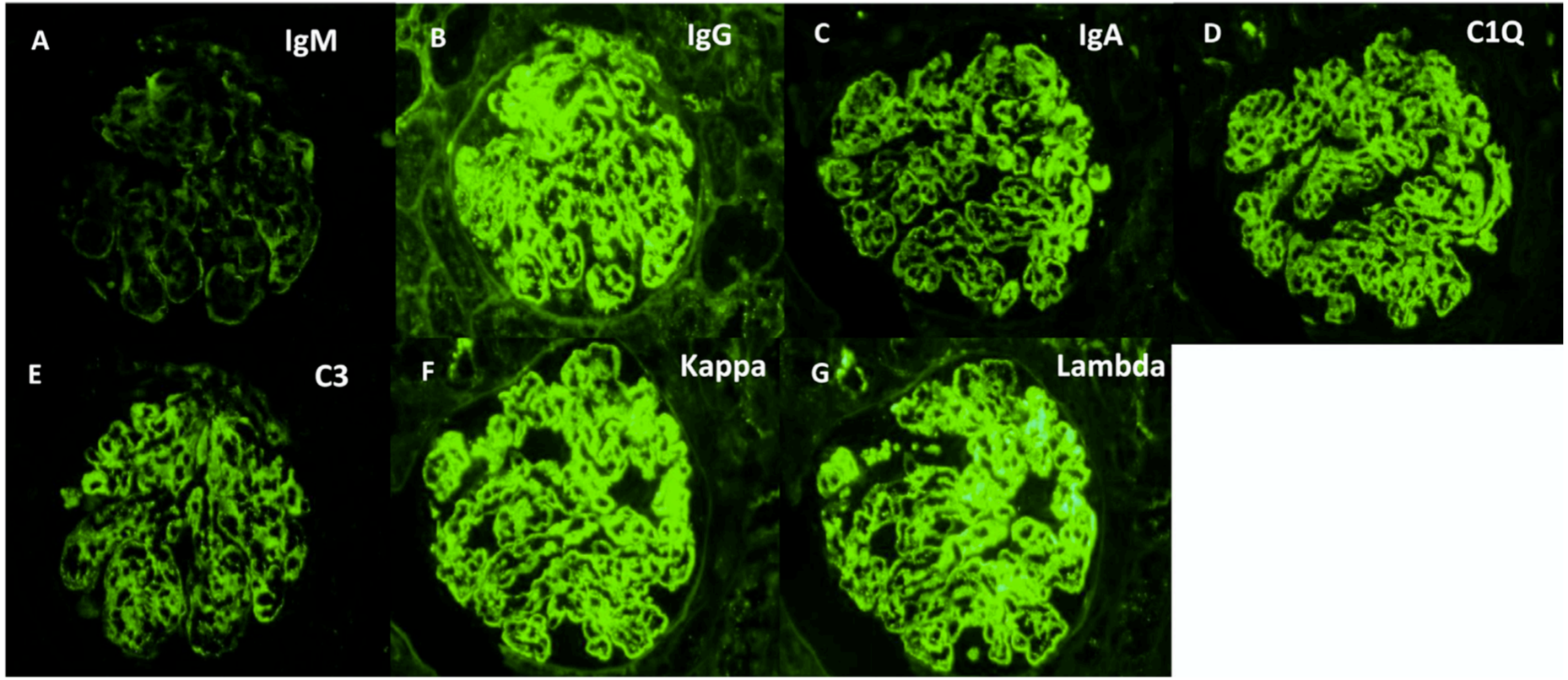
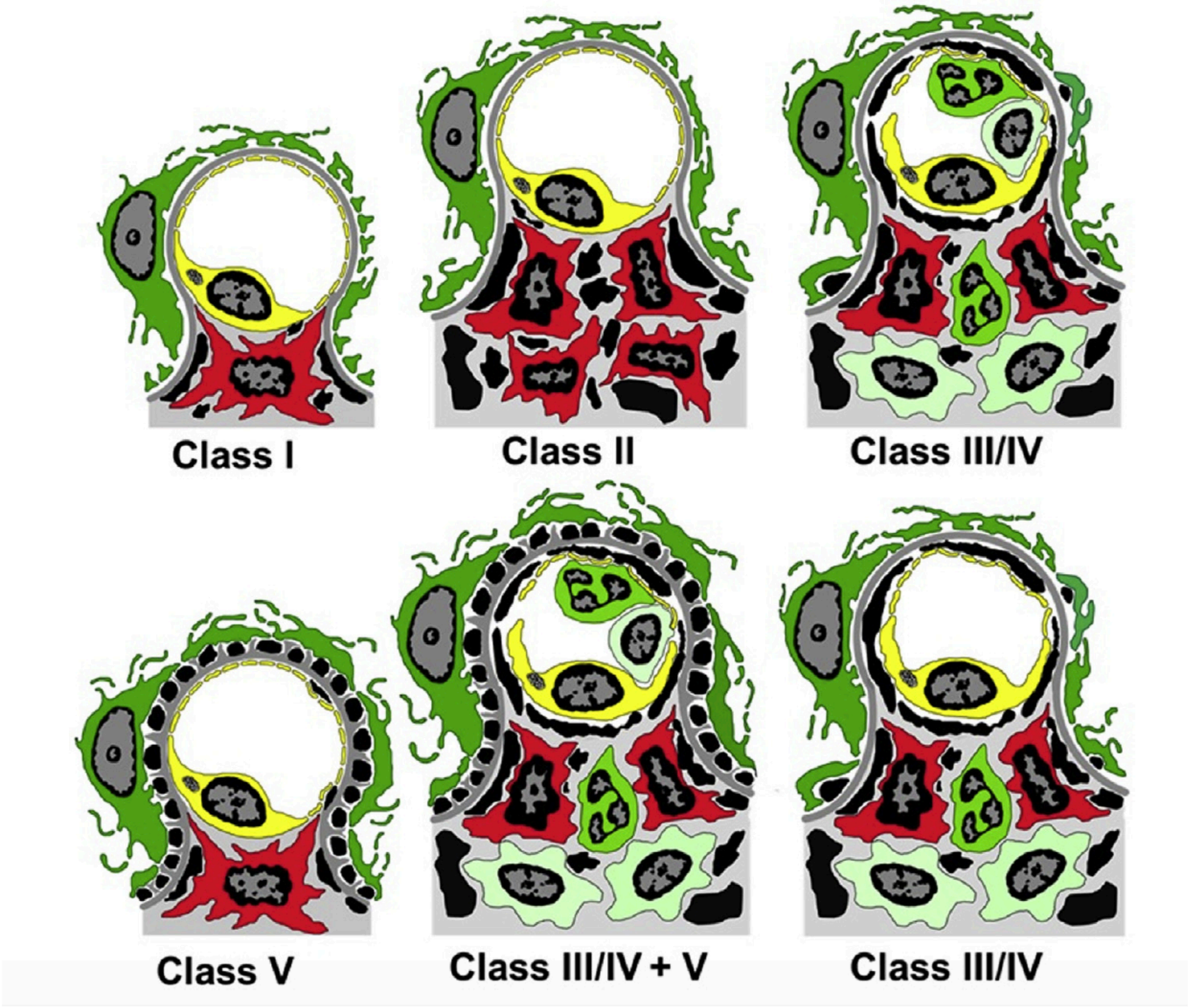
Immunofluorescence (IF) staining in lupus nephritis



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

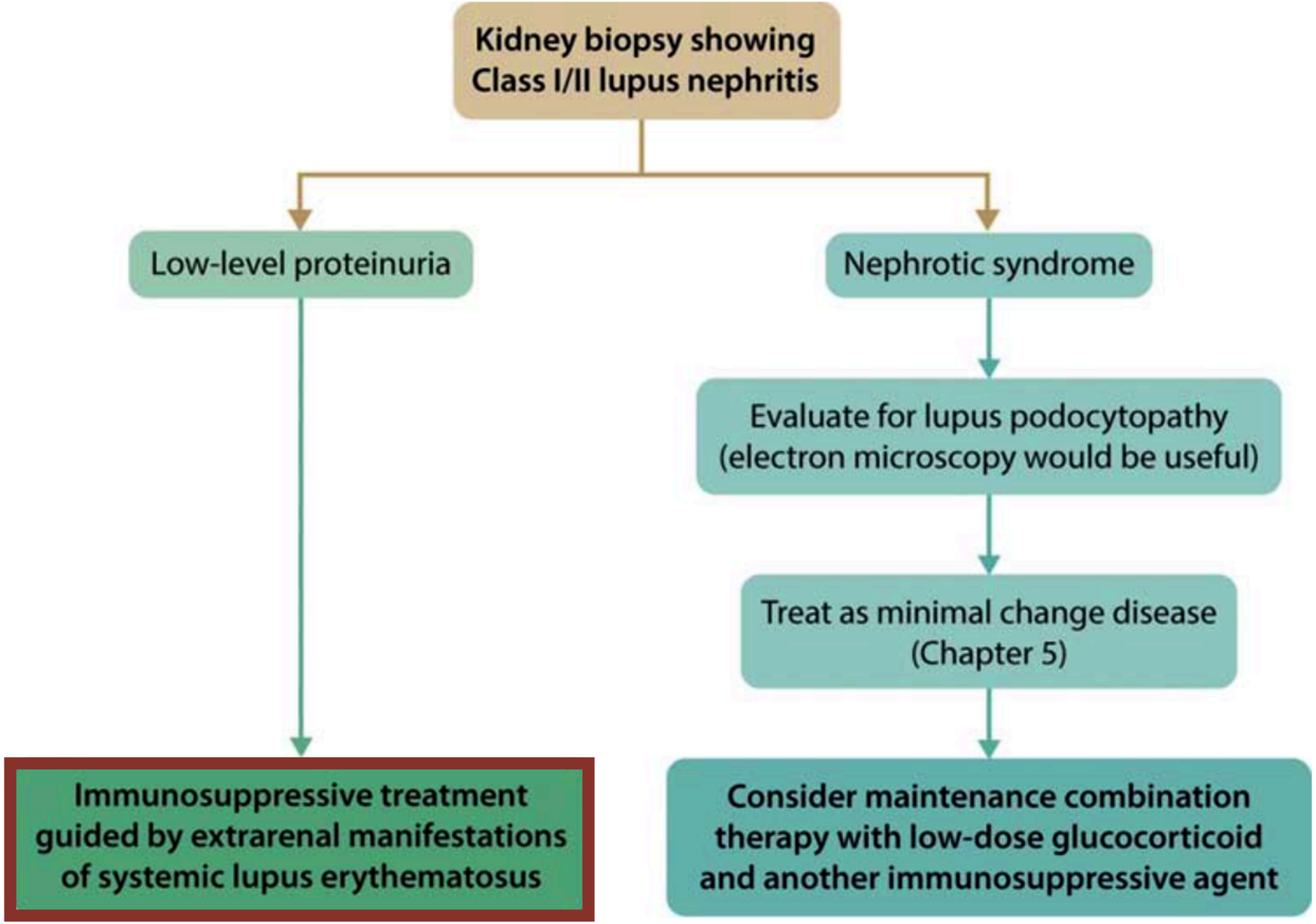
Weening JJ, et al. Kidney Int, 2004: 65: 521–530.

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

Treatment of Lupus Nephritis (Class I-II)



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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

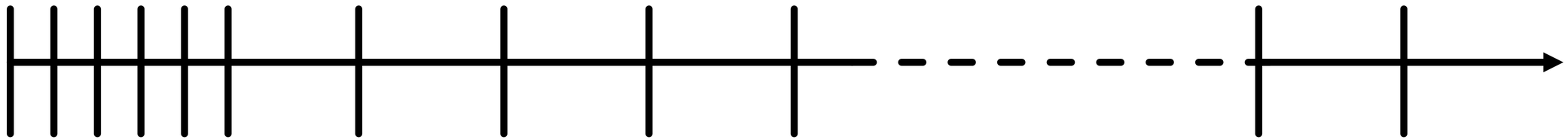
Austin H, et al. NEJM 1984; 314: 614

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

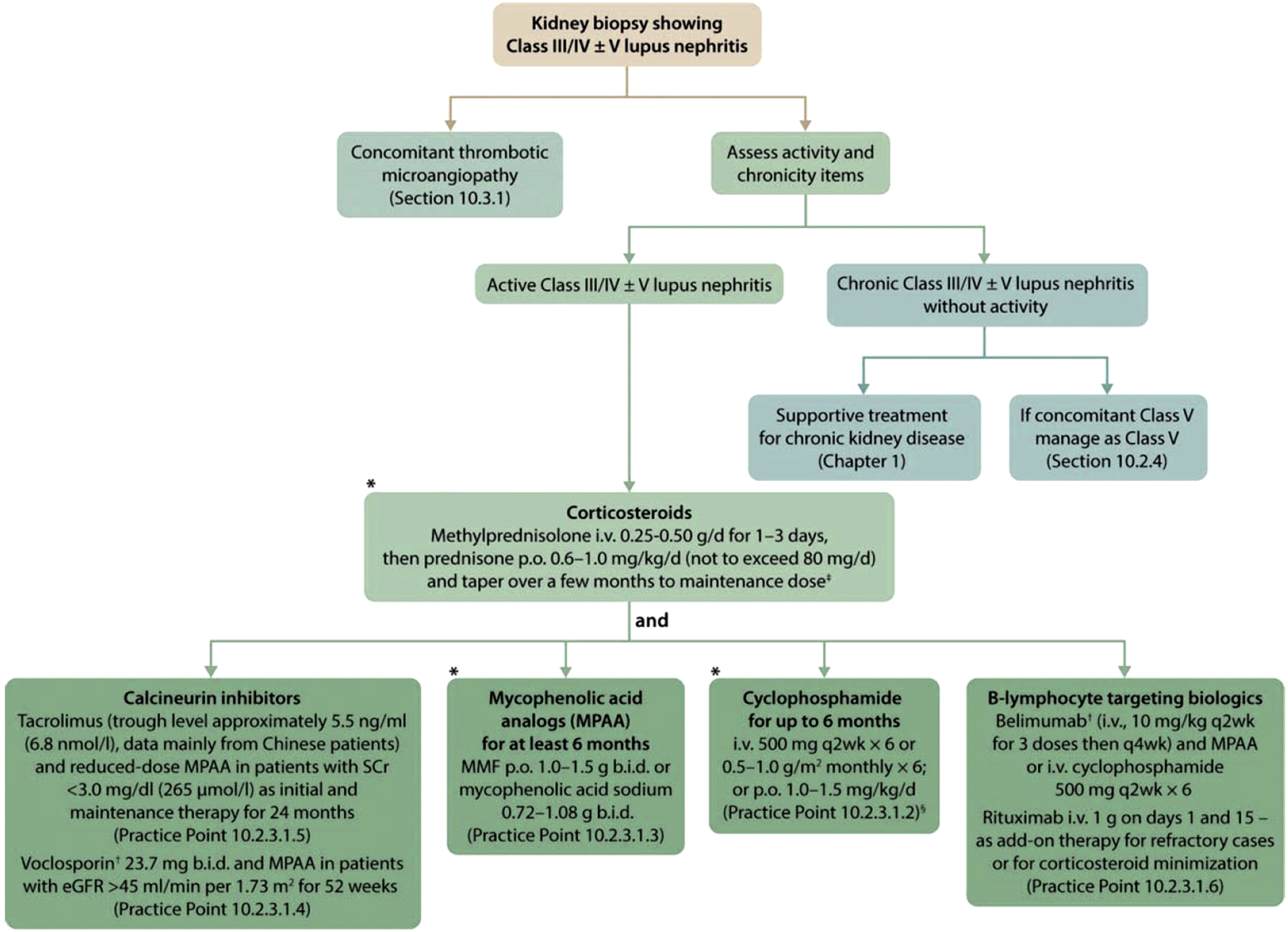
- **Initial IVCY 0.5-1.0 g/m^2 (0.5 g/m^2 if GFR 1/3 normal)**
- **Adjust subsequent IVCY to maximum dose of 1 g/m^2 unless WBC nadir at 10-14 days after ICVY falls below 1,500/mm^3**
- **Prednisolone 0.5-1 mg/kg/day for 4-8 weeks, which is subsequently tapered to low dose maintenance therapy**

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.



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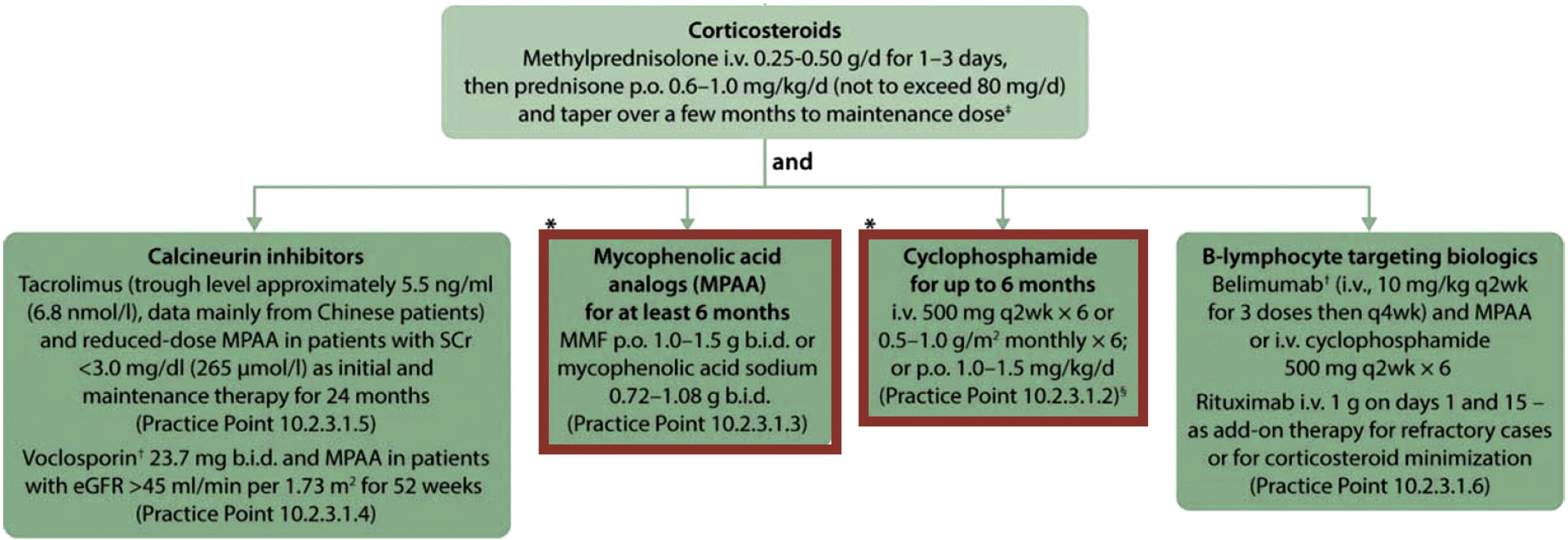
Treatment of Lupus Nephritis (Class III-IV)



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Cyclophosphamide dosing regimens

	Intravenous cyclophosphamide – modified (NIH regimen)	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 Afro/Caribbean descent, Hispanic descent, Indian patients, and other Asian countries	Efficacy data included patients of different races/ethnicities

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Glucocorticoids dosing regimens

	Standard-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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Assessing treatment response in LN

Criteria	Definition
Complete response	• Reduction in proteinuria to <0.5 g/g measured as the PCR from a 24-hour urine collection • Stabilization or improvement in kidney function (±10-15% of baseline)
Partial response	• Reduction in proteinuria by at least 50% and to < 3 g/g measured as the PCR from a 24-hour urine collection • Stabilization or improvement in kidney function (±10-15% of baseline) • Within 6-12 months of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6-12 months of starting therapy

KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES 2020

The NEW ENGLAND JOURNAL of MEDICINE

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

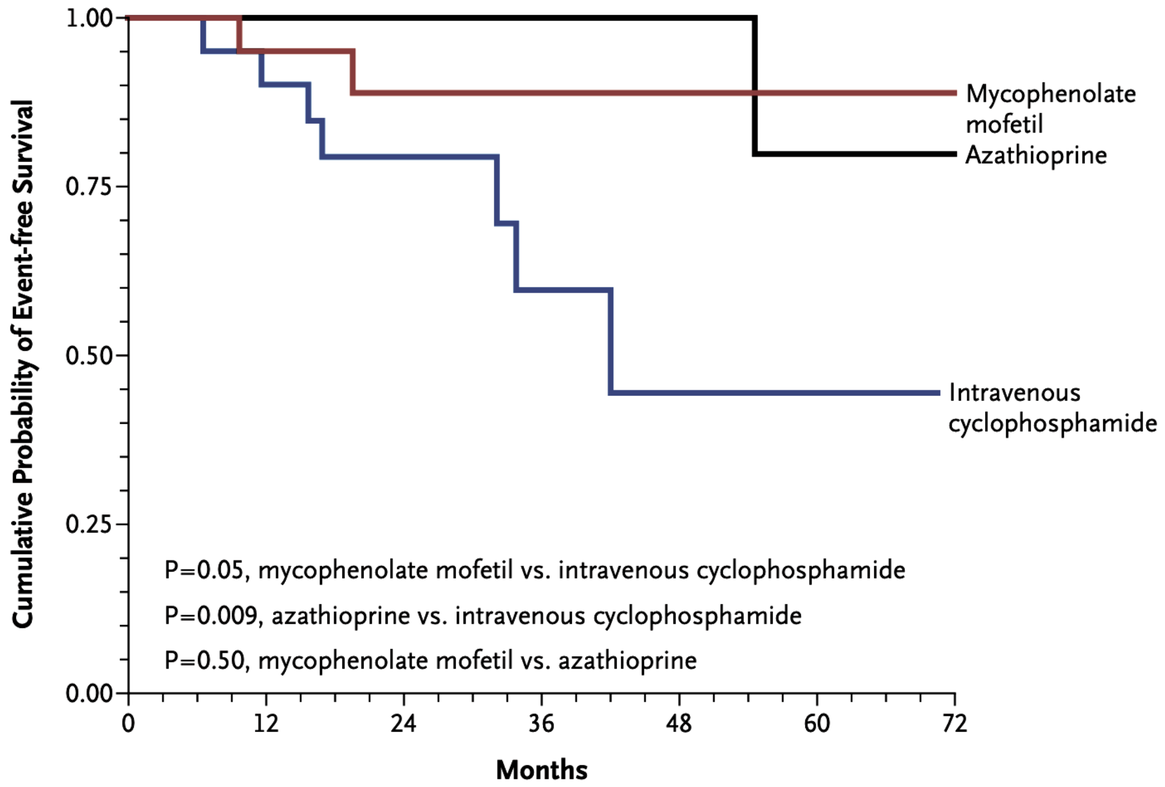
Sequential Therapies for Proliferative Lupus Nephritis

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.

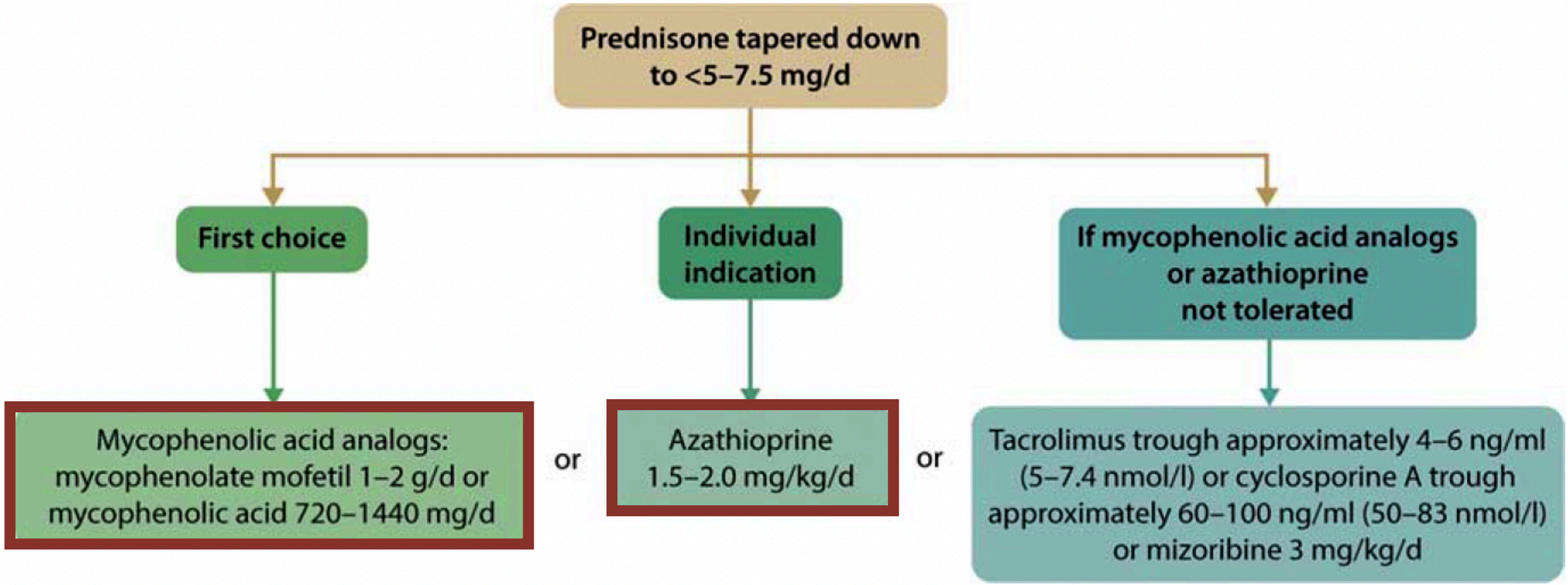
Maintenance therapy: AZA vs MMF

- 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.

Maintenance therapy for Class III and Class IV LN



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Maintenance therapy for Lupus Nephritis (III-IV)

Practice Point

- **The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should not be <36 months.**
- **No optimal duration of maintenance immunosuppression for proliferative LN, most patients will require at least three years of therapy.**

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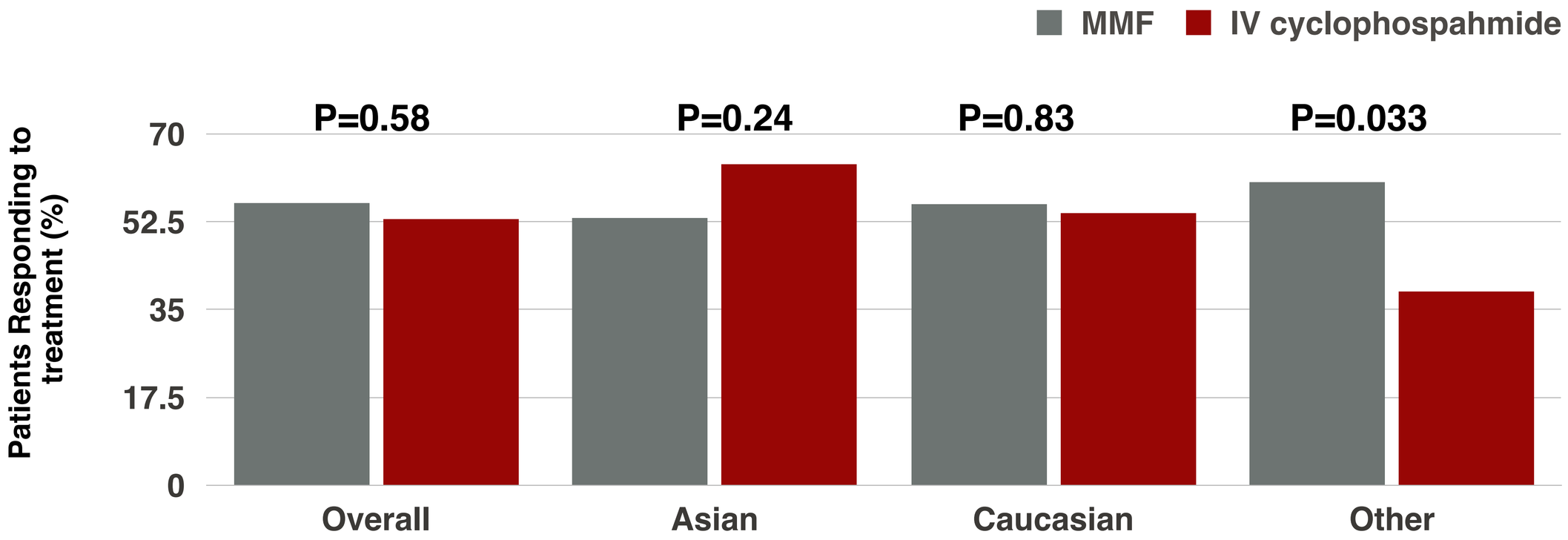
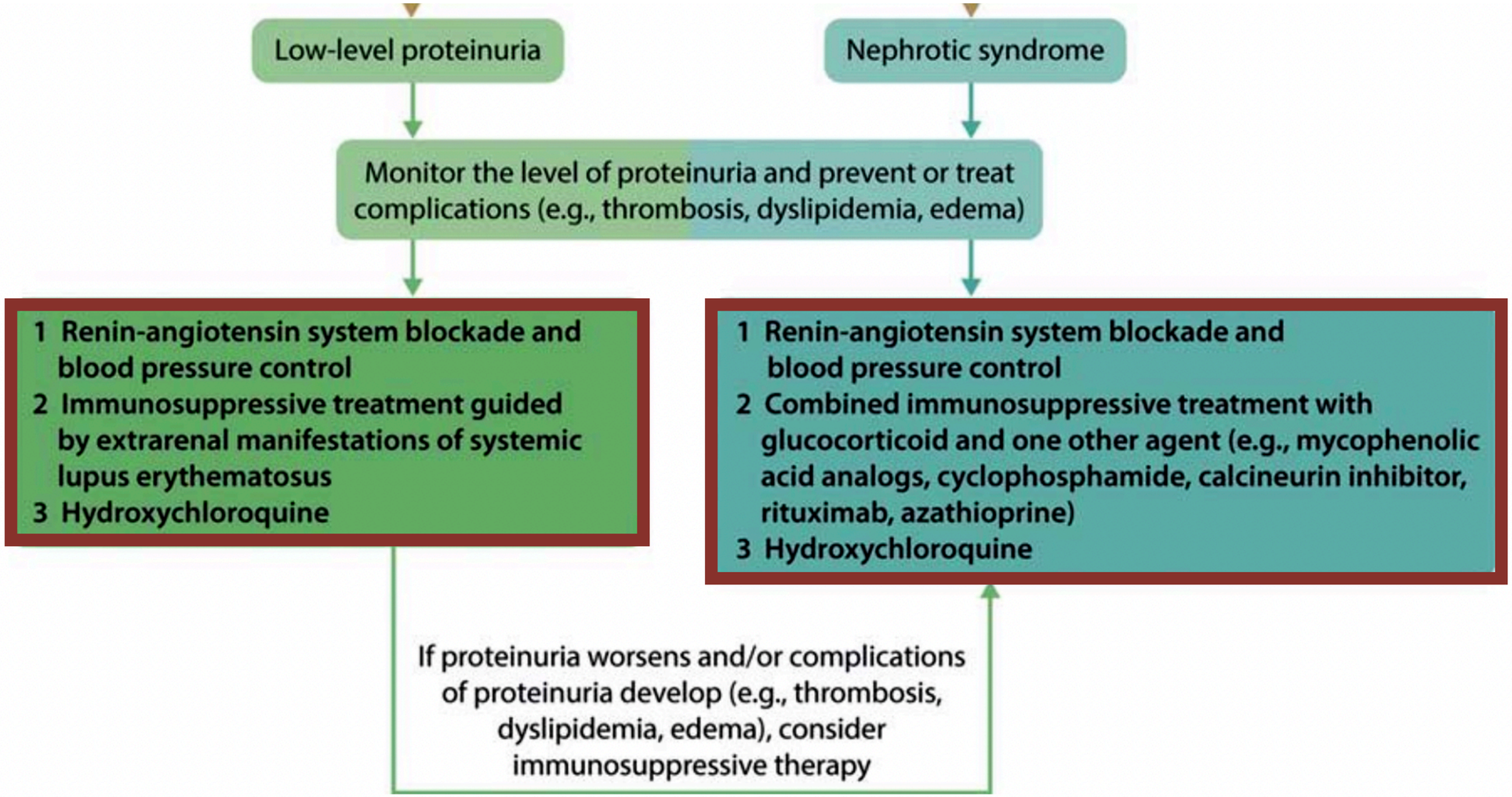
Post-hoc analyses of ASPREVA study

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

Treatment of Lupus Nephritis (Class V)



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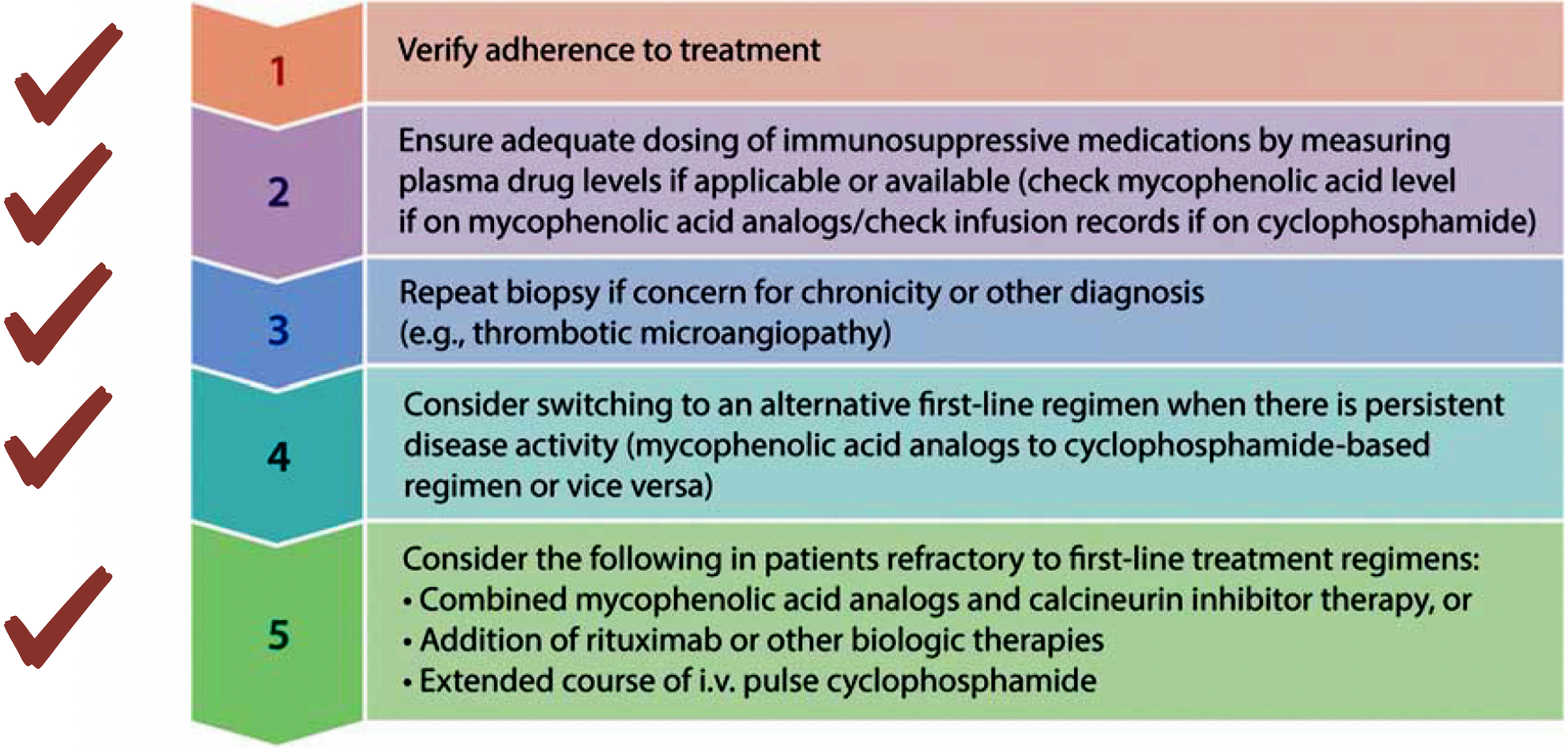
Resistant lupus nephritis

- 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 patients who show unsatisfactory response to initial therapy for active LN



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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.,
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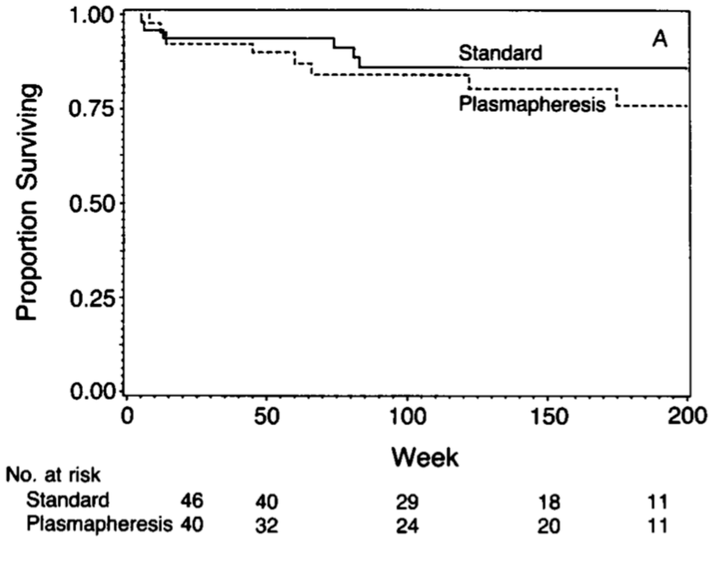

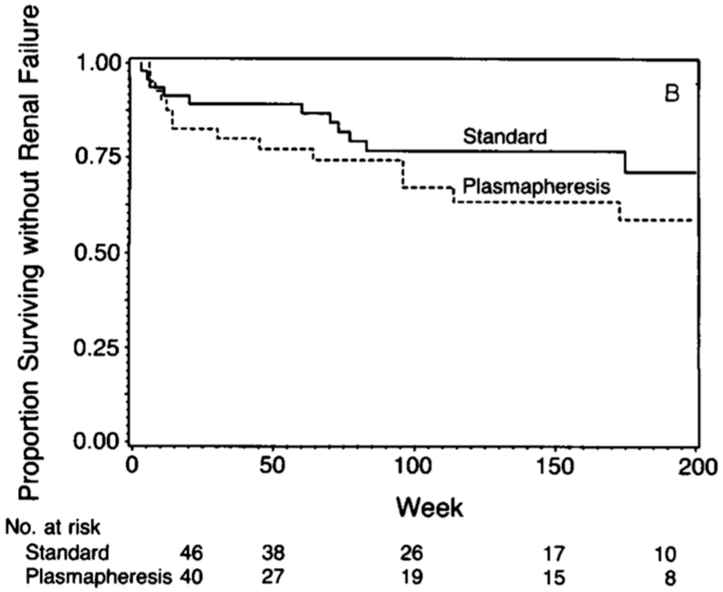

Treatment with plasmapheresis plus a standard regimen of prednisone and cyclophosphamide therapy does not improve the clinical outcome in patients with severe nephritis

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

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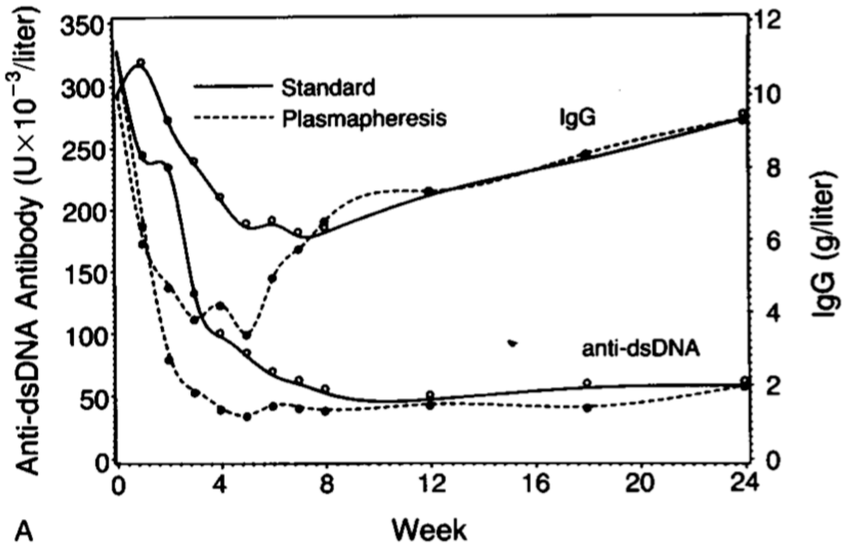

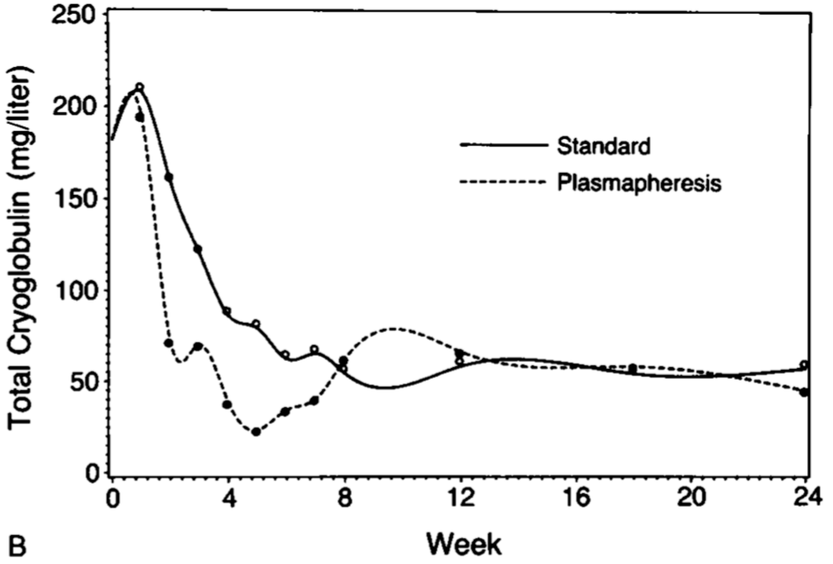

Patients treated with plasmapheresis had a significantly more rapid reduction of serum concentrations of antibodies against double-stranded DNA and cryoglobulins

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 first-line therapy.**

Lifetime maximum of 36 g cyclophosphamide in patients with systemic lupus

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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

- **Patients with LN be treated with hydroxychloroquine or an equivalent antimalarial unless contraindicated (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 at least six 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**
- **Only corticosteroids, hydroxychloroquine, azathioprine, and CNIs 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.

Causes of death in Lupus nephritis

	Percentage
Infection	52
Uremia	27
Cardiovascular disease	10
Nervous system	7
Others: GI bleeding, Respiratory failure	5

Shayakul C, et al. Am J Kidney Dis. 1995; 26(2):300-7.

DEPARTMENT OF MEDICINE
PHRAMONGKUTKLAO HOSPITAL

NEPHROLOGY
PHRAMONGKUTKLAO HOSPITAL

Intelligence Dialysis Center
Nephrology Unit
Phramongkutklao Hospital and College of Medicine