Lupus Nephritis

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Organ Involvement in the Course of SLE

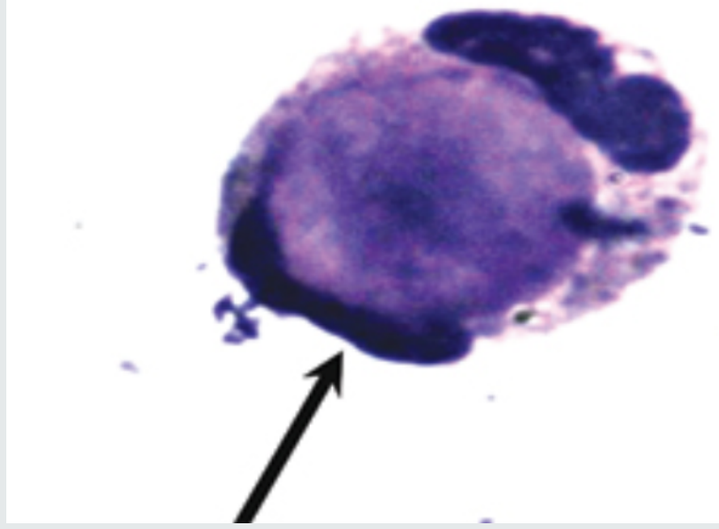
- Systemic (fatigue, malaise, fever) 95%
- Musculoskeletal 95%
- Cutaneous 80%
- Hematologic 85%
- Neurological 60%
- Cardiopulmonary 60%
- Kidney 30–50%
- Gastrointestinal 40%
- Thrombosis 15%
- Ocular 15%
- Vasculitis 5%

Adapted from Harrison's Principle of Internal Medicine 19th edition

American College of Rheumatology criteria for the diagnosis of lupus

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

1. Malar rash
2. Discoid rash
3. Photosensitivity
4. Oral ulcers
5. Nonerosive arthritis
6. Pleuropericarditis
7. Renal disease (proteinuria and/or ce
8. Neurologic disorder (seizures or psy
   precipitating circumstances)
9. Hematologic disorder (hemolytic an
   lymphopenia, thrombocytopenia)
10. Positive
    anti-Sm
11. Positive fluorescent antinuclear antibody test



Typical single LE cell consisting of a neutrophil with flattened nucleus engulfing a central paler homogenous mass.

Sensitivity 86% and specificity 93%, 4/11 item

Systemic Lupus International Collaborating Clinics Classification Criteria for SLE

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

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

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
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DOI 10.1002/art.40930

SPECIAL ARTICLE

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

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
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
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid 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
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

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

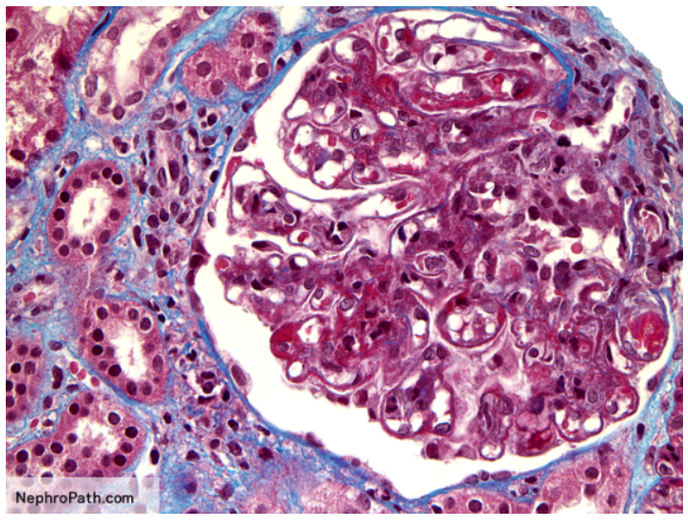
	ACR 1997 criteria	SLICC 2012 criteria	EULAR/ACR 2019 criteria
Derivation			
Sensitivity (95% CI)	0.85 (0.81–0.88)	0.97 (0.95–0.98)	0.98 (0.97–0.99)
Specificity (95% CI)	0.95 (0.93–0.97)	0.90 (0.87–0.92)	0.96 (0.95–0.98)
Combined (95% CI)	1.80 (1.76–1.83)	1.87 (1.84–1.90)	1.94 (1.92–1.96)
Validation	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

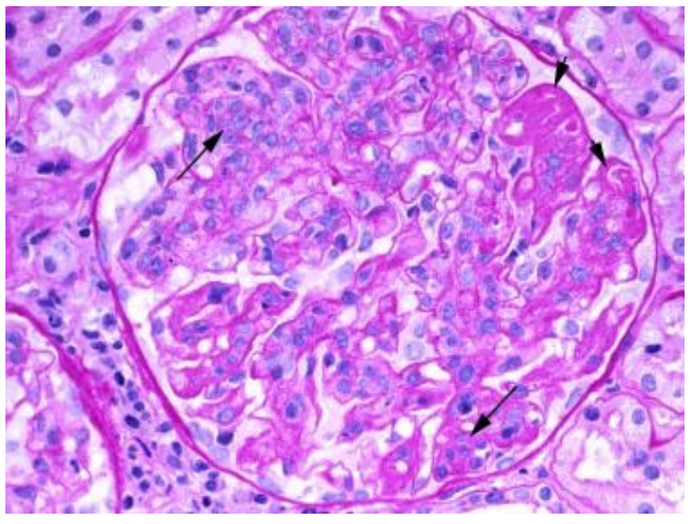
* ACR = American College of Rheumatology; SLICC = Systemic Lupus International Collaborating Clinics; EULAR = European League Against Rheumatism; 95% CI = 95% confidence interval.

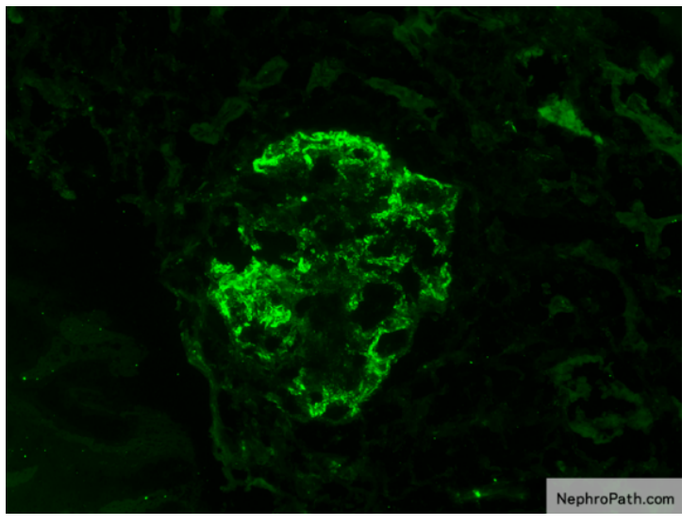
Arthritis & Rheumatology 2019, 71: 1400–12.

2012 American College of Rheumatology criteria for lupus nephritis

- Spot urine protein/creatinine ratio >0.5
- "Active urinary sediment" (5 RBCs/HPF, 5 WBCs/HPF in the absence of infection, or cellular casts limited to RBC or WBC casts)

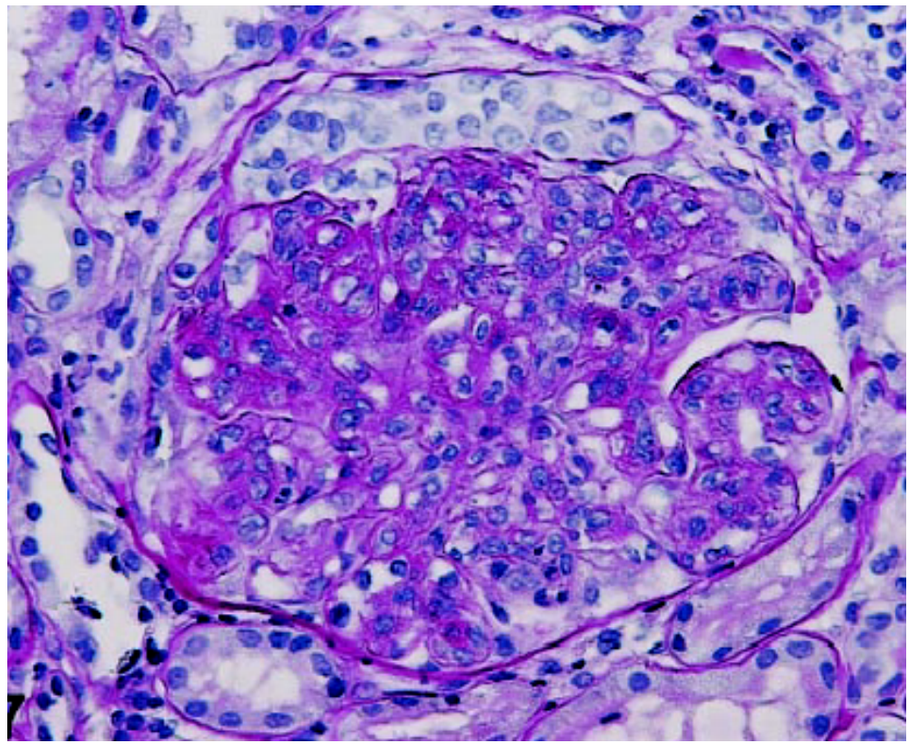






2019 American College of Rheumatology criteria for lupus nephritis

- 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.

Pathogenesis of 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

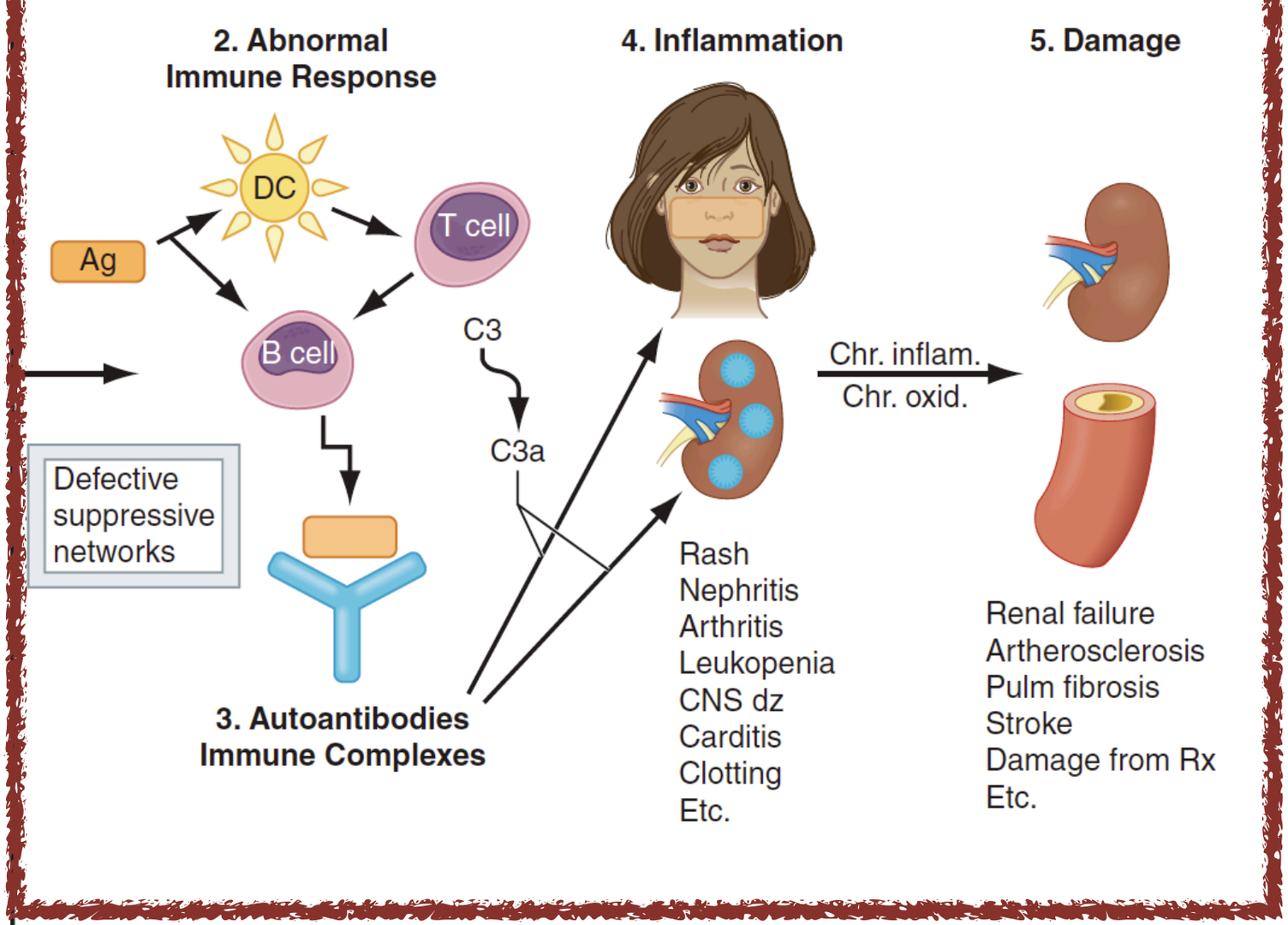
ENVIRONMENT/MICROENVIRONMENT

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

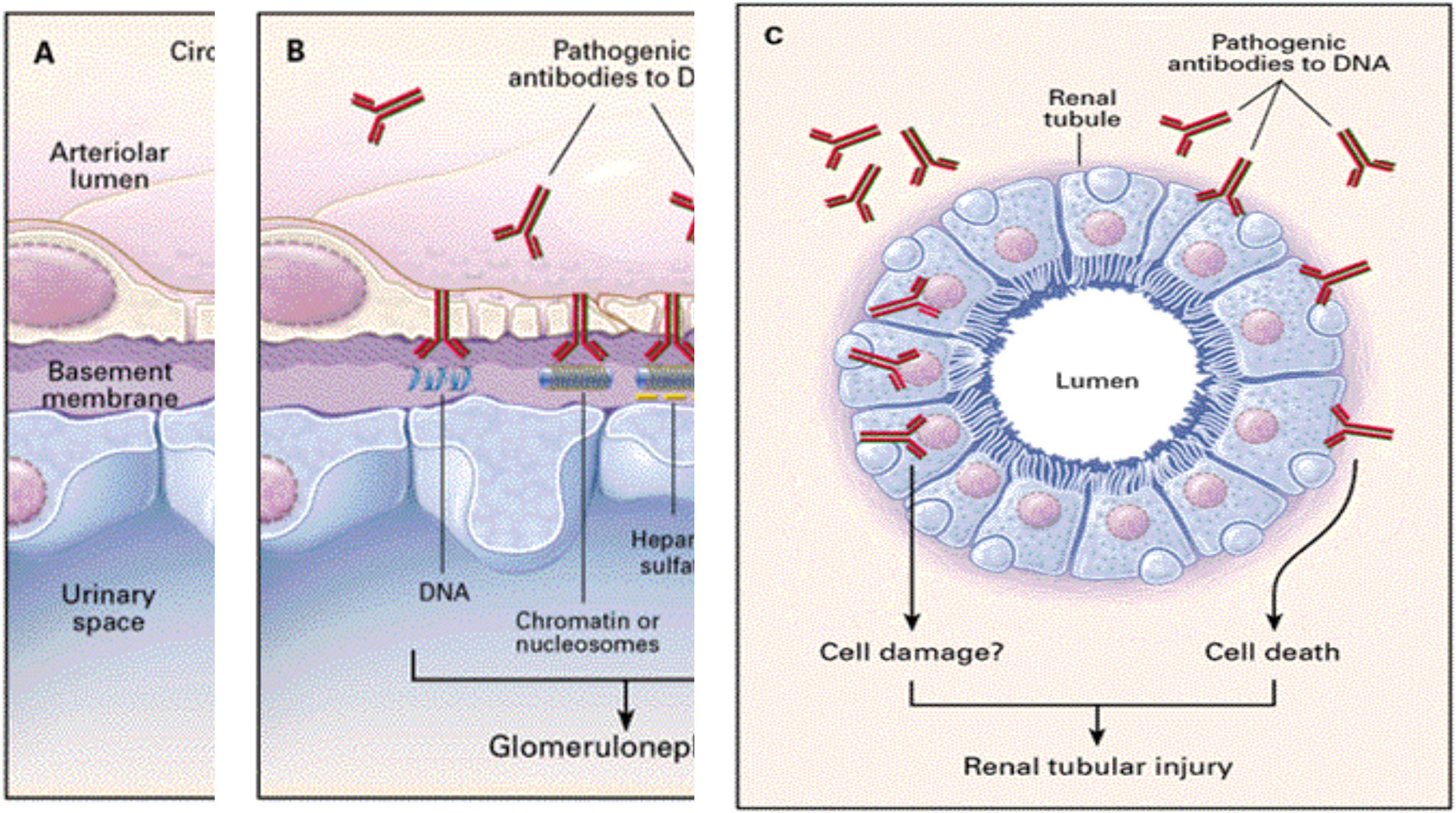


Harrison's Principle of Internal Medicine 20th edition

Lupus nephritis

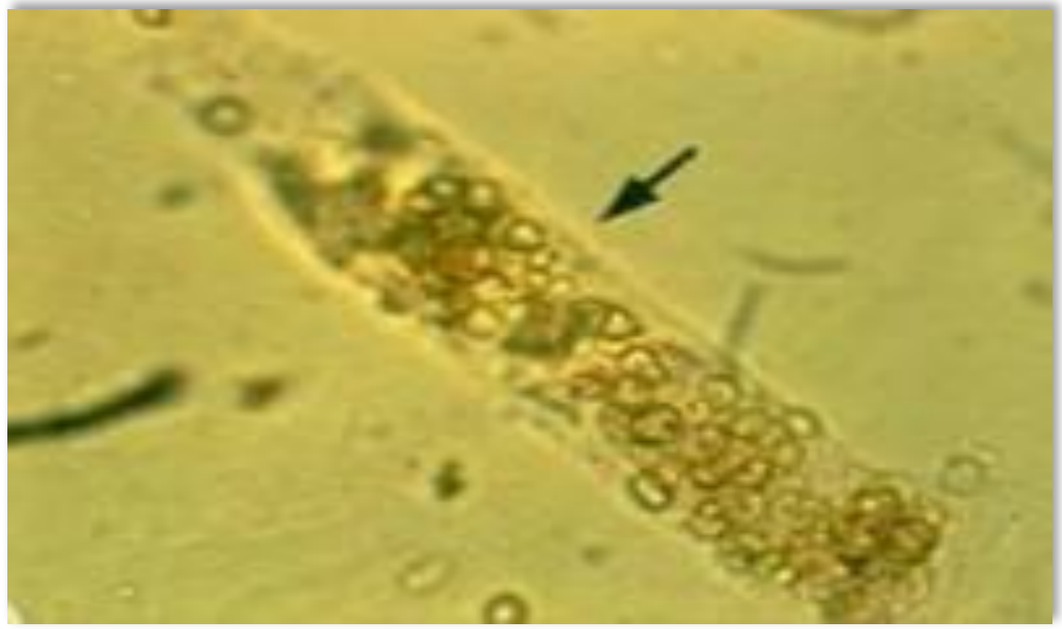
Classic Chronic Immune Complex–Induced Glomerulonephritis

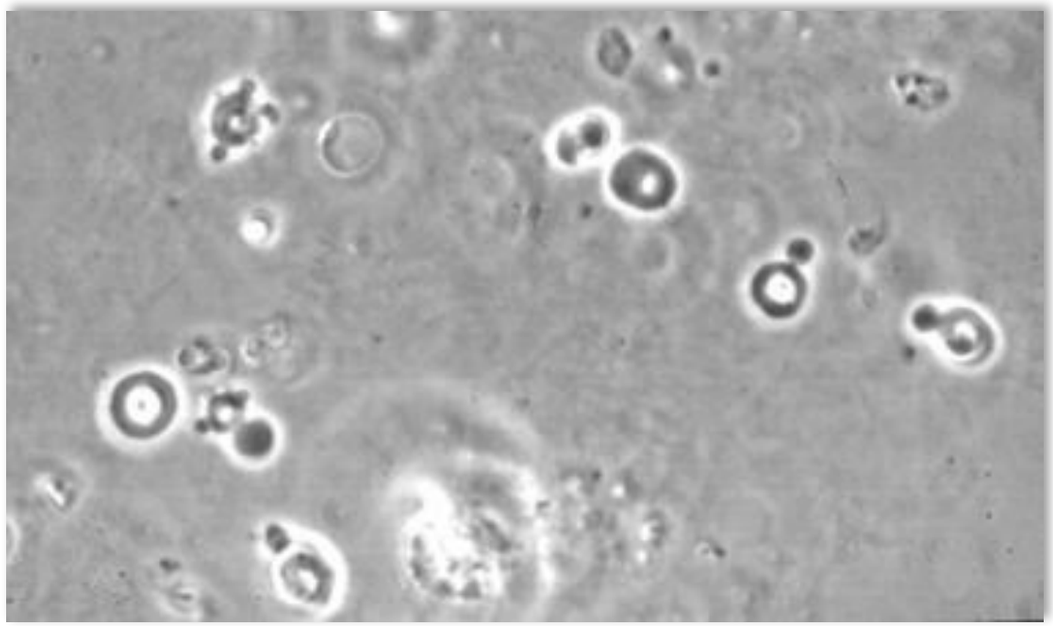
Mechanisms of renal damages



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 antibody titer
- Kidney biopsy

ACR Guidelines for Indication for Kidney biopsy

- Increasing serum Cr without compelling alternative causes
- Confirmed proteinuria >1.0 g/24 hrs
- At least 2 tests done within a short period of time:
  - Proteinuria ≥0.5 g/24 hrs plus hematuria, defined as ≥ 5 RBCs/HPF
  - Proteinuria ≥ 0.5 g/24 hours plus cellular casts

level C evidence

ACR Guidelines for Lupus Nephritis . Arthritis Care & Research; 2012, 797–808

Kidney biopsy

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

Renal Pathology/Renal Classification

ISN/RPS 2003 classification

Class	% involved glomeruli	Pathology of each glomerulus	Activity and chronicity
I	Minimal mesangial LN (normal LM and immune-complex deposit in IF)		
II	Mesangial proliferation		
III – focal	< 50% of total glom	S=segment G=global	A=active C=chronic
IV - diffuse	> 50% of total glom	S=segment G=global	A=active C=chronic
V	Membranous		
VI	Diffuse glomerulosclerosis		

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

Weening J. J., et al. Journal of the American Society of Nephrology. 2004; 241–250.

Proposed modified NIH lupus nephritis activity and chronicity scoring system

Modified NIH activity index	Definition	Score
Endocapillary hypercellularity	Endocapillary hypercellularity in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
[illegible]	[illegible]	[illegible]
Fibrinoid necrosis	Fibrinoid necrosis in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	(0–3) × 2
Hyaline deposits	Wire loop lesions and/or hyaline thrombi in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Cellular/fibrocellular crescents	Cellular and/or fibrocellular crescents in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	(0–3) × 2
Interstitial inflammation	Interstitial leukocytes in <25% (1+), 25%–50% (2+), or >50% (3+) in the cortex	0–3
Total		***0–24***

Modified NIH chronicity index	Definition	Score
Total glomerulosclerosis score	Global and/or segmental sclerosis in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Fibrous crescents	Fibrous crescents in <25% (1+), 25%–50% (2+), or >50% (3+) of glomeruli	0–3
Tubular atrophy	Tubular atrophy in <25% (1+), 25%–50% (2+), or >50% (3+) of the cortical tubules	0–3
Interstitial fibrosis	Interstitial fibrosis in <25% (1+), 25%–50% (2+), or >50% (3+) in the cortex	0–3
Total		***0–12***

NIH, National Institutes of Health.

Fibrinoid necrosis	(0–6)
Cellular crescents	(0–6)

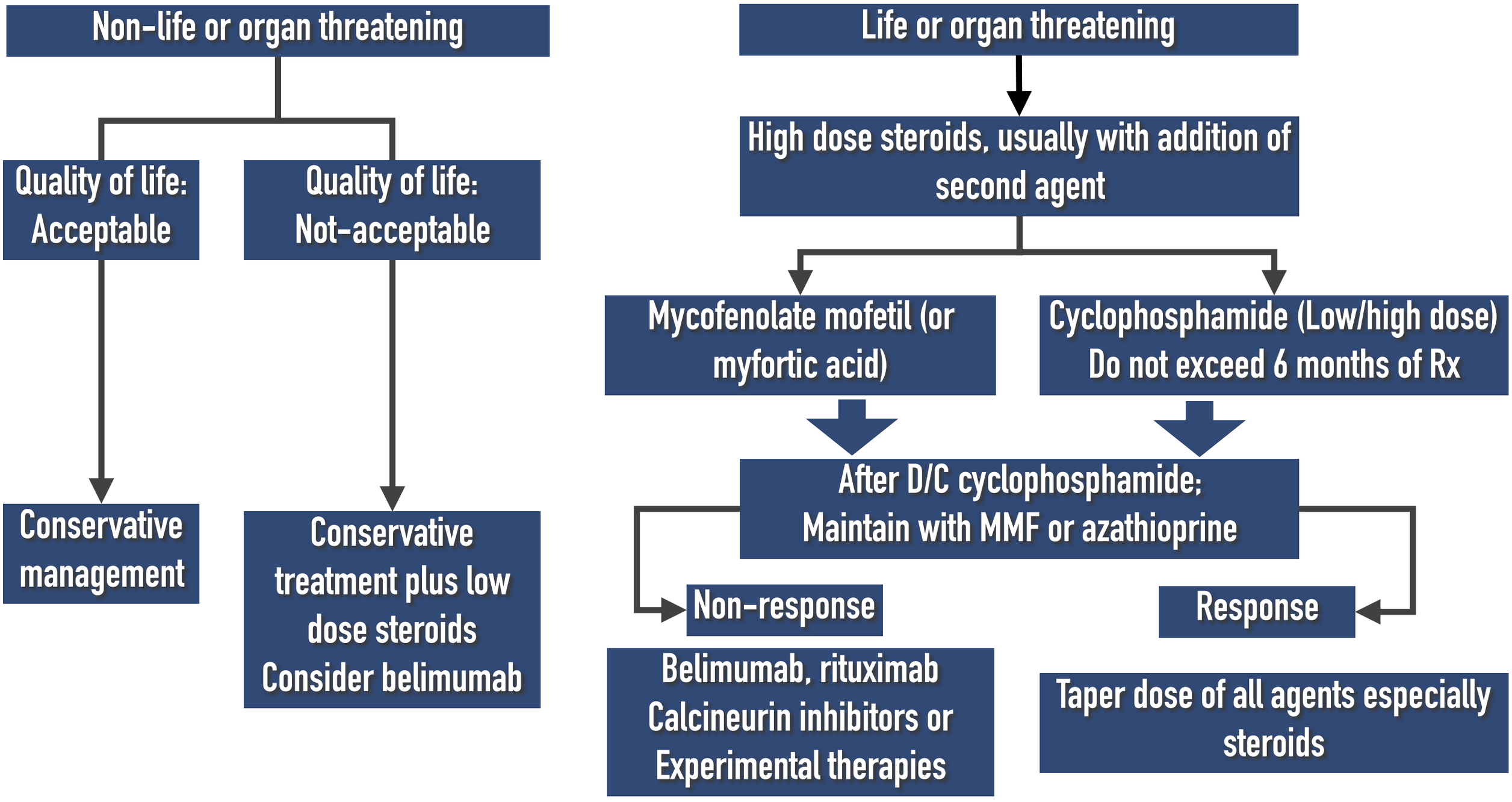
Bajema IM, et al Kidney Int 2018; 93(4): 789–96.

Clinico-pathological Correlation

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%

Initial therapy of SLE



Harrison's Principle of Internal Medicine 20th edition

Treatment of lupus nephritis

- Class I
  - Treated as dictated by the extrarenal clinical manifestations of lupus (2D)
- Class II
  - Proteinuria <1 g/d as dictated by the extrarenal clinical manifestations of lupus (2D)
  - Proteinuria >3 g/d be treated with corticosteroids or CNIs as described for MCD (2D)

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

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.

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

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.

KDIGO guideline: Class III–IV: initial therapy

- Corticosteroids (1A), combined with
- Cyclophosphamide (1B)
- OR
- Corticosteroids (1A), combined with MMF (1B)

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

ACR Guidelines for induction Rx in LN class III–IV

MMF 2–3 gm a day for 6 mo (preferred to CYC in AA and Hispanics)
PLUS
GC IV pulse x 3 days then prednisone 0.5–1.0
MKD tapered after a few weeks to lowest effective dose (1 MKD if crescents seen)

CYC

PLUS
GC IV pulse x 3 days then prednisone 0.5–1.0
MKD tapered after a few weeks to lowest effective dose (1 MKD if crescents seen)

- High dose CYC
  500–1000 mg/m2 BSA IV q 1 mo x 6
- Low dose CYC
  500 mg IV q 2 wks x 6 followed by maintenance with oral MMF or AZA (regimen for white with European background))

Adaped form ACR Guidelines for Lupus Nephritis . Arthritis Care & Research; 2012, 797—808

2019 update of the EULAR recommendations for the management of SLE

Renal disease	Level of agreement
Mycophenolate (1a/A) or low-dose intravenous cyclophosphamide (2a/b) are recommended as initial treatment, as they have the best efficacy/ toxicity ratio	9.85
In patients at high risk for renal failure (reduced GFR, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/ interstitial fibrosis], similar regimens may be considered but high-dose intravenous cyclophosphamide can also be used (1b/A).	9.45

Fanouriakis A, et al. Ann Rheum Dis. 2019; 78(6):736-745.

2019 update of the EULAR recommendations for the management of SLE

Renal disease	Level of agreement
Mycophenolate may be combined with low dose of a calcineurin inhibitor in severe nephrotic syndrome (2b/C) or incomplete renal response (4/C), in the absence of uncontrolled hypertension, high chronicity index at kidney biopsy and/or reduced GFR	9.50

Fanouriakis A, et al. Ann Rheum Dis. 2019; 78(6):736–745.

Definitions of response to therapy

- Complete response
  - Return of SCr to previous baseline, plus a decline in the uPCR to <500 mg/g
- Partial response
  - Stabilization (±25%), or improvement of SCr, but not to normal, plus a ≥50% decrease in uPCR
  - If there was nephrotic-range proteinuria, improvement requires a ≥ 50% reduction in uPCR, and a uPCR <3000 mg/g
- Deterioration
  - A sustained 25% increase in SCr is widely used but has not been validated

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

KDIGO guideline: Class III–IV: maintenance therapy

- AZA (1.5–2.5 mg/kg/d) or MMF (1–2 g/d in divided doses), and low-dose prednisolone (<10 mg/d) (1B)
- CNIs with low-dose corticosteroids be used for maintenance therapy in patients who are intolerant of MMF and azathioprine (2C)
- Maintenance therapy be continued for at least 1 year before consideration is given to tapering the immunosuppression (2D)

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

2019 update of the EULAR recommendations for the management of SLE

Renal disease	Level of agreement
For maintenance therapy, mycophenolate (1a/A) or azathioprine (1a/A) should be used.	9.75
In cases with stable/improved renal function but incomplete renal response (persistent proteinuria >0.8–1 g/24 hours after at least 1 year of immunosuppressive treatment), repeat biopsy can distinguish chronic from active kidney lesions (4/C).	9.85

Fanouriakis A, et al. Ann Rheum Dis. 2019; 78(6):736–745.

Class V: Membranous lupus nephritis

- 10–20 % of lupus nephritis
- Proteinuria
- Nephrotic syndrome: hypercoagulability and hyperlipidemia

Immunosuppressive therapy

- Persistent severe and symptomatic nephrotic syndrome
- Increased or rising serum creatinine
- Mixed membranous and proliferative lesions on biopsy

Sloan RP; et al. J Am Soc Nephrol 1996;7(2):299–305

Class V: Membranous lupus nephritis

- Normal kidney function, and non–nephrotic-range proteinuria be treated with anti-proteinuric and antihypertensive medications (2D)
- Persistent nephrotic proteinuria be treated with corticosteroids plus:
  - Cyclophosphamide (2C)
  - CNI (2C)
  - MMF (2D)
  - Azathioprine (2D)

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

General treatment of LN

- All patients with any class LN
- Hydroxychloroquine (maximum daily dose of 6–6.5 mg/kg ideal body weight) (2C) or Level C

KDIGO. Kidney International Supplements (2012) 2, 143–153
ACR Guidelines for Lupus Nephritis . Arthritis Care & Research; 2012, 797–808

None specific treatments

General therapy	Renal replacement therapies
Anticoagulant (massive proteinuria and serum albumin <2.0 g/dL)	
Dyslipidemia (LDL<100 mg/dL): Statin	Dialysis
Hypertension (BP<130/80 mmHg): ACEI/ ARB	Renal transplantation
Proteinuria (<0.5–1 g/day)	

Beyond Disease Activity: Hydroxychloroquine

- Reduced damage accrual (renal, skin)
- Decrease in flares
- Improved survival
- Improved lipid profiles (TC, LDL)
- Less neonatal lupus
- Less the risk of clotting events in SLE

LUMINA (Multiethnic longitudinal cohort, n=635)
Guillermo J Arthritis Care Res 2010
Alarcon GS Ann Rheum Dis 2007

Resistant lupus nephritis

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

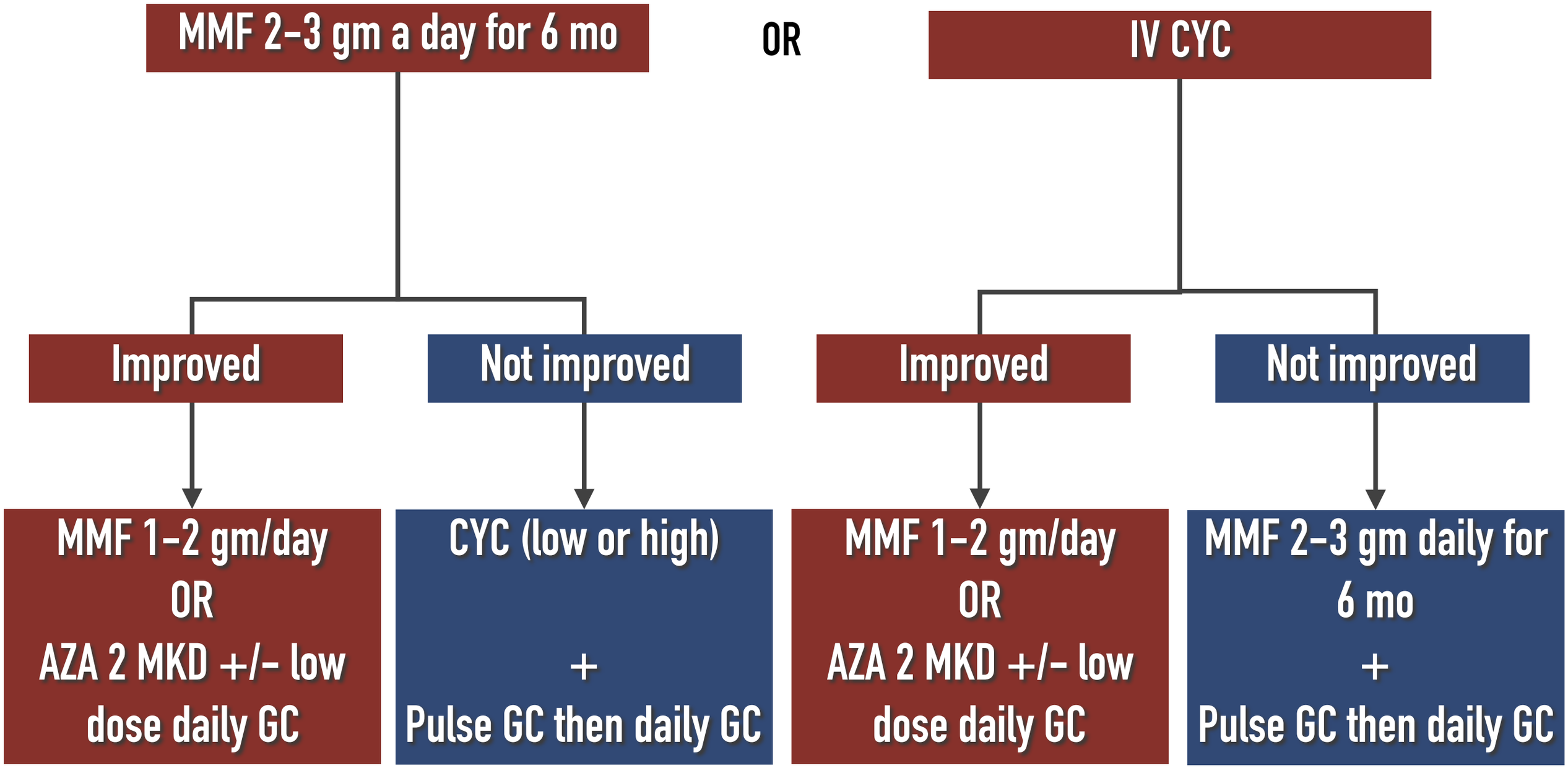
KDIGO Clinical Practice Guideline for LN Class III–IV

- 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 (2D)

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

ACR Guidelines for induction Rx in LN class III–IV



Adapted from ACR Guidelines for Lupus Nephritis . Arthritis Care & Research; 2012, 797—808

KDIGO: Treatment of resistant disease

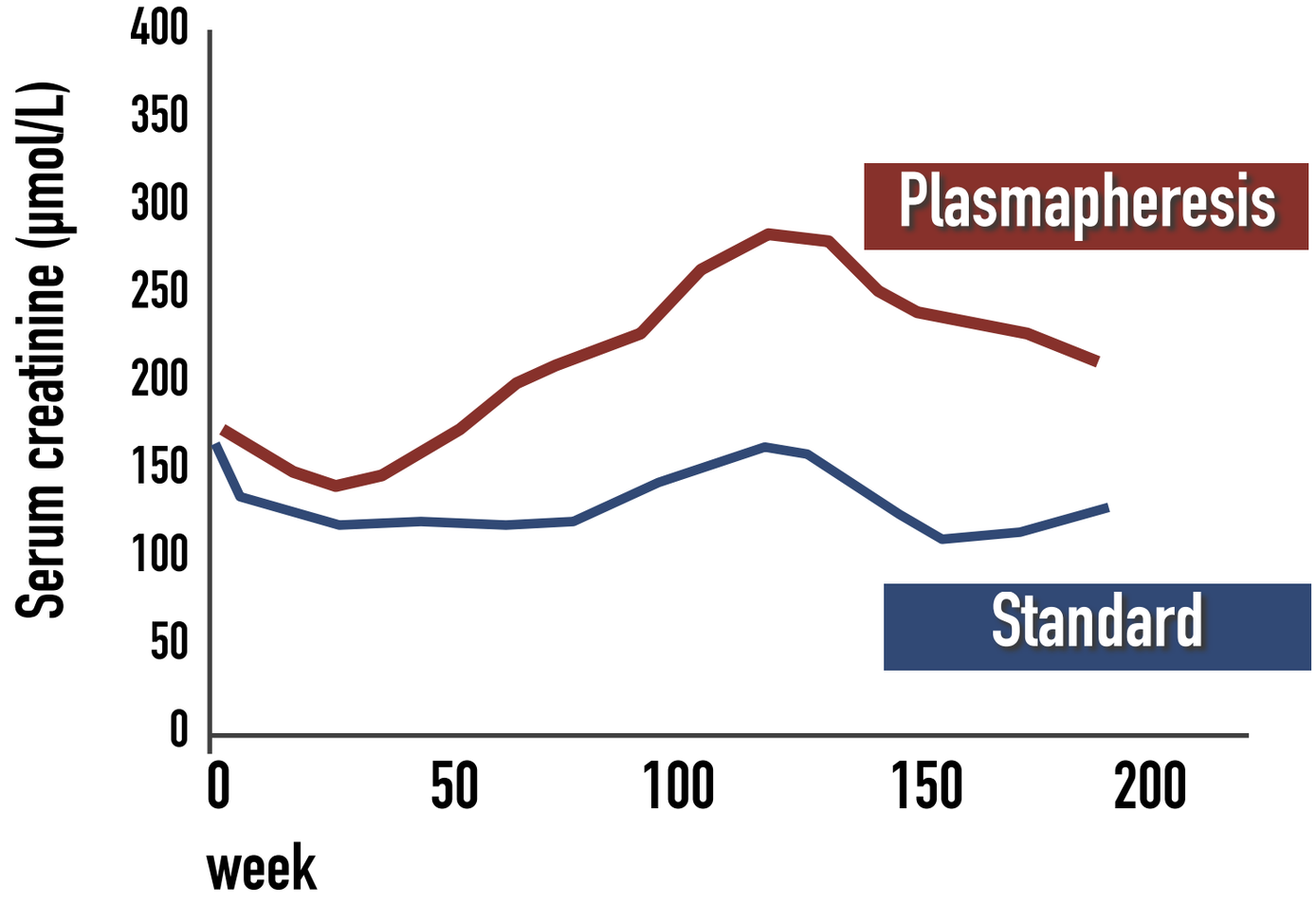
- Performing a repeat kidney biopsy to distinguish active LN from scarring (Not Graded)
- Non-responders may be considered for treatment with
  - Rituximab
  - Immunoglobulin
  - CNIs (2D)

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

Plasmapheresis

Plasmapheresis
+Cyclophosphamide

- **Prospective controlled trial :**
- **More rapid decline in circulating autoantibody levels**
- **No advantage in addition**



Role only in SLE with TTP

- **Severe antiphospholipid syndrome**
- **Severe crescentic LN who require dialysis especially those with concomitant ANCA**

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

Relapse lupus nephritis

KDIGO: Relapse of LN

- Treated with the initial therapy followed by the maintenance therapy that was effective in inducing the original remission (2B)

- Risk for excessive lifetime cyclophosphamide exposure: a non–cyclophosphamide–based initial regimen: MMF (2B)

Lifetime maximum of 36 g cyclophosphamide in patients with systemic lupus

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

Systemic lupus and pregnancy

- Delay pregnancy until a complete remission of LN has been achieved (2D)
- Cyclophosphamide, MMF, ACE-I, and ARBs not be used during pregnancy (1A)
- Hydroxychloroquine continued during pregnancy (2B)

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

Systemic lupus and pregnancy

- Treated with MMF be switched to azathioprine (1B)
- Relapse during pregnancy, treated with corticosteroids and, depending on the severity of the relapse, azathioprine (1B)
- If pregnant patients are receiving corticosteroids or azathioprine, these drugs should not be tapered during pregnancy or for at least 3 months after delivery (2D)
- low-dose aspirin during pregnancy to decrease the risk of fetal loss (2C)

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

Further investigation and Monitoring

- Clinical monitoring:
  - Systemic symptoms and signs
  - BUN, serum creatinine
  - CBC
  - Urinalysis
  - Spot or 24 hr urine protein
  - Serum albumin, cholesterol
  - Infections: CXR, stool examination
- Immunologic monitoring:
  - Complements: CH50, C3, C4
  - Anti-ds DNA antibody titer
  - Kidney biopsy

Delay in treatment decisions constitutes an important risk factor for ESRD

Prognostic factors	RR
Nephritic symptoms > 6 mo	9.3
Diffuse proliferative GN	8.9
Serum creatinine > 1.5 mg/dL	5.6
Tubular atrophy	3.1

Faurshou M, et al. J Rheumatol 2006; 33, 1563

Poor prognostic factors

- Demographic
  - Black race
  - Asian race
  - Male gender
  - Age < 24 years
  - Non-compliant patients
- Clinical and Laboratory
  - Failure to achieve to renal remission
  - Multiple relapses of nephritis
  - Renal insufficiency (SCr > 1.2)
  - Hypertension
  - Anemia
  - Low complement level

Austin HA et al. Kidney Int 1994;45(2):544-50
Contreras G, et al. Lupus. 2005;14(11):890-5

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. AJKD 1995

DEPARTMENT OF MEDICINE
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NEPHROLOGY
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