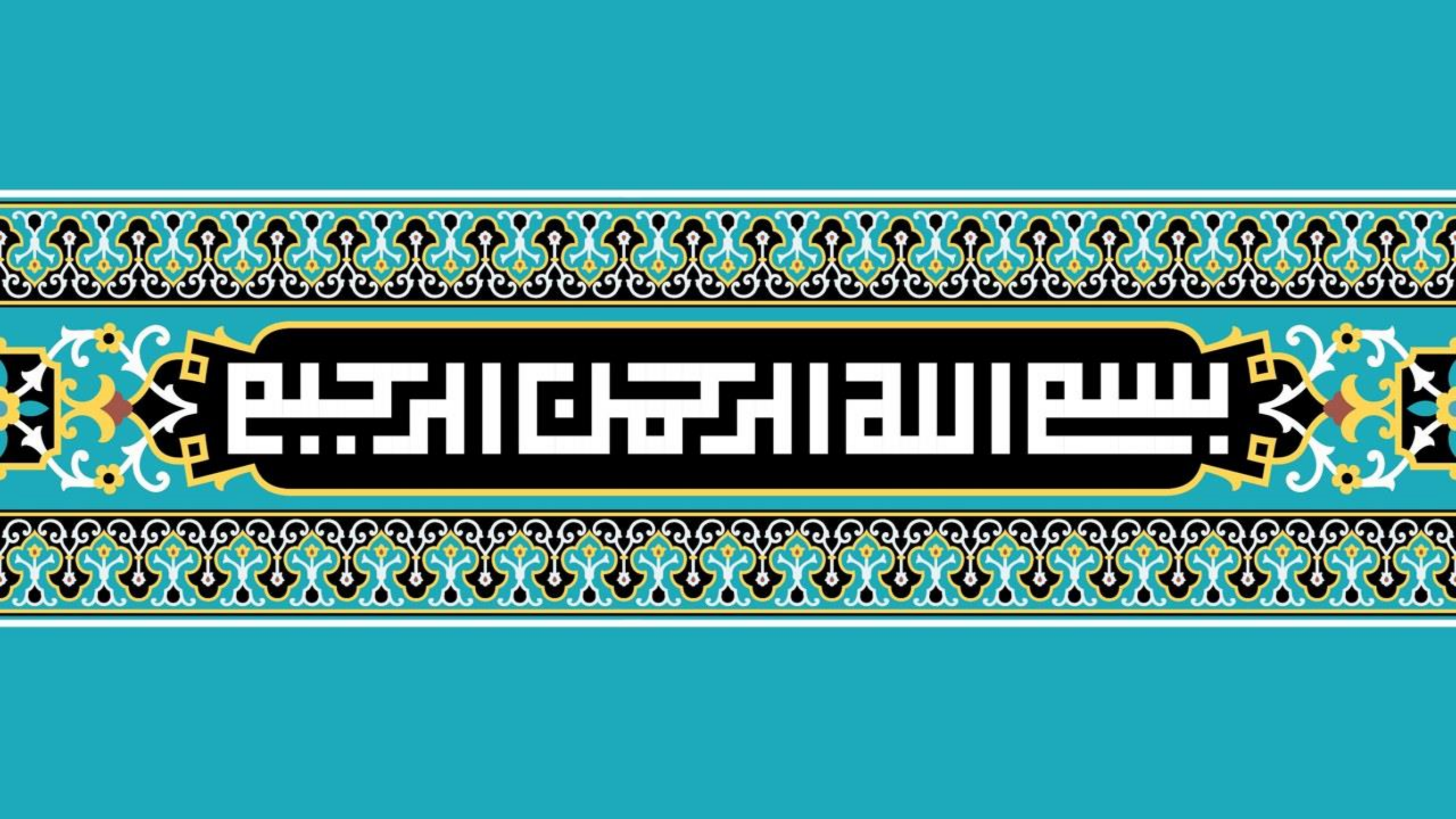
بسم الله الرحمن الرحيم

Lupus nephritis diagnosis

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Rheumatologist

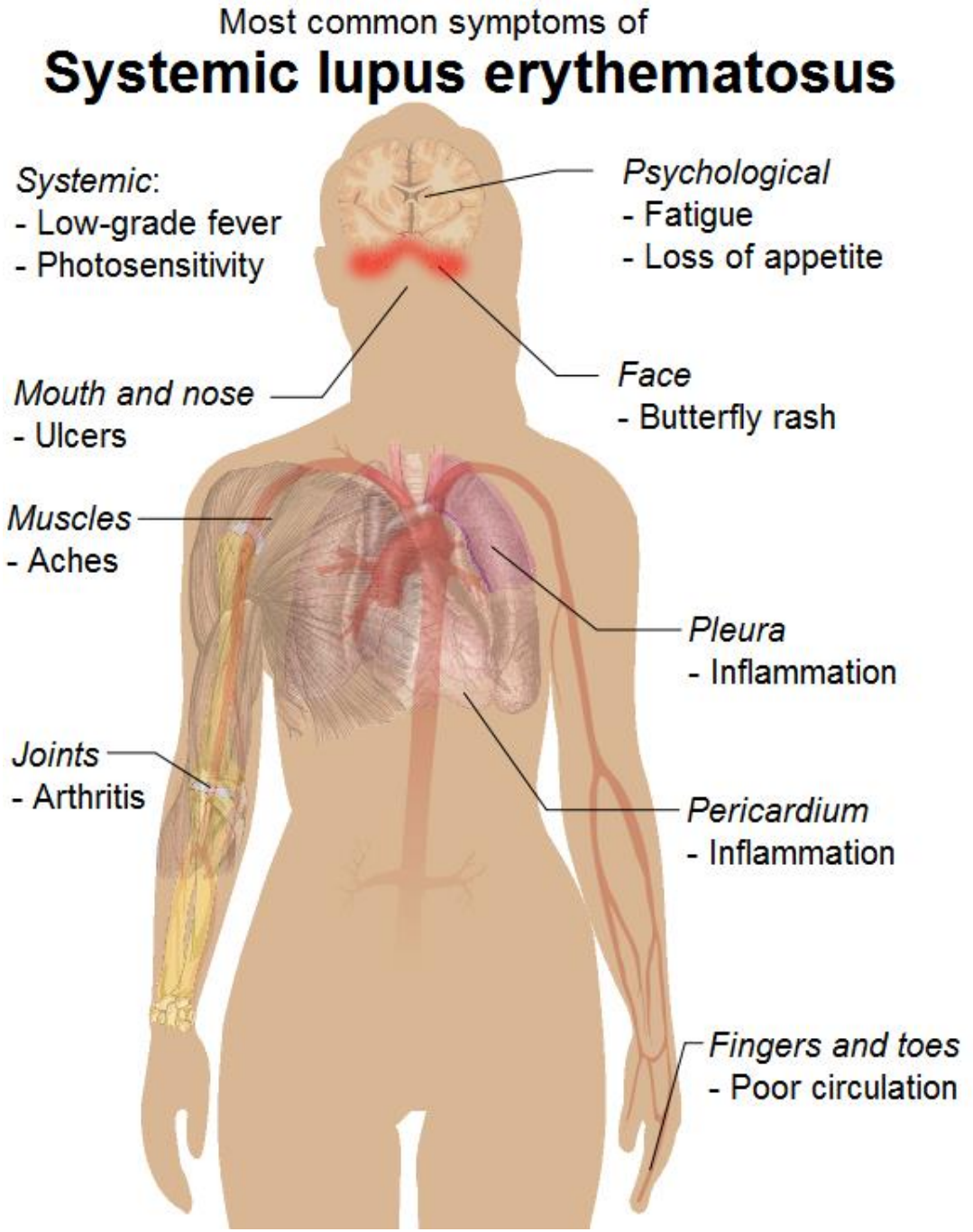
GUMS

Jan 2024

SLE

- a chronic autoimmune disease of unknown cause
- It can affect virtually any organ of the body
- Immunologic abnormalities, especially the production of ANA >95%
- clinical features :mild joint & skin involvement to life-threatening kidney, hematologic, or CNS involvement
- The clinical heterogeneity of SLE & the lack of pathognomonic features or tests pose a diagnostic challenge for the clinician.

Uptodate Oct 2023.



Epidemiology of SLE

- Geography & race :

- prevalence / the frequency / severity / laboratory manifestation

- **Sex** : F/M : 3/1 in children, childbearing 7:1 to 15:1 , post-menopausal 8:1 (estrogen effect, X chromosome)

- men tend to have worse outcomes

- **Age at onset** 65%: onset between the ages of 16 - 55

Uptodate Oct 2023.

Epidemiology

- In unselected patients with SLE, **25–50% have signs or symptoms of kidney disease at SLE onset**, and as many as **60% of adult patients with SLE develop these renal signs or symptoms during the disease course**

- Most cohort : **higher LN in male** than in female patients (27–75% versus 16–52%, respectively), the male-to-female ratio ranges from **1.1:1 to 1.7:1** & does not vary with ethnicity

Factors affecting disease outcome

- African American individuals are more likely to have anti-Sm, anti-RNP, DLE, proteinuria, psychosis, & serositis
- Social factor: poorer in those with less education (poor compliance ?)
- poorer in lower socioeconomic status (inadequate access to medical care ?)

- children : symptomatically more severe ,high incidence of malar rashes, nephritis(2 times) pericarditis, hepatosplenomegaly, & hematologic abnormalities

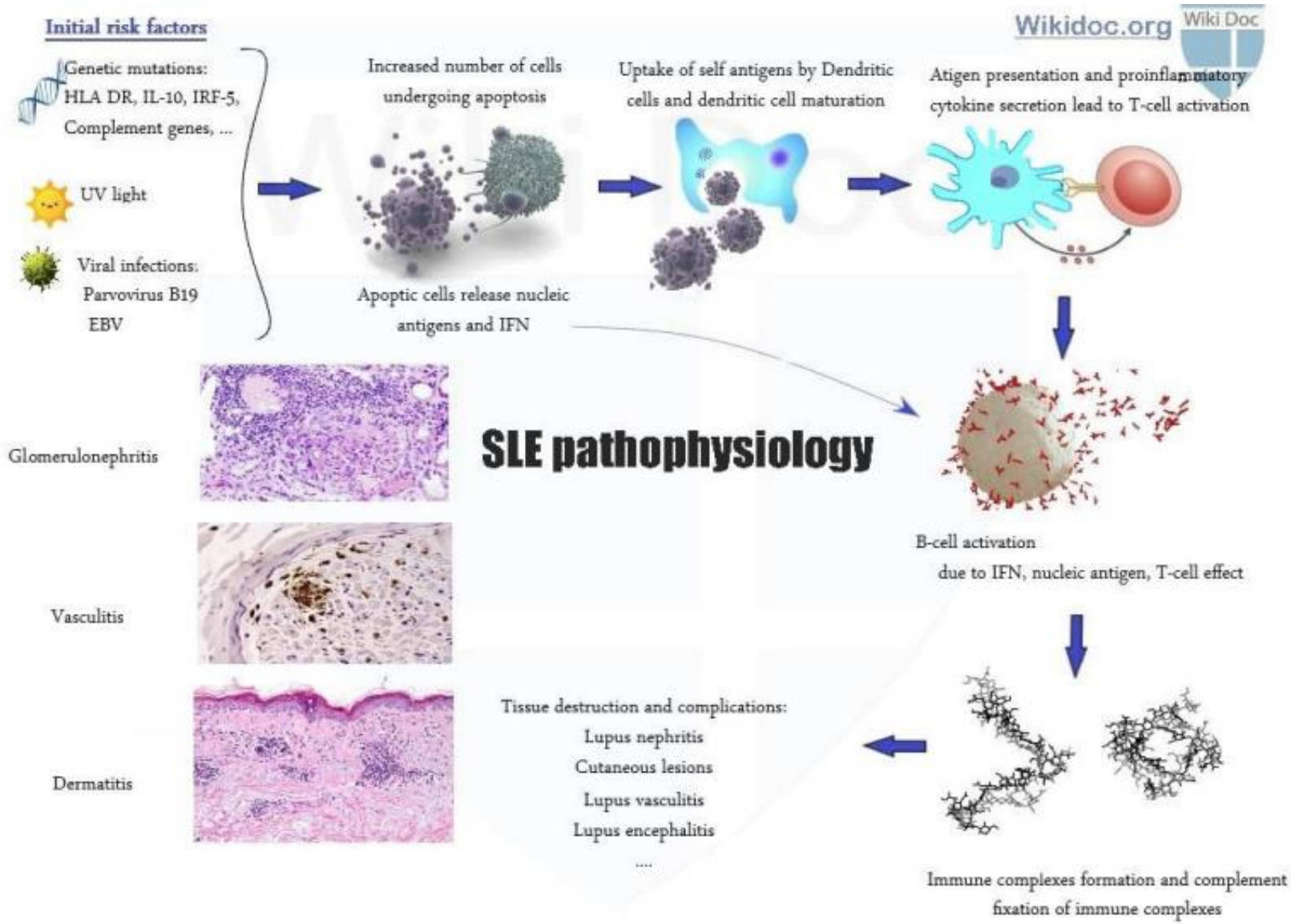
Uptodate Oct 2023.

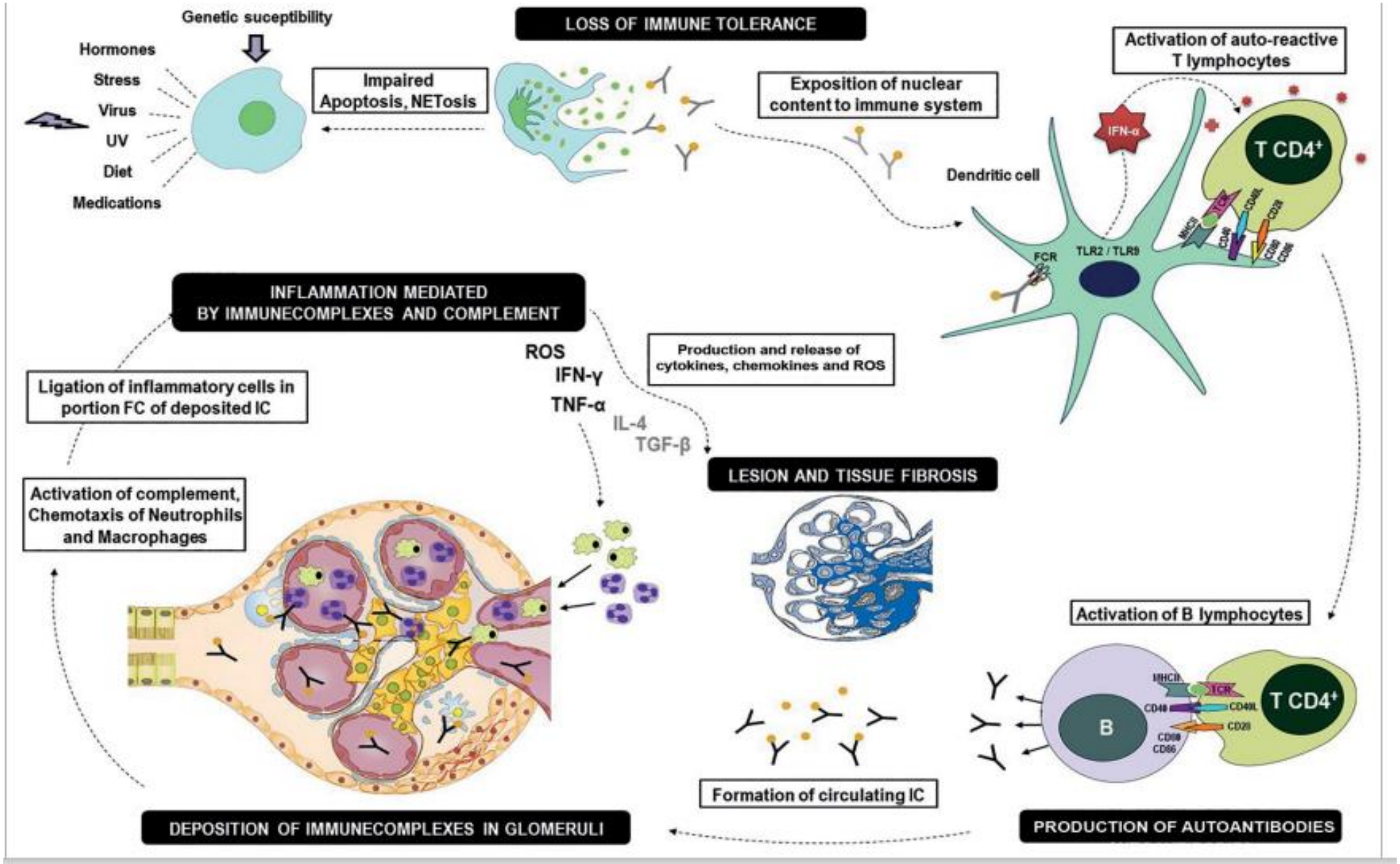
Lupus nephritis(LN)- epidemiology

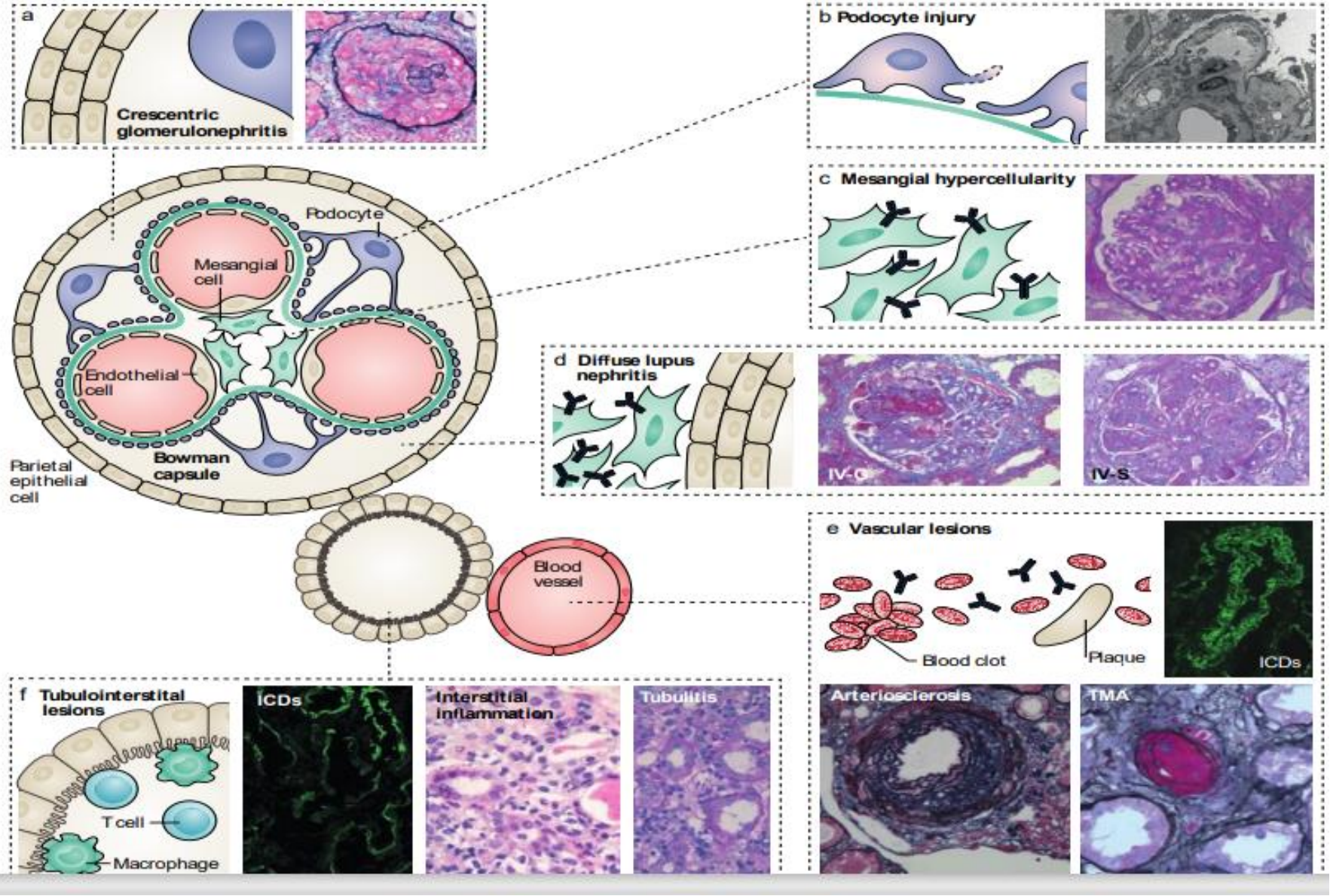
- **typically early** in the disease course
- **up to 10% of LN will develop ESKD**
- **LN : a threefold increased risk of death.**

- **greater risk for progressive kidney disease** : African or Hispanic ancestry, male sex, pediatric onset, frequent relapses or incomplete remission, & proteinuria >4 g/day at diagnosis

Uptodate Oct 2023.


Initial risk factors
Genetic mutations:
HLA DR, IL-10, IRF-5,
Complement genes, ...
UV light
Viral infections:
Parvovirus B19
EBV
Increased number of cells undergoing apoptosis
Apoptic cells release nucleic antigens and IFN
Uptake of self antigens by Dendritic cells and dendritic cell maturation
Atigen presentation and proinflammatory cytokine secretion lead to T-cell activation
Wikidoc.org
Wiki Doc
SLE pathophysiology
Glomerulonephritis
Vasculitis
Dermatitis
B-cell activation
due to IFN, nucleic antigen, T-cell effect
Tissue destruction and complications:
Lupus nephritis
Cutaneous lesions
Lupus vasculitis
Lupus encephalitis
....
Immune complexes formation and complement fixation of immune complexes


Genetic suceptibility
Hormones
Stress
Virus
UV
Diet
Medications
LOSS OF IMMUNE TOLERANCE
Impaired Apoptosis, NETosis
Exposition of nuclear content to immune system
Activation of auto-reactive T lymphocytes
IFN-α
T CD4+
Dendritic cell
FCR
TLR2 / TLR9
INFLAMMATION MEDIATED BY IMMUNECOMPLEXES AND COMPLEMENT
Production and release of cytokines, chemokines and ROS
ROS
IFN-γ
TNF-α
IL-4
TGF-β
Ligation of inflammatory cells in portion FC of deposited IC
LESION AND TISSUE FIBROSIS
Activation of complement, Chemotaxis of Neutrophils and Macrophages
Activation of B lymphocytes
B
T CD4+
Formation of circulating IC
DEPOSITION OF IMMUNECOMPLEXES IN GLOMERULI
PRODUCTION OF AUTOANTIBODIES


a
Crescentric glomerulonephritis
b Podocyte injury
c Mesangial hypercellularity
Podocyte
Mesangial cell
Endothelial cell
Bowman capsule
Parietal epithelial cell
d Diffuse lupus nephritis
IV-G
IV-S
e Vascular lesions
Blood clot
Plaque
ICDs
Blood vessel
f Tubulointerstitial lesions
T cell
Macrophage
ICDs
Interstitial inflammation
Tubulitis
Arteriosclerosis
TMA

LN - Pathogenesis

- **A classic form of IC GN**

There is a variety of mechanisms

- the expression of genes leading to neutrophil activation
- increased expression of genes for IFN & other pro-inflammatory mediators in myeloid & other immune cell populations
- release of neutrophil extracellular traps (NETs), & complement activation
- The pattern of glomerular injury is generally related to the site of formation of the immune deposits

Diagnosis of SLE

- based on clinical & laboratory findings after excluding alternative diagnoses

- In the absence of SLE diagnostic criteria, SLE classification criteria are often used by clinicians as guidance to help identify some of the salient clinical features when making the diagnosis.

Definite SLE

- excluding alternative Dx, diagnose SLE as:
- 1997 ACR criteria,
- the ACR criteria require that a patient satisfy at least 4 of 11 criteria

- the 2012 SLICC criteria ,

- the 2019 EULAR/ACR criteria

Uptodate Oct 2023.

2012 SLICC criteria

- mucocutaneous: Malar rash, Photosensitivity, Discoid rash, Oral ulcers
- Arthritis
- Serositis
- Renal disorder
- Neurologic disorder
- Hematologic disorder
- ANA
- Immunologic disorders(Anti-DNA , Anti-Sm , APL , low complement)
- It requires either that a patient satisfy at least 4 of 17 criteria, including at least 1 clinical and one immunologic criteria

A biopsy-proven lupus nephritis in the presence of ANAs or anti-dsDNA antibodies

Uptodate Oct 2023.

2019 EULAR/ACR classification criteria for SLE

- **Entry criterion:** ANA at a titer of **≥1:80**
- **At least 1 clinical criterion required to classify SLE.**

Clinical domains and criteria (point)	
Constitutional : Fever 2	
Hematologic : Leukopenia 3, thrombocytopenia 4, Autoimmune hemolysis 4	
Neuropsychiatric : Delirium 2, Psychosis 3, Seizure 5	
Mucocutaneous: alopecia 2, Oral ulcers 2, Subacute cutaneous or DLE 4, malar rash 6	
Serosal : Pleuropericardial effusion 5, Acute pericarditis 6	
Musculoskeletal : Joint involvement 6	6
Renal: Proteinuria >0.5 g per 24 hours(4), Renal Bx Class II or V LN (8), Renal Bx Class III or IV LN(10)	
Immunology domains and criteria	
Antiphospholipid antibodies : ACL **or** anti-beta-2GP1 **or** LA (2)	
Complement proteins : Low C3 **or** low C4 (3), Low C3 **and** low C4 (4)	
SLE-specific antibodies : Anti-dsDNA antibody$^{\Delta}$ **or** anti-Smith antibody (6)	
A total score of ≥10 and ≥1 clinical criterion are required to classify SLE.	

2019 EULAR/ACR classification criteria for SLE

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Mucocutaneous: alopecia 2, Oral ulcers 2, Subacute cutaneous or DLE 4, malar rash 6	
Serosal : Pleuropericardial effusion 5, Acute pericarditis 6	
Renal Bx: Class III or IV LN(10)	
Antiphospholipid antibodies : ACL **or** anti-beta-2GP1 **or** LA (2)	
Complement proteins : Low C3 **or** low C4 (3), Low C3 **and** low C4 (4)	
SLE-specific antibodies : Anti-dsDNA antibody$^{\Delta}$ **or** anti-Smith antibody (6)	
A total score of ≥10 and ≥1 clinical criterion are required to classify SLE.	

LN-Clinical Features

- an **abnormal urinalysis** is typically detected with or without an elevated plasma creatinine
- in LN, the most frequently observed abnormality is proteinuria
- **microscopic hematuria with or without red cell casts, kidney function impairment, NS, & HTN**

- **Rare : silent LN**, significant abnormalities only on kidney Bx without any clinical signs
- silent LN often remains clinically silent & is associated with a benign kidney outcome ,**but some patients, progress to overt nephritis**

Uptodate Oct 2023.

Original Article
Yonsei Med J 2020 Nov;61(11):951-957
https://doi.org/10.3349/ymj.2020.61.11.951
Yonsei Medical Journal YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Worse Renal Presentation and Prognosis in Initial-Onset Lupus Nephritis than Early-Onset Lupus Nephritis

- Patients with LN at SLE onset may have more severe renal presentations & worse renal outcomes than those who develop LN within 5 years
- more class IV LN ,impaired renal function ,& higher UPCR (4626.1 mg/g vs. 2410.0 mg/g, at LN diagnosis.
- more renal relapse (46.3% vs. 25.7%, p=0.039)
- more progression to CKD or ESRD

Establishing the diagnosis

- **ideally confirm by a kidney biopsy:**
- Define the nature of kidney involvement, exclude other causes & determine the histopathologic subtype of LN & assess disease activity & chronicity.

- However, as with any other invasive procedure, an individualized **risk-benefit assessment** is required

- **a kidney biopsy in :**

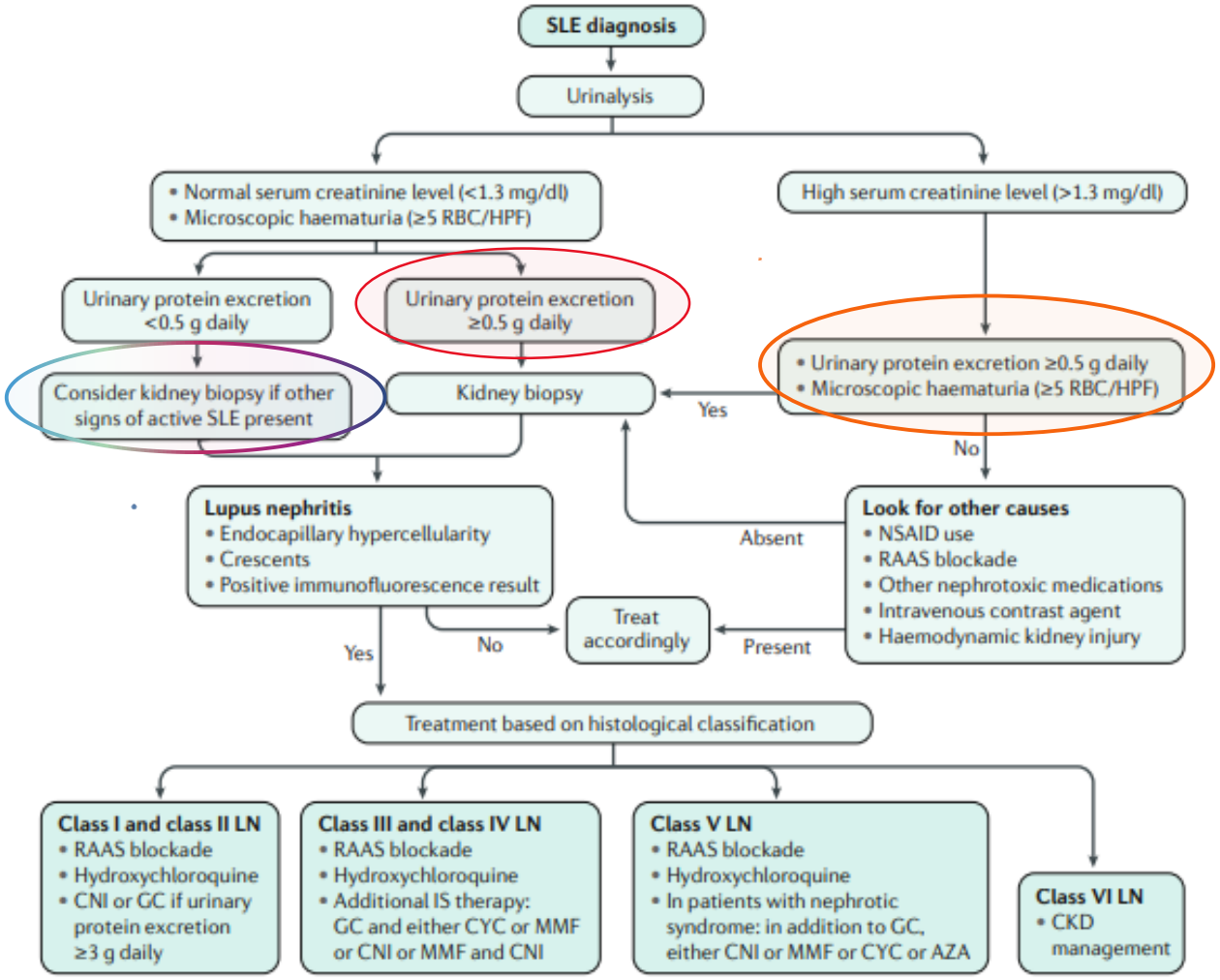
➢ **Urine protein excretion greater than 500 mg/day.**

➢ **An active urinary sediment with persistent hematuria and/or cellular casts.**

➢ **A rising serum creatinine that is not clearly attributable to another mechanism**.

UpToDate 2024

Proposed algorithm for the diagnosis and treatment of LN



NATUrE REvIEwS | DISEASE PRIMERS | Article citation ID: (2020) 6:7

Kidney biopsy :

- Treatment is guided by the histologic subtype (ie, ISN/RPS class, activity & chronicity index)

- Is there entities other than LN?

- NS due to podocytopathy without major IC deposition but with effaced foot processes as seen in minimal change disease

- a thrombotic microangiopathy (TMA)

-predominant tubulointerstitial involvement

UpToDate 2024

Characteristic histopathologic findings

- some time LN may be confused with **other IC-mediated GN**.

highly characteristic histopathologic features of LN:

- Glomerular deposits that stain dominantly for IgG & contain co-deposits of IgA ,IgM, C3, & C1q, the so-called "full house" immunofluorescence pattern
- intense staining for C1q has also been shown to have a similar sensitivity & specificity for LN as the "full house" staining pattern .
- Glomerular deposits simultaneously seen in the mesangial, subendothelial, & subepithelial locations.
- Extraglomerular immune-type deposits within tubular basement membranes, the interstitium, & blood vessels.

UpToDate 2024

Timing of initial biopsy

- promptly (ie, within days to weeks),when there is an indication, because prompt Dx & subsequent therapy are associated with improved outcomes, regardless of the histologic class

- A rapidly rising serum creatinine and/or the development of new nephrotic-range proteinuria are indications for urgent kidney biopsy

- Patients with kidney disease for six or more months prior to Bx had a much higher rate of ESKD than those with earlier Bx; (HZ 9.3)

Uptodate Oct 2023.

repeat the biopsy ?

- There is no consensus
- Some feel a repeat biopsy may not be necessary in patients with **successfully treated diffuse LN** who develop **a recurrent active sediment** that almost certainly represents recurrent diffuse disease. Kidney biopsy is unlikely to provide any additional data that would affect treatment in most such patients.

- **Others : there may be a discordance between the clinical findings suggesting remission & persistent histologic activity in the repeat biopsy**

Uptodate Oct 2023.

When repeat kidney biopsy is helpful ?

- A new or worsening NS in patients with treated **class III or IV LN**
- **An active urine sediment & a rapidly rising serum creatinine : crescentic disease ?**
- **Slowly rising serum creatinine or persistent proteinuria** (active LN / class VI)
- kidney disease unrelated to LN (eg, drug-induced acute interstitial nephritis).
- **long-term maintenance therapy with clinical remission(**tapering , withdrawal R/)

Per-protocol repeat Bx & long-term outcome in proliferative LN

- **no association was seen between baseline AI or CI scores & renal relapse**
- **In contrast, AI scores >2 in reBx were associated with an increased probability and/or shorter time to renal relapse ; (more prominent for AI scores >3 (OR 6.0))**

- **High CI scores (>3) in the in reBx were associated with a sustained increase in cr in a median FUP time of 131.5 months, being also the case for acute TI inflammation & interstitial fibrosis/tubular atrophy in repeat Bx**

Rheumatology 2020;59:3424–3434

REV COLOMB REUMATOL. (2021);28(S1):44–52

Revista Colombiana de REUMATOLOGÍA

www.elsevier.es/rcreuma

Review Article

The value of repeat kidney biopsy in lupus nephritis. A systematic review

- 15 studies were included in the review & a total of **1167** repeat Bx
- Bx for **relapse (44-78%)** , lack of response (13-51%)
- repeat Bx are more predictive of long-term kidney & patient outcomes than reference Bx.
- aggressive immunosuppression & rapid control of clinical disease activity did not necessarily prevent chronic damage in LN.
- the clinical findings after induction therapy may not reflect kidney inflammation & chronic damage

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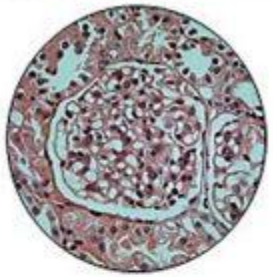
Table 1. Relative contraindications to percutaneous renal biopsy

Condition
Small kidneys or ESRD
Inability to provide informed consent
Multiple bilateral cysts
Uncorrectable bleeding diathesis, recent antiplatelet or anticoagulant therapy, or severe thrombocytopenia
Uncontrolled severe hypertension, which cannot be controlled with antihypertensive medications
Hydronephrosis
Urinary tract infection, pyelonephritis, or perirenal abscess/infection
Horseshoe kidney
Uncooperative patient or inability to follow instructions during biopsy

HISTOPATHOLOGICAL CLASSIFICATION OF LUPUS NEPHRITIS

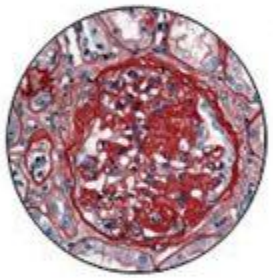


Class I

Minimal Mesangial Lupus Nephritis

- Deposition of imune complexes detectable by immunofluorescence techniques.

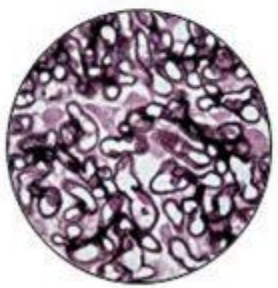
Class III



Focal Lupus Nephritis

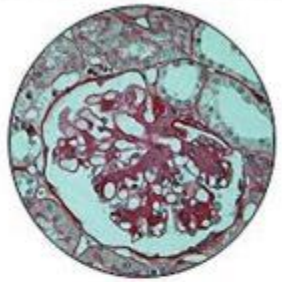
- Active or inactive focal, segmental or global endo/extracapillary glomerulonephritis involving <50% of all glomeruli.
- Manifestations include active lesions (A), chronic inactive lesions (C) or active and chronic lesions (A/C)

Class V



Membranous Lupus Nephritis

- Global or segmental subepithelial immune deposition or their morphologic sequelae detectable by light, immunofluorescence or electron microscopy, with or without mesangial alterations.
- It can occur in combination with class III or IV and it can manifest advanced sclerosis.

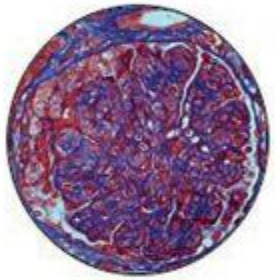


Class II

Mesangial Proliferative Lupus Nephritis

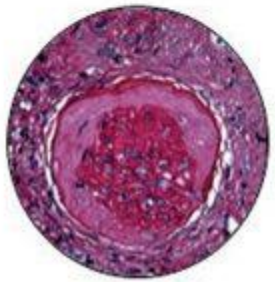
- Mesangial hipercelularity of any degree or mesangial matrix expansion with immune deposits detectable by light microscopy.

Class IV



Diffuse Lupus Nephritis

- Active or inactive diffuse, segmental or global endo/extracapilarry glomerulonephritis involving ≥50% of all glomeruli. Subendothelial diffuse immune deposits, with or without mesangial alterations, are common.
- This class is also divided in: diffuse segmental (IV-S), when ≥ 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G), when ≥ 50% of the involved glomeruli have global lesions.
- It can also manifest A, C or A/C lesions.



Class VI

Advanced Sclerosis Lupus Nephritis

- Lupus Nephritis with terminal prognosis.
- 90% of the glomeruli in global sclerosis.

Table 1 | Phase 1 recommendations for lupus nephritis classification

Category	Recommendation	Comments on ISN/RPS guidelines
Class II	Definition for mesangial hypercellularity adjusted: Four or more nuclei fully surrounded by matrix in the mesangial area not including the hilar region (A)	Cuttoff for mesangial hypercellularity unclear
Class III and IV	The term endocapillary proliferation is replaced by endocapillary hypercellularity (B)	Definition for endocapillary proliferation unclear; the term proliferation was considered imprecise
	The term crescent is used for a lesion consisting of extracapillary hypercellularity, composed of a variable mixture of cells. Fibrin and fibrous matrix may be present; 10% or more of the circumference of Bowman's capsule should be involved. Cellular crescent: more than 75% cells and fibrin and less than 25% fibrous matrix (C) Fibrous crescent: more than 75% fibrous matrix and less than 25% cells and fibrin (D) Fibrocellular crescent: 25%–75% cells and fibrin and the remainder fibrous matrix (E)	Extracapillary proliferation involving > 25% of the circumference of Bowman's capsule was original cutoff. There were no definitions for fibrous or fibrocellular crescents

Kidney International (2018) 93, 789–796

Table 1 | Phase 1 recommendations for lupus nephritis classification

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Class III and IV	The term endocapillary proliferation is replaced by endocapillary hypercellularity (B)	Definition for endocapillary proliferation unclear; the term proliferation was considered imprecise
	Fibrinoid necrosis: fibrin associated with glomerular basement membrane disruption and/or lysis of the mesangial matrix; this lesion does not require the presence of karyorrhexis	There was no definition for fibrinoid necrosis
	Elimination of segmental and global subdivions of class IV	Definitions for segmental and global were unclear; interobserver variability was large; clinical significance uncertain
	Modification of the NIH lupus nephritis activity and chronicity scoring system (Table 2) to be used instead of the currently used A, C, and A/C parameters	Designation of activity/chronicity through A, C, and A/C considered too broad and nonspecific; preference for a semiquantitative approach to describe active and chronic lesions
Tubulointerstitial lesions	Indicate whether interstitial inflammation occurs in presence or absence of interstitial fibrosis	Lack of cut-off values for reporting the severity of tubulointerstitial lesions

Kidney International (2018) 93, 789–796

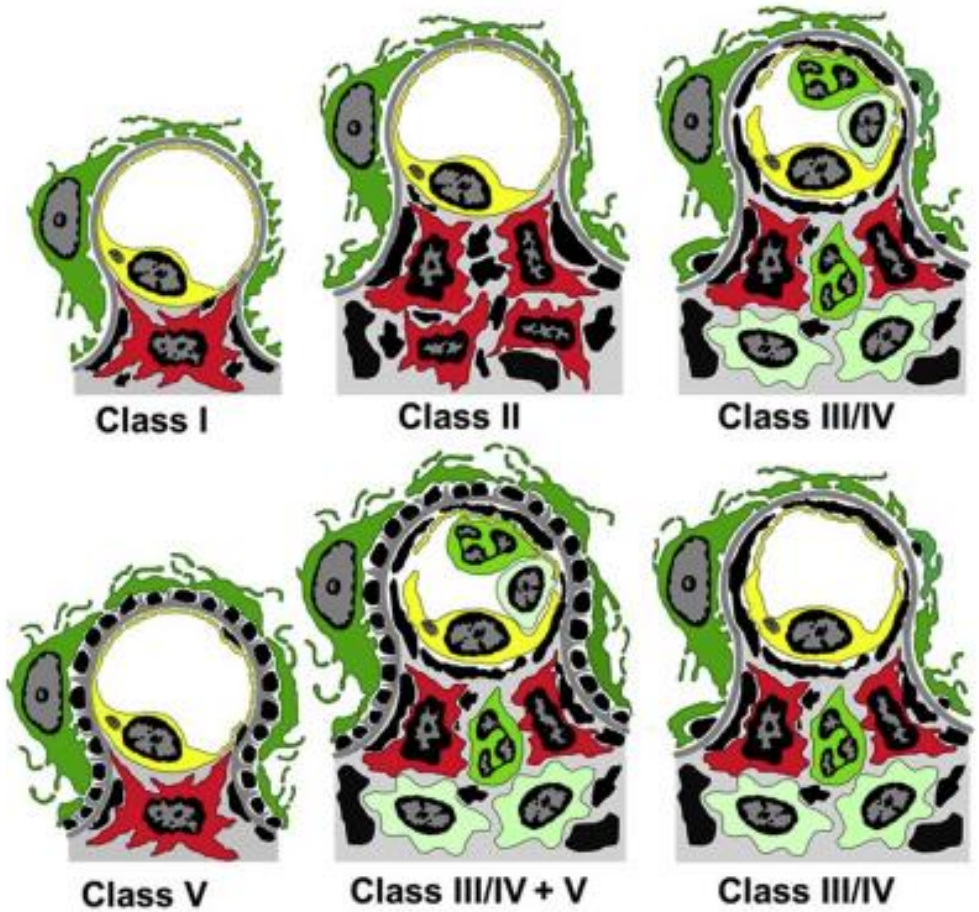


Figure 2 | Drawings depicting the ultrastructural features of a single glomerular capillary affected by lupus glomerulonephritis: class I with mesangial immune deposits (black) but no mesangial cell (red) hypercellularity or influx of leukocytes; class II with mesangial immune deposits and mesangial cell hypercellularity but no influx of leukocytes; class III/IV (upper right) with mesangial and capillary influx of leukocytes; class III/IV (lower right) with subendothelial capillary wall immune deposits that can be seen by LM and mesangial but no capillary influx of leukocytes (dark green neutrophils and light green monocytes/macrophages); class III/IV + V with an influx of leukocytes and numerous subepithelial immune deposits in addition to subendothelial deposits; and class V with numerous subepithelial immune deposits but no influx of leukocytes (podocyte = outer green cell, endothelial cell = yellow cell, mesangial cell = red cell, neutrophil = green cell with segmented nucleus, monocyte/macrophage = light green cell). LM, light microscopy.

Kidney International (2018) 93, 789–796

Activity and chronicity assessment

- It was refined to improve interobserver reproducibility & to validate prognostic value.
- the usage of these indices, but modified, for all classes in a modified classification for LN, thereby not restricting them to classes III and IV

- total scores of 24 in the activity index and 12 in the chronicity index, in particular for comparing the scores recorded for earlier renal biopsy

Kidney International (2018) 93, 789–796

Activity and chronicity

- **Active lesions** : inflammatory or proliferative (potentially reversible):

-endocapillary hypercellularity

- neutrophils & karyorrhexis
- fibrinoid necrosis
- hyaline wire loops
- cellular or fibrocellular crescents
- interstitial inflammation.

- **Chronic lesions** : irreversible damage (generally no immunosuppression)

- glomerulosclerosis
- fibrous crescents
- interstitial fibrosis
- tubular atrophy.

- The activity and chronicity indices are defined by a summation of scoring of the above findings weighted for more severe components.

Uptodate Oct 2024

other forms of lupus kidney disease

- tubulointerstitial nephritis
- vascular disease
- lupus podocytopathy
- collapsing glomerulosclerosis

- Many of these can only be diagnosed with a Bx

ISN/RPS classification LN :

- the presence & severity of tubulointerstitial & vascular involvement should be noted in any Bx specimen

UpToDate 2024

Tubulointerstitial(TI) lesions

- **interstitial infiltrate or tubular injury; with or without immune deposits along the tubular basement membrane is a common finding in LN**

- almost always associated with concurrent glomerular disease

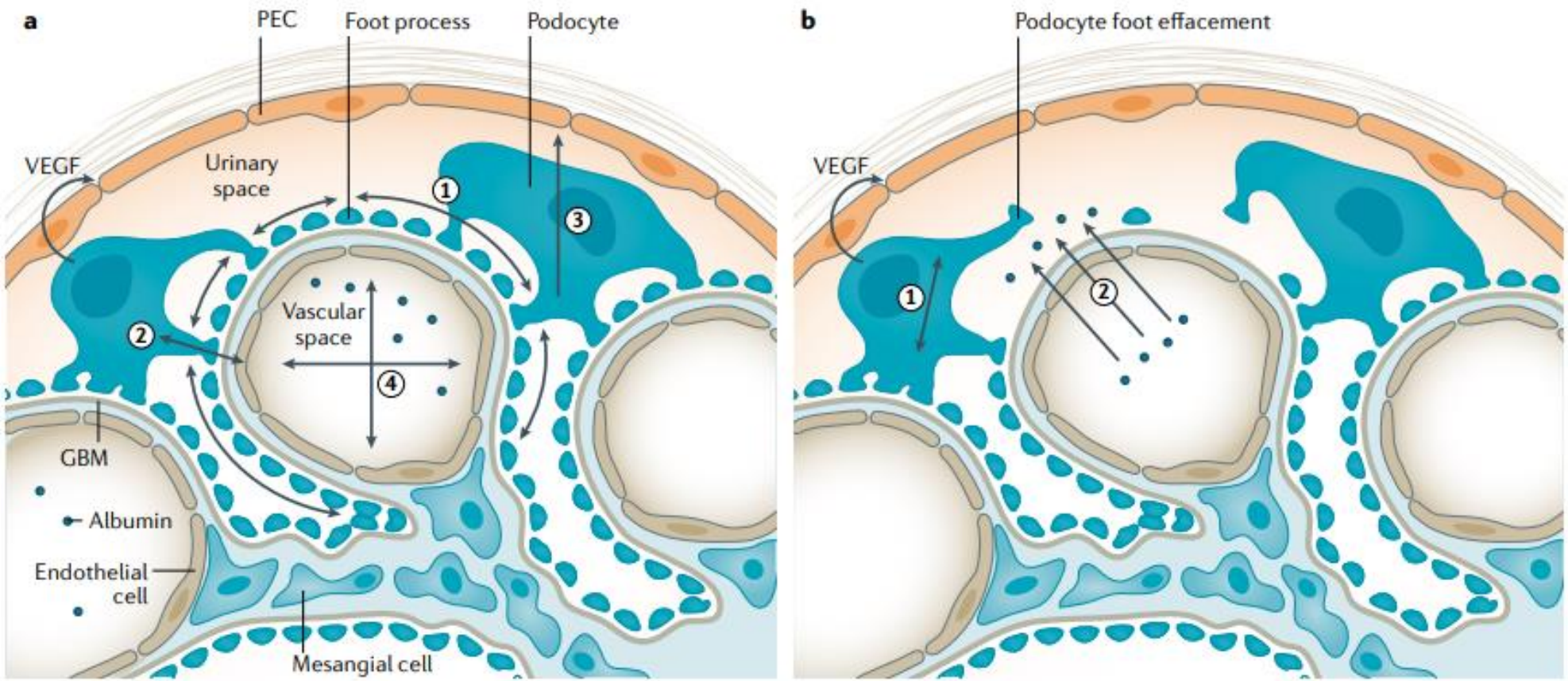
- Its' severity is an important prognostic sign: correlating positively with of HTN, an elevated plasma creatinine & a progressive clinical course (twofold risk of developing ESKD)

- both tubular atrophy & interstitial fibrosis were also associated with an increased risk

Uptodate Oct 2024

Mechanical podocyte stress

PRIMER



NATURE REVIEWS | Disease Primers | Article citation ID: (2020) 6:68

Lupus podocytopathy (LP)

- most commonly affects **females in the age range of 20-30 years**
- **NS in 90% presents as the onset symptom of SLE**
- **usually correlate with lupus activity & extrarenal involvement**
- LP mimics **minimal change disease** or **primary FSGS** & represents approximately 1% of LN Bx
- LP should be divided into MCD or FSGS subtypes
- LP with FSGS : worse outcomes, higher rates of HTN & AKI & more severe TI involvement on kidney biopsy compared with MCD/mesangial proliferative lesions
- LP with FSGS : less likely to respond to therapy, & later remissions
- LP FSGS with collapsing lesions have even worse outcomes, progressing to ESRD in more than 50% of the cases

Adv Chronic Kidney Dis. 2019;26(5):369-375

Lupus podocytopathy(LP)

- severe FPE in the absence of deposits in the glomerular capillary wall implies a mechanism that is independent of IC deposition, presumably similar to the mechanism of primary minimal change disease or primary FSGS.
- Mechanisms? direct Ab binding to podocyte slit diaphragm proteins, production of a cytokine or lymphokine toxic to podocytes, or podocyte injury driven by T cell dysfunction.

- A number of lupus podocytopathy cases have been linked to NSAID use for SLE

UpToDate 2024

Table 1. Proposed Criteria for Diagnosis of Lupus Podocytopathy

Parameter	Features
Clinical	Diagnosis of SLE by ACR criteria; full nephrotic syndrome (ie, nephrotic-range proteinuria, hypoalbuminemia, and edema)
Light microscopy	Normal glomeruli or FSGS; mesangial proliferation permitted; endocapillary proliferation, necrosis, and/or crescents not permitted
Immunofluorescence microscopy	Deposits absent or confined to mesangium
Electron microscopy	Diffuse and severe foot process effacement (typically >70%); deposits absent or confined to mesangium

Abbreviations: ACR, American College of Rheumatology; FSGS, focal segmental glomerulosclerosis; SLE, systemic lupus erythematosus.
Adapted from Bomback and Markowitz.[11]

Adv Chronic Kidney Dis. 2019;26(5):369-375

Lupus Nephritis Biomarkers

LN - biomarkers

- the gold standard technique is kidney Bx that allows for LN histological assessment & prognosis
- **but its use is limited due to invasiveness.**

- to establish an active LN & monitor LN therapeutic response & relapses, the classical LN biomarkers include:

- complement consumption with C3, C4 plus total complement hemolytic activity (CH50)

-the detection of ds-DNA antibodies (Abs) or their derivative anti-chromatin Abs, plus anti-C1q Abs & 24 h proteinuria.

- these classical LN biomarkers are limited in their capacity to predict an active LN & early relapse/remission. Then, new biomarkers have to be introduced & compared to classical LN biomarkers

Int. J. Mol. Sci. 2023

Anti-C1q Abs positivity

- useful biomarker for an active & proliferative LN (60–89% in active LN vs. 0–15% in inactive LN & non-renal SLE

- but anti-C1q Abs capacity to predict therapeutic response & early relapse is limited

Int. J. Mol. Sci. 2023

IFN I , II, III

- Proliferative **class III/IV** LN are characterized by prominent **type I & type II IFN signatures** in renal epithelial cells.
- **Membranous class V LN** : elevated type I IFN & TNF-α signatures

- **Type I IFN level in renal tubular cells correlates with an elevated IFTA chronicity index**
- in renal leukocytes, the type I IFN response drives an extrafollicular B cell response with aged/autoreactive B cells (ABC) & T follicular regulatory CD4+ T cells.

- **a minor subset of SLE patients (5%) present neutralizing type I anti-IFN Abs & this subset is associated with lower disease activity**

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Nephropathic Antibodies in LN

- Abs targeting RNA/DNA nucleic acids
- Abs targeting glomerular antigens, particularity the part of them which cross-react with anti-dsDNA Abs.
- **Functional Abs targeting pathophysiological pathways (e.g., anti-DNAse1L3 Abs, anti-C1q Abs, anti-IFN Abs)**
- Abs targeting anti-phospholipids & cofactors.

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Table 5. Lupus nephritis (LN)-associated autoantibodies (see also Table 4) [60,61].

Autoantibody (Ab)	Predict LN (Histology)	Predict Disease Activity	Therapeutic Response	Predict Flares	Predict ESKD
Anti-dsDNA Abs	High levels (III & IV > V)	High levels	Responder	High levels	Low
Anti-Sm Abs	No	Suspected	Unknown	Suspected	Suspected
Anti-SSB Abs	No	No	No	No	No
Anti-α actinin Abs	Yes	Yes	Unknown	Unknown	Unknown
Anti-CL/β2 GPI Abs	No	No	Low	No	Yes (thrombotic microangiopathy)

Abbreviations: ESKD: end-stage kidney disease; dsDNA: double-stranded DNA; Sm: Smith; SSB: sicca syndrome B; CL: cardiolipin; β2 GPI: beta 2 glycoprotein I.

Table 4. Lupus nephritis (LN) signaling pathways and related biomarkers.

Biomarker	Predict LN	Disease Activity	Therapeutic Response	Predict Flares	Predict ESKD
Anti-DNASE1L3 Abs, DNase activity	Yes	Yes	Responder	Unknown	Unknown
Anti-C1q Abs	Proliferative LN	Low	No	Mild	Unknown
Serum C3/C4/CH50	No	Consumption	Responder	Consumption	No
IFN signature (I ± II); IFN-alpha	Elevated levels	Elevated levels	Responder	Elevated levels	Elevated levels

Abbreviations: ESKD: end-stage kidney disease; Abs: autoantibodies; DNASE1L3: deoxyribonuclease 1-like 3; IFN: interferon; LN: lupus nephritis.

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LN associated urinary biomarkers

Biomarker	Active LN/Glomerulonephritis	Therapeutic Response	Predict Flares	Predict ESKD
Renal markers	24 h proteinuria, SUA, uGAL3BP	24 h proteinuria	24 h proteinuria	24 h proteinuria, SUA, GFR
Cytokine/chemokines	TWEAK, MCP-1/CCL2	TWEAK, MCP-1/CCL2, BAFF	MCP-1/CCL2	TWEAK, MCP-1/CCL2
Cell adhesion molecules	ALCAM, VCAM, NGAL, KIM1, sCD163	VCAM1, sCD163,	VCAM1, sCD163, KIM1	NGAL, ALCAM, VCAM1, KIM1, sCD163
miRs	miR-146a, miR-204, miR-30c, miR-3201, miR-1273e	miR-135	miR-146a	miR-146a

Abbreviations: ESKD: end-stage kidney disease; SUA: serum uric acid; uGAL3BP: urinary galectin-3 binding protein; GFR: glomerular filtration rate; TWEAK: tumor necrosis factor (TNF)-like weak inducer of apoptosis; MCP-1/CCL2: monocyte chemoattractant protein-1 or CCL2; BAFF: B-cell-activating factor of the tumor necrosis factor family or BLySS; VCAM1: vascular cell adhesion molecule; ALCAM: activated leukocyte CAM; NGAL: neutrophil gelatinase-associated lipocalin; KIM1: kidney injury molecule-1; miR: micro-RNA.

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Proteinuria and Protein to Creatin Ratio

- **(KDIGO) clinical practice guideline considers complete remission, within 6–12 months of initiating therapy, when the PCR is <0.5g/g,with a stabilized eGFR from the baseline**

- complete remission , after 12 months of therapy: when both the 24 h proteinuria is <0.5-0.7g/g & the eGFR is (near)normalized

- Importantly, renal damage (e.g., ESKD, nephrotic syndrome) & urinary tract infections are the main limitations to the use of proteinuria to monitor LN patients, as these two conditions can affect the capacity to indicate LN activity/flare & therapeutic response evaluation

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- early decrease of proteinuria levels **over 6months of treatment (>%50%)** has shown ability to predict a more favorable long-term renal outcome

- **Persistent microscopic hematuria does not add prognostic value**

Lupus Science & Medicine 2020;

Proteinuria & Protein to Creatin Ratio

- an elevated **proteinuria at baseline (>1–2 g/24 h) negatively predicts complete remission**
- a partial improvement or an increase in **proteinuria (>2 g/24-h**) are likely to **predict relapse & progression to ESKD**

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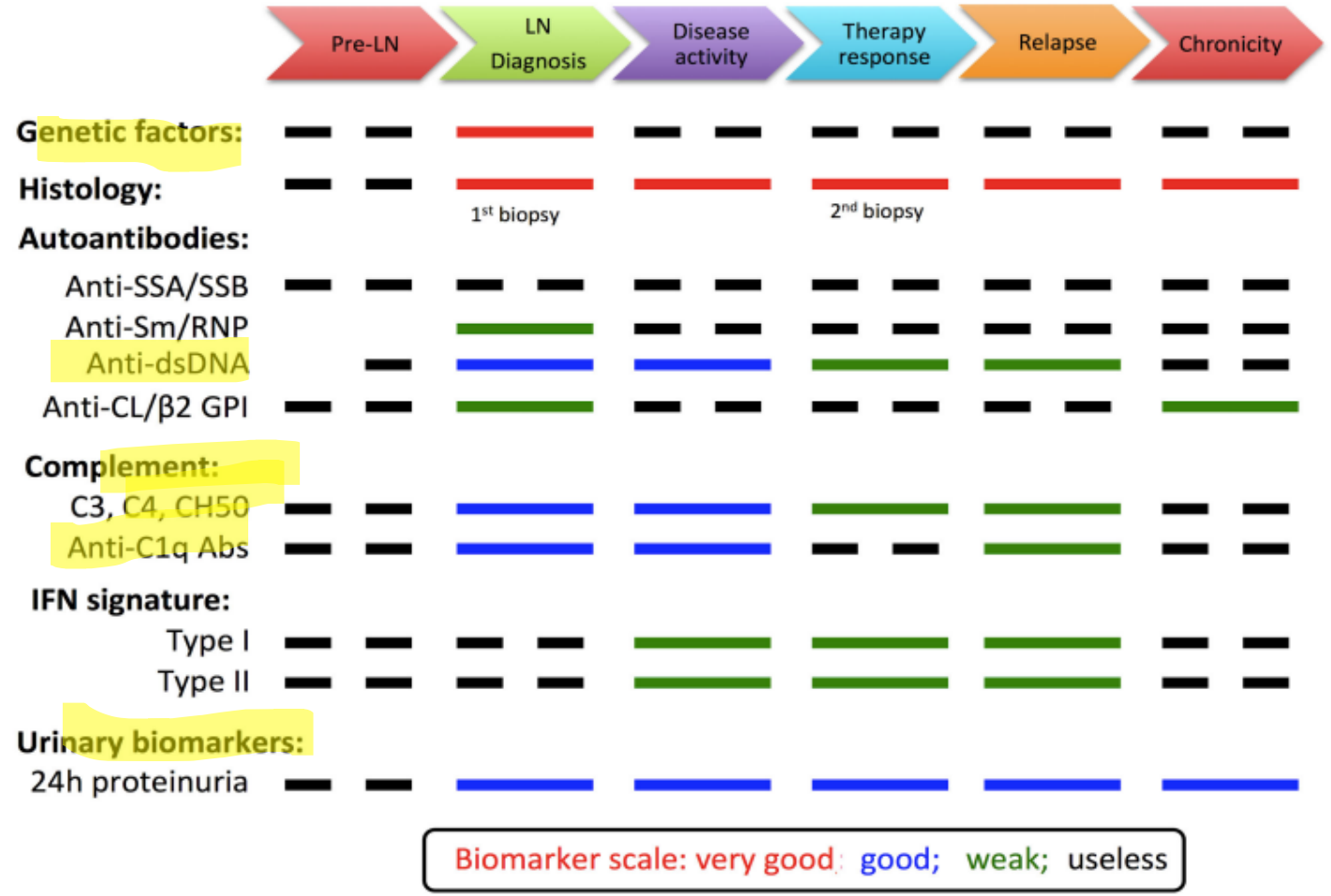
Urine-soluble CD163

- usCD163 is released from activated macrophages involved in the resolution of inflammation in glomeruli

  In in 261 SLE patients in Taiwan ,high usCD163 levels tended to be :
- Younger, a higher hospital admission rate
- lower estimated GFR, higher UPCR
- higher levels of inflammatory markers
- higher rates of anemia, neutropenia, & lymphopenia
- lower C3, higher anti-dsDNA Ab, higher disease activity scores ($p < 0.05$)
- usCD163 levels were significantly higher in patients with active LN than in those with extrarenal or inactive SLE and correlated with UPCR, disease activity, & anti-dsDNA Ab levels.
- SLE patients with high usCD163 levels tended to have a higher CKD

Front. Immunol. 2022



LN biomarkers & their level of performance used to monitor the different steps of the disease; dotted lines represent negative associations

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Conclusion

- **Novel non-invasive imaging methods**
- and employment of the evolving **artificial intelligence** in pattern recognition may also be helpful towards these goals.

- Undoubtedly, the molecular & cellular characterization of SLE & LN will result in novel therapeutic modalities, maybe new taxonomy perspectives, & **ultimately personalized management of the patients**

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