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New age of Lupus Nephritis: Updates in guidelines, biomarkers, and therapies

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ABSTRACT

Lupus nephritis (LN) is the most common visceral organ manifestation of systemic lupus erythematosus (SLE). It affects approximately 50% of SLE patients, accounting for significant morbidity and mortality especially in ethnic minorities. Building on decades of landmark trials, the field has continued to evolve. The 2024 American College Rheumatology (ACR) Lupus Nephritis guideline represents an important shift toward earlier triple therapy. The guideline also recommends routine proteinuria screening and reaffirms kidney biopsy as the diagnostic gold standard. In parallel, urinary biomarkers are emerging as potential tools to better track infrarenal pathology. Furthermore, the therapeutic pipeline continues to expand with emerging strategies targeting B-cells, cytokine receptors, and co-stimulatory mechanisms. In this article, we review updates from the ACR guideline, the emerging data on urinary biomarkers, and highlight novel targeted therapies in LN.

1. Introduction

Systemic lupus erythematosus (SLE) is a heterogenous, systemic autoimmune disease in which immune-complex mediated inflammation can lead to irreversible organ damage [1]. SLE disproportionately affects women and typically occurs in childbearing years with 9:1 female predominance [2]. In the Georgia Lupus Registry, the standardized morality ratio from 2002 to 2016 was 2.3-3.3 times higher for a patient with SLE compared to the general population [3]. In subgroup analysis, Black females with SLE were three times more likely to die compared to Black females without SLE [3]. Also notably, the burden of disease is not evenly distributed across ethnic groups. A 2021 review paper highlights that Black, Asian, and Hispanic patient populations have higher SLE burden compared to their White counterparts and the aforementioned ethnic minority groups experience greater morbidity and mortality [4].

One of the most consequential manifestations of SLE is lupus nephritis (LN), which causes high morbidity in SLE patients. LN is a common manifestation of SLE, impacting about 50% of patients [5]. LN may be the initial presentation of SLE, or it may occur over months to years after initial diagnosis. LN typically develops within the first 6 to 36 months of diagnosis [6]. In a prospective study of 1827 newly diagnosed SLE patients from the United States, Europe, Canada, Asia, and Mexico, LN was identified in 700 patients (38.3%) with 566 out of the 700 patients (80.9%) had LN at the time of study enrollment and 134 (19.1%) was diagnosed with LN during a follow-up visit [7]. The study reported that the cumulative incidence of end-stage renal disease (ESRD) in LN patients after 10 years of diagnosis was 10.1%. In the Hopkins Lupus Cohort, Petri and colleagues analyzed 2528 SLE patients and reported the risk of

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Table 1
Comparison of the American College of Rheumatology (ACR) and Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines for the management of lupus nephritis. Key areas of divergence between the two guidelines are bolded.

	2024 ACR LN [15]	2024 KDIGO LN [16]
Treatment for Class I/II	**No formal guideline** Evaluate for lupus podocytopathy; if yes, GC and other immunosuppression upon discussing with nephrology colleagues	**Low level proteinuria** - Immunosuppression for extra-renal manifestations **Nephrotic syndrome** - **Evaluation for lupus podocytopathy on electron microscopy** - **Treat as minimal change disease** - Consider maintenance combination therapy with **LD GC & another immunosuppressive agent**
Treatment for Class III/IV (± V)	HCQ, RAASi + **Triple therapy:** GC (MP IV 0.25-**1 g**/d for 1-3 days, then prednisone (≤0.5 mg/kg/day, **max dose 40 mg**/day) +MPAA +Belimumab **or** CNI **Alternative Triple therapy:** GC pulse/oral taper +LD CYC + Belimumab	HCQ, RAASi + GC (MP IV 0.25-**0.50 g**/d for 1-3 days, then pred PO at approx. 0.35-**1.0** mg/kg/d (not to exceed **80 mg**/day) + Selection of: A) MPAA B) LD IV CYC C) Belimumab plus MPAA or Belimumab plus LD IV CYC D) MPAA and CNI
Treatment for Class V	**If proteinuria ≥1g:** HCQ, RAASi + *Triple therapy:* GC pulse IV followed by prednisone taper ≤0.5 mg/kg/day oral, max 40 mg + MPAA +CNI **If proteinuria <1g:** HCQ, RAASi + GC + **Immunosuppression with MPAA, AZA, or CNI**	**If nephrotic range proteinuria:** HCQ, RAASi + GC pulse IV followed by prenidosne taper ≤0.5 mg/kg/day oral, max 40 mg + MPAA, CYC, CNI, RTX, **or** AZA **If low level proteinuria:** HCQ, RAASi + **Immunosuppression guided by extrarenal manifestations**
LN with kidney failure	Kidney transplant is preferred over dialysis	Kidney transplant is preferred over dialysis
LN with suspected TMA	**No formal guideline**	Test for ADAMST13 activity, antibodies to ADAMTS13, and antiphospholipid antibodies Assess PLASMIC score
Treatment Response Definitions	CRR: - Reduction in proteinuria <0.5 g/g (50 mg/mmol) (24h urine collection, **or UPCR), AND** - Stabilization or improvement in kidney function (+**20%** baseline) - Within 6-12 months of starting treatment (may take >12 months)	CRR: - Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24hr urine collection - Stabilization or improvement in kidney function (± **10–15%** of baseline) - Within 6-12 months of starting treatment (may take >12 months) **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 1.73m2 No use of rescue therapy for treatment failure
	PRR: - Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) 24hr collection or UPCR; **AND** - Stabilization of kidney function **(+20%** baseline)	PRR: - Reduction in proteinuria by at least 50% and to < 3 g/g (300 mg/mmol) measured as the PCR from a 24hr urine collection - Stabilization or improvement in kidney function (± **10–15%** of baseline)
	Nonresponse/Inadequate Renal Response: - lack of achieving at least a PRR despite adherence to appropriate treatment for active LN of any class by 6-12 months	No kidney response: - Failure to achieve a PRR or CRR within 6-12 months of starting treatment
Treatment Duration	**At least 3–5 yrs**	**≥ 2–3 years**

Abbreviation Legend.
LN: lupus nephritis.
GC: glucocorticoid.
LD: low-dose.
HCQ: hydroxychloroquine.
RAASi: renin-angiotensin-aldosterone system inhibitors.
MP: methylprednisolone.
MPAA: mycophenolic acid analog.

CNI: calcineurin inhibitor.
CYC: cyclophosphamide.
RTX: rituximab.
AZA: azthioprine
PCR: Protein-creatinine ratio.
PRR: partial renal response.
CRR: complete renal response.

renal failure (defined as requirement of dialysis or renal transplant) 5, 10, and 20 years after SLE diagnosis were 2.7%, 4.7%, and 8.4% respectively [8]. In a systematic review and meta-analysis of world-wide data, 22% overall and 44% of those with class IV GN had developed ESRD by 15 years [9].

In the United States, LN occurs in 34-51% in Black, 31-43% in Hispanic, and 33-55% in Asian patients with SLE compared to 14-23% in White patients [6]. Black and Hispanic patients are more likely to have worse underlying histopathology, higher serum creatinine levels, higher proteinuria, and more likely to progress to renal failure compared to White patients. Although SLE is less common in males, men with SLE have a higher risk of developing LN [10]. Constenbader and colleagues analyzed 12,633 patients with ESRD secondary to SLE and found that 82% were women, 49% were Black and the Black patients had higher mortality rates [11]. They also noted a rising incidence of ESRD during 1995-2006 in Black patients and those living the southeastern states in the United States. Genetic variations may also contribute to ethnic disparities seen in LN. Genome studies have identified apolipoprotein L1 (APOL1) to be associated with increased risk of renal failure in Black patients and the presence of two APOL1 alleles increased the odds by 2.57 fold of developing LN-ESRD [12].

Access to care also influences the pace of progression from LN to ESRD. Studies have used insurance status as a surrogate marker for socioeconomic status and access to care. In the United States Renal Data System from 1996 to 2004, 7971 patients had ESRD secondary to LN [13]. Patients with private insurance were older when starting ESRD treatment compared to their counterparts with Medicaid or no insurance. More specifically, White patients with private insurance had onset of ESRD 7.5 years later than uninsured patients and 8.2 years later than Medicaid patients. In a study of California SLE patients between 1999 and 2004, the incidence of LN-ESRD was higher in ZIP code regions with greater proportions of Medicaid coverage, suggesting that access to healthcare may be a contributing factor for the development of ESRD in LN patients [14].

Against this epidemiological backdrop, the collective understanding of LN continues to be rapidly evolving leading to changes in current treatment, changes to screening and monitoring, role of renal biopsy, new biomarkers, and emerging therapeutic strategies for LN.

2. Current lupus nephritis management

In 2024, the American College of Rheumatology (ACR) released its updated guideline on the screening, treatment and management of LN [15]. Also published in 2024 were the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Lupus Nephritis [16]. While the two guidelines agree in many areas, the KDIGO guideline is more nuanced and provides scenario-specific guidance that are not explicitly addressed by the ACR guideline. The comparison of the ACR and KDIGO LN guidelines are outlined in Table 1.

3. Recommendations on screening, diagnosis and monitoring of LN

From a screening standpoint, the 2024 ACR guideline emphasizes the importance of identifying LN early through routine surveillance. Regular screening for proteinuria is strongly recommended at least every 6-12 months and during extra-renal disease flares. Rheumatologists are encouraged to maintain a low threshold for kidney biopsy when LN is suspected, particularly in the presence of proteinuria >0.5 g/g and/or unexplained decline in kidney function. Kidney biopsy is crucial as histopathologic classification guides treatment selection. Repeat kidney biopsy may be warranted in cases of suspected flare or inadequate response, supporting dynamic reassessment of disease activity over time.

For longitudinal monitoring during treatment, the 2024 ACR guideline recommends quantifying proteinuria at least every 3 months until complete renal response (CRR) is achieved and every 3-6 months thereafter, alongside routine monitoring of complement levels and anti-double-stranded DNA antibodies at clinic visits. CRR is defined as reduction in proteinuria <0.5 g/g on 24-h urine collection or urine protein creatine ratio (UPCR) and stabilization or improvement in kidney function. The guideline also underscores the importance of sustained collaboration with nephrology, particularly for patients with progressive kidney dysfunction, noting a preference for kidney transplantation over dialysis when renal replacement therapy is required. Even after the initiation of renal replacement therapy, it is important to maintain longitudinal follow-up with rheumatology.

4. Recommendations on treatment of LN

The therapeutic landscape of LN has been shaped over the past four decades by sequential pivotal trials on SLE. In 1986, a landmark trial established that IV cyclophosphamide preserved kidney function better than prednisone alone, initially anchoring cyclophosphamide as the standard induction for LN [17]. Then, subsequent studies refined the strategy and moved toward toxicity-sparing regimens. In 2002, the Euro-Lupus Nephritis Trial demonstrated low-dose cyclophosphamide was as effective as NIH high-dose

Table 2
Summary of key findings from sequential pivotal clinical trials informing lupus nephritis management.

Trial Year	Study size	Treatment Regimen & Dose	Key Inclusion/Exclusion	Primary Outcome	Result	Key Adverse Events	Take-home point for clinical practice
IV CYC, 1986	107	1) Oral pred – 1 mg/kg/day, then tapered over months 2) Oral AZA – up to 4 mg/kg/day 3) Oral CYC – up to 4 mg/kg/day 4) Combined oral AZA (up to 4 mg/kg/day) + oral CYC (up to 1 mg/kg/day) 5) IV CYC q 3 months - 0.5 to 1 g/m^2 of BSA for WBC nadir $\geq$2	Inclusion: diagnosis of SLE, clinical or histologic evidence of active LN (with or without kidney bx). Exclusion: CrCl <20 ml/min, infection in the last 2 wks, WBC <2, pregnancy, cytotoxic drugs within 8 wks	Time to renal failure (ESRD or stable doubling in SCr)	Renal function worsened over time on pred alone compared to IV CYC.	Infection occurred more in pred group. Herpes Zoster seen more in CYC groups (PO or IV). Premature ovarian failure was greater in the CYC groups (PO and IV). Daily PO CYC increased risk of hemorrhagic cystitis; it did not occur in IV CYC group.	Intermittent IV CYC preserved renal function and reduced progression to renal failure compared to pred alone. Notable to be aware of premature ovarian failure and Herpes Zoster with CYC.
PLEX, 1992	86	Standardized background: Pred 60 mg/day for 4 wks then taper + PO CYC 2 mg/kg/day PLEX arm: Plus PLEX 3x/wk for 4 wks (target 12 sessions), each 4L/exchange	Inclusion: Bx proven LN Class III/IV/V Exclusion: SCr > 6 mg/dL, pregnancy, prior PLEX, history of primary myocardial disease, history of cancer within the past 5 yrs, & active liver disease	Length of time to death, to renal failure (initiation of HD or renal transplant), and changes in the levels of 24-hr urinary protein excretion & SCr, IgG, anti-ds-DNA Ab, cryoglobulins, C3, & C4.	No significant difference in death or ESRD between PLEX & non-PLEX groups after long-term follow-up. SCr and 24-hr urine protein were not statistically significant.	PLEX arm had more procedure-related complications (hypotension, line issues) & a trend toward more infection	The addition of PLEX to standardized treatment of steroids and CYC did not improve patient or kidney survival outcomes.
MP and IV CYC, 1996	82	Background steroids for all patients. Randomized into 3 arms: • IV MP alone: 1 g/day x 3 days, then monthly single infusions for 12 months • IV CYC alone: IV CYC 0.5–1 g/m^2 monthly x 6 then q3months x 2 yrs. WBC nadir >3 • Combo: IV MP reigmen + IV CYC regimen.	Inclusion: GN defined as UA with $\geq$10 RBC/HPF or WBC casts. Bx within 3 months. Exclusion: Received CYC for 2+ wks during the 6 wks prior to study entry or received CYC for >10 wks. Received pulse steroids in the 6 wks prior to study entry. Need for pred >0.5 mg/kg. Active or chronic infection, pregnancy, presence of only one kidney, and insulin-dependent DM	RR defined as <10 dysmorphic RBC/HPF, no cellular casts, and proteinuria < 1g/day without doubling of SCr.	RR occurred in 61% combo group, 48% CYC group, & 26% MP group	Amenorrhea/ovarian failure, leukopenia, and infection (Herpes Zoster) more common in CYC groups.	Confirms that MP pulses alone are inadequate for severe proliferative LN. This study demonstrates greater efficacy with combination of IV MP and CYC, supporting the use of pulse dose steroids in the beginning of CYC.
Euro-Lupus Nephritis Trial, 2002	90	Standardized background: IV MP x 3, then oral pred 0.5 mg/kg/day for 4 wks, then tapered 2.5 mg q2 wks until pred 5-7.5 mg/day. Randomized to induction: • LD CYC (Euro Lupus): six 500 mg IV CYC pulses q2wks, then AZA	Inclusion: Bx proven LN Class III/IV/V, proteinuria $\geq$500 mg in 24hrs. Exclusion: Received CYC or AZA within 12 months, pred$\geq$15 mg of within 1 month prior to study entry, renal TMA,	Treatment failure (absence of primary response after 6 months, occurrence of a steroid resistant flare, or a doubling of SCr)	No significant difference in long-term renal outcomes between HD & LD arms.	Severe infections occurred more often in the HD CYC group. Both groups experienced similar number of hematologic and gonadal toxicity. 1 patient (age 20, in HD group) developed premature ovarian failure.	For mainly Caucasian pts, LD "Euro-Lupus" IV CYC followed by AZA is as effective as NIH dosing with less toxicity.

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Table 2 (*continued*)

Trial Year	Study size	Treatment Regimen & Dose	Key Inclusion/Exclusion	Primary Outcome	Result	Key Adverse Events	Take-home point for clinical practice
		maintenance (2 mg/kg/day). • HD CYC: eight IV CYC pulses (6 monthly, 2 quarterly, dose escalated by WBC nadir), then AZA maintenance (2 mg/kg/day).	pre-existing renal failure, pregnancy, prior malignancy, DM, anticipated poor compliance with protocol.				
Sequential therapy, 2004	59	Standardized backbone: induction with up to 7 monthly IV CYC 0.5–1 g/m^2 with WBC nadir $\geq$2 + steroids. Randomized to maintenance for 1–3 yrs: • IV CYC pulses 0.5-1g q3 months (received mesna and granisetron) • AZA 1–3 mg/kg/day PO • MMF 500–3000 mg/day PO	Inclusion: Bx proven LN Class III/IV/V Exclusion: CrCl <20 mL/min, infection, pregnancy, >7 prior IV CYC doses, >8 wks prior AZA.	Death or chronic renal failure (sustained increase in SCr to at least twice the lowest value reached during induction) or the need for dialysis/renal transplant.	72-month event-free survival (death or chronic renal failure) higher with AZA & MMF vs continued CYC (both P $\leq$ 0.05). Relapse-free survival best with MMF (better than continued CYC, P = 0.02).	Infection, nausea, vomiting, hospitalization higher in CYC group. Leukopenia similar among the three groups. No episode of hemorrhagic cystitis or cancer observed.	For proliferative LN, short IV CYC induction followed by AZA or especially MMF maintenance is associated with better long-term event-free survival and less toxicity than long-term IV CYC.
MMF vs CYC 2005	140	Open-label, 24-wk induction: • MMF PO target dose 3 g/day. • IV CYC (NIH): 0.5–1 g/m^2 monthly with WBC nadir 7-10 days post-infusion. All received pred 1 mg/kg and tapered 10-20% q1-2 wks	Inclusion: Bx proven LN class III/IV/V, decrease in renal function (proteinuria >500 mg in 24hr urine, SCr >1, microscopic hematuria defined as >5 RBC/HPF, or presence of cellular casts). Exclusion: CrCl <30 mL/min, SCr > 3 mg/dL, previously received MMF, received IV CYC within 12 months, monoclonal antibody therapy within the past 30 days, pregnancy, lactation	CRR at 24 wks: normal SCr or within 10% of normal values of SCr, proteinuria, & urine sediments	CRR: 22.5% MMF vs 5.8% CYC. Overall response also higher with MMF; fewer early treatment failures.	More severe infections with CYC compared to MMF. Also, CYC group had more alopecia, menstrual irregularities including amenorrhea. MMF group had more diarrhea.	For induction therapy of LN, MMF group achieved higher rates of CRR than NIH IV CYC with a more favorable side effect profile. Rationale for MMF-based induction.
ALMS induction, 2009	370	MMF vs IV CYC induction (both with steroids): • MMF PO target dose 3 g/day • IV CYC 0.5–1 g/m^2 q4wks for 6 mo. All pred 60 mg/day and tapered.	Inclusion: Bx proven LN Class III/IV/V within 6 months, proteinuria $\geq$2 g/day, SCr <3 mg/dL, active urinary sediment. Exclusion: Prior treatment with MMF or IV CYC within 12 months, dialysis >2 weeks, pancreatitis, severe viral infection,	RR at 24 wks: UPCR decrease to <3 or $\geq$50% reduction UPCR & stabilization or improvement in SCr.	Similar response: 56.2% MMF vs 53.0% CYC overall. Subgroup: MMF performed better in Black/Hispanic pts (statistically significant); CYC slightly better in some Asian pts (not statistically significant)	Infection was common AE in both groups. MMF with more diarrhea and IV CYC with more nausea, vomiting, and alopecia.	For induction therapy of LN, this study demonstrated MMF + pred is not superior to monthly IV CYC + pred. MMF showed higher response in Black and Hispanic subgroups.

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Table 2 (*continued*)

Trial Year	Study size	Treatment Regimen & Dose	Key Inclusion/Exclusion	Primary Outcome	Result	Key Adverse Events	Take-home point for clinical practice
			severe cardiovascular disease, current infection, bone marrow insufficiency				
Euro-Lupus Follow-up, 2010	90	Standardized background: IV MP x 3, then oral pred 0.5 mg/kg/day for 4 wks, then tapered 2.5 mg q2 wks until pred 5-7.5 mg/day. Randomized to induction: • LD CYC (Euro Lupus): six 500 mg IV CYC pulses q2wks, then AZA maintenance (2 mg/kg/day). • HD CYC: eight IV CYC pulses (6 monthly, 2 quarterly, dose escalated by WBC nadir), then AZA maintenance (2 mg/kg/day).	Inclusion: Bx proven LN Class III/IV/V, proteinuria ≥500 mg in 24hrs. Exclusion: Received CYC or AZA within 12 months, pred≥15 mg of within 1 month prior to study entry, renal TMA, pre-existing renal failure, pregnancy, prior malignancy, DM, anticipated poor compliance with protocol.	Renal impairment defined as SCr ≥1.4 mg/dl. Major events categorized as sustained doubling of SCr, ESRD, cancer, cardia event, or death.	Death, ESRD, sustained doubling of SCr did not statistically differ between LD vs HD IV CYC. Early drop in proteinuria (month 3 & 6) predicted good long term renal outcome.	Cumulative CYC exposure was lower in LD group. Cancer diagnosed in 7 pts (6 in LD, 1 in HD): breast, cervical, squamous skin, thyroid, and Burkitt lymphoma. Cardiac events in 7 pts (3 in LD, 4 in HD). Reproductive rates were similar in LD and HD.	After 10 yrs, Euro-Lupus LD CYC regimen remains as effective as HD in predominantly Caucasian pts, with less cumulative CYC exposure. Reinforces LD CYC + AZA as a durable, lower-toxicity option.
ALMS Maintenance, 2011	227	Maintenance after response: • MMF: target 2 g/day PO • AZA: 2 mg/kg/day PO Both groups permitted pred ≤10 mg/day	Inclusion: at least PRR after 6 months of induction (MMF or CYC) LN class III/IV/V. Exclusion: Non-responders, unstable renal function, poor adherence.	Time to treatment failure (death, ESRD, doubling SCr, renal flare, need for rescue)	Treatment failure: 16.4% with MMF vs 32.4% with AZA	Any AE similar in both groups; infection most common. AZA had more leukopenia while MMF had more gastroenteritis.	MMF is superior to AZA for maintenance after induction, reducing relapses and renal events regardless of induction regimen, geographic location, and race. If tolerated, MMF is the preferred maintenance agent in LN.
LUNAR 2012	144	Standardized background: MMF (3 mg/day by wk 4) + IV MP with taper to pred ≤10 mg by wk 16. HCQ allowed in background. Randomized to: • RTX 1000 mg IV on days 1, 15, 168, 182. • Placebo on same IV schedule.	Inclusion: Bx proven LN Class III/IV/V within 12 months, proteinuria (UPCR >1.0), active urinary sediments (>10 RBC/HPF or presence of RBC casts) Exclusion: >50% glomerular sclerosis or interstitial fibrosis, eGFR <25 mL/min/1.73 m^2	At wk 52, CRR: normal SCr or a SCr of 115% of baseline; inactive urinary sediment; and UPCR< 0.5. PRR: SCr 115% of baseline; RBCs/HPF 50% above baseline & no RBC casts; & at least 50% decrease in the UPCR <1.0.	CRR: 26.4% RTX vs 30.6% placebo. PRR: 30.6% RTX vs 15.3% placebo. Overall RR, 56.9% RTX vs 45.8% placebo (p = 0.18). Primary endpoint not met. Improvement in C3, C4, and dsDNA in RTX group. Subgroup of Black patients had higher proportion of RR, not statistically significant.	Serious AE, including infection, were similar in both groups. RTX arm: more neutropenia, leukopenia, hypotension. No new safety signals.	Adding RTX to standard therapy did not show statistically significant difference in renal response. RTX showed improved serologies and potential improved RR in Black patients although not statistically significant.
Multitarget Trial 2015	362	24-wk, open-label with standardized backbone of 3 days IV MP followed by taper to pred 10 mg/day. Randomized to:	Inclusion: Bx proven LN Class III/IV/V and significant proteinuria (≤1.5g/day) with SCr <3.0 mg/dL	Time to overall response. CRR: 24-hr urinary protein ≤0.4 g, absence of active urine sediments, serum	CRR: 45.9% multitarget vs 25.6% CYC (P < 0.001). Overall response incidence at wk 24:	Similar incidence of AE. Infection common in both. Multitarget had greater percentage of HTN, tremor. CYC had greater percentage of	In a largely Asian cohort, multitarget therapy with tacrolimus + MMF was superior to IV CYC as it achieved higher incidence

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Table 2 (*continued*)

Trial Year	Study size	Treatment Regimen & Dose	Key Inclusion/Exclusion	Primary Outcome	Result	Key Adverse Events	Take-home point for clinical practice
		• Multitarget: tacrolimus 4 mg/day (mean trough 5 ng/mL) + MMF 1 g/day • Control: IV CYC 0.75 g/m^2 q4wk for 6 doses	Exclusion: Previous treatment with MMF, CYC, tacrolimus, or high-dose MP; current renal replacement therapy, PLEX within 12 months; pathologic chronicity >3.	albumin ≥35 g/L, & normal SCr. PRR: ≥50% reduction in proteinuria & urine protein <3.5 g/24 h, serum albumin ≥30 g/L and normal or ≤25% increase in SCr from baseline.	83.5% multitarget vs 63.0% IV CYC (P < 0.001). Mean time to overall response: 8.9 wks multitarget vs 13.0 wks IV CYC. Repeat renal bx revealed reduced pathologic activity index in both groups, more pronounced in multitarget group.	leukopenia, alopecia, menstrual disorder.	of remission and more rapid overall response.
BLISS-LN, 2020	448	Standardized background: • Induction with MMF or CYC-AZA, plus steroids. HCQ and ACEi/RB allowed throughout Randomized to: • BEL 10 mg/kg IV day 1, 15, 29 then q 28 days to wk 100. • Placebo IV on same schedule.	Inclusion: Bx proven LN Class III/IV/V; UPCR ≥1 Exclusion: eGFR <30 mL/min/1.73 m^2, dialysis within 1 yr, prior failure of CYC & MMF induction, received CYC induction within 3 months before trial, received B-cell targeted therapy within 1 yr	RR at wk 104: UPCR ≤0.7, eGFR decline ≤20% or ≥60 mL/min/1.73m^2, no rescue. CRR at wk 104: UPCR <0.5, eGFR no worse that 10% below pre-flare, no rescue.	Primary RR: 43% BEL vs 32% placebo (p = 0.03). CRR: 30% vs 20% (p = 0.02). Risk of renal event or death: HR 0.51 in favor of BEL.	Infection, infusion reactions, depression/suicidality, malignancy comparable between groups	BEL added to MMF or CYC-AZA significantly improves renal response with comparable adverse event profile.
CALIBRATE, 2021	43	Standardized background (wks 0 & 2): • RTX 1000 mg IV at wks 0 & 2. • CYC 750 mg IV at wks 0 & 2. • MP 100 mg IV with each RTX/CYC dose, then oral pred 40 mg/day tapering to 10 mg/day by wk 12, then ≤10 mg/day through wk 96. • HCQ and ACEi/ARB allowed throughout. Randomization at wk 4: • RCB arm (RTX–CYC–BEL): BEL 10 mg/kg IV at wks 4, 6, 8, then q4 wks to wk 48. • RC arm (RTX–CYC only): no further biologic	Inclusion: Bx proven LN Class III/IV±V within 18 months; recurrent or refractory LN despite prior MMF or CYC; UPCR >1. Exclusion: prior RTX within 12 months, significant active infection, advanced CKD, major comorbidities.	Proportion with ≥1 infectious AE of grade ≥3 by wk 48. Exploratory efficacy: CRR/PRR at wks 24, 48, 96.	Infectious AE between RCB and RC arms were not statistically significant. CRR/PRR rates were similar in both arms. Numerically higher CRR with add-on BEL but difference not statistically significant. BEL prolonged B-cell depletion & altered B-cell reconstitution, but not statistically significant.	Infection (including PNA, UTIs, cellulitis) occurred in both groups but were manageable; no excess severe infections or opportunistic infections with BEL. IgG levels were lower with BEL but severe hypogammaglobulinemia with serious infection did not occur. No deaths reported.	RTX + CYC followed by BEL did not show significantly higher infectious AE. This study is underpowered and its results does not show statistically significant clinical benefit of additional BEL to RTX and CYC.
AURORA-1, 2021	357	Standardized background: • MMF 1 g BID (2 g/day). • IV MP then rapid taper of oral pred. Target pred 2.5 mg/day by wk 16 Randomized to:	Inclusion: Bx proven LN Class III/IV/V, UPCR ≥1.5 mg/mg (≥2.0 for pure V), eGFR ≥45 mL/min/1.73 m^2	CRR at 52 wks: UPCR ≤0.5, stable eGFR, pred ≤10 mg/day, no rescue medication	CRR: 41% with voclosporin vs 23% placebo group	AEs similar in both groups; most common: infections, diarrhea. Serious AE & mortality rates comparable.	Voclosporin added to background therapy of MMF and steroid taper lead to faster proteinuria reduction and greater CRR by wk 52.

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Table 2 (*continued*)

Trial Year	Study size	Treatment Regimen & Dose	Key Inclusion/Exclusion	Primary Outcome	Result	Key Adverse Events	Take-home point for clinical practice
		• Voclosporin 23.7 mg BID. • Placebo BID.	Exclusion: Prior CNI use for LN, advanced CKD				
TULIP-LN, 2022	147	All pts on MMF + oral steroid + anifrolumab IV q4wks: • Basic regimen (BR): 300 mg q4wk. • Intensified regimen (IR): 900 mg q4wk × 3, then 300 mg q4wk. • Placebo q4wk.	Inclusion: Bx proven LN Class III/IV within 3 months of screening, 24hr UPCR ≥1, eGFR ≥35 mL/min/1.73 m^2 Exclusion: Pure Class V LN, hx of dialysis within 12 months, received B-cell depleting therapy within 26 wks, infection within 2 wks, pregnancy, lactation	Change from baseline in 24-hr UPCR at wk 52 for combined anifrolumab (IR + BR) vs placebo groups.	Primary endpoint not met – UPCR improved similarly (≈69–70% reduction) in both anifrolumab & placebo groups. However, IR arm showed numerically higher CRR (45.5% vs placebo 31.1%)	Herpes zoster higher with anifrolumab IR + BR (16.7%) vs placebo (8.2%). Overall serious AE rate similar.	Primary endpoint was not met. However, the intensified regimen of anifolumab showed numerical improvement in CRR, which is encouraging for further investigation of type 1 interferon blockade.
WIN-Lupus, 2022	96	Pts with proliferative LN in CRR or PRR after 2–3 yrs of maintenance: • Maintenance immunosuppressive therapy (IST) = AZA or MMF + HCQ, pred <10 mg/day Randomized to: • Continuation of IST for 2 more yrs. • Taper and discontinue IST over 3 mo, continue HCQ.	Inclusion: Bx proven LN Class III/IV/V, ≥2–3 yrs maintenance AZA/MMF, achieved CRR or PRR (low proteinuria, inactive urinary sediments, normal eGFR). Exclusion: eGFR <30, recent extra-renal flare, pregnancy or wishing to become pregnant in 2 years, lactation	Relapse rate of proliferative LN at 24 months with UPCR >0.5g/24hr, doubling of pre-existing proteinuria, recurrence of microscopic hematuria, or 25% in SCr	LN relapse: 12.5% continuation vs 27.3% discontinuation. Relapse occurred after median of 9 months. Severe SLE flares less frequent with continuation (12.5%) vs discontinuation (31.8%), p = 0.035.	No significant difference in adverse events between the two groups.	Non-inferiority of therapy discontinuation was not demonstrated. However, after 2–3 yrs of maintenance, discontinuation of therapy is associated with higher risk of severe SLE flare (renal or extrarenal). Antiphospholipid syndrome, higher UPCR at baseline, low C3, and higher SLEDAI were associated with LN relapse.
REGENCY, 2025	271	Obinutuzumab 1000 mg IV day 1 & wks 2, 24, 26, 52 (with or without wk 50 dose) vs placebo. All received MMF + pred taper (target 7.5 mg/day by wk 12, 5 mg/day by wk 24)	Inclusion: Biopsy proven LN Class III/IV/V within 6 months, 24h UPCR ≥1. Exclusion: eGFR <30, ESRD/dialysis/transplant, active infection, anti-CD20 within 9 months prior, recent CYC/tacrolimus/cyclosporine/voclosporin within 2 months	CRR at wk 76: 24h UPCR <0.5, eGFR ≥85% baseline, & no intercurrent event (i.e. rescue therapy, treatment failure, death, or early trial withdrawal).	CRR at wk 76: 46.4% obinutuzumab vs 33.1% placebo (p = 0.02). Greater mean change in C3, C4, and dsDNA as well as greater CD19 B cell depletion in obinutuzumab group.	Any serious AE: 32.4% vs 18.2%; infection as serious AE: 16.9% vs 7.6%; grade ≥3 infection 15.4% vs 6.8%; drug-related neutropenia 12.5% vs 3.8%; deaths 2.2% vs 0.8%	Adding obinutuzumab to standard therapy of MMF and steroids enhanced CRR by week 76, supporting deeper B cell depletion as an effective add-on strategy. Serious infections and neutropenia seen in the obinutuzumab group underscore importance of infection risk mitigation.

Legend (abbreviations)

Years: yrs
Weeks: wks
Body surface area: BSA
Chronic kidney failure: CKD
Renal Response: RR
Complete Renal Response: CRR
Adverse event: AE
Hypertension: HTN
Pneumonia: PNA
Infection: ifxn
Biopsy: Bx
Every: q

(*continued on next page*)

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Table 2 (*continued*)

Legend (abbreviations)	
Partial Renal Response: PRR	Plasmapharesis: PLEX
Glomerulophenphritis: GN	Cyclophosphamide: CYC
Lups nephritis: LN	Azathioprine: AZA
End-stage renal disease: ESRD	Methylprednisolone: MP
Urinanlysis: UA	Prednisone: Pred
High-power field: HPF	Low-dose: LD
Thrombotic microangiopathy: TMA	High-dose: HD
Diabetes mellitus: DM	Rituximab: RTX
White blood cell: WBC	Belimumab: BEL
Red blood cell: RBC	Hydroxychloroquine: HCQ
Hour: hr	Urine protein/creatintine ratio: UPCR
Antibody: Ab	Mycophenolate mofetil: MMF
Serum creatinine: SCr	
Systemic lupus erythematosus: SLE	
SLE Disease Activity Index: SLEDAI	

regimen with less toxicity at 6 months [18]. In the 2009 Aspreva Lupus Management Study (ALMS) trial, mycophenolate emerged as an effective LN induction agent compared to IV cyclophosphamide at 6 months, especially in a diverse patient population including those of African American and Hispanic descent [19]. The maintenance phase of the ALMS trial in 2011 demonstrated mycophenolate was preferred over azathioprine [20]. Trials with add-on therapies demonstrated improved renal outcomes with belimumab in BLISS-LN [21]and voclosporin in AURORA-1 [22]. The 2024 ACR LN guideline is based on data from these trials and others that are summarized in Table 2 and from expert opinion [23–33]. The inclusion and exclusion criteria, primary outcomes, and adverse events vary over time and amongst studies. This table highlights those differences and aids the practitioner in the application of the study results to their individual patient.

The 2024 ACR LN guideline emphasizes glucocorticoid-sparing strategies and individualized selection of therapy tailored to patient-specific factors. Hydroxychloroquine is strongly recommended for all patients without contraindications, and renin-angiotensin-aldosterone system (RAAS) inhibition should be initiated for any degree of proteinuria. For proliferative LN (class III/IV, with or without class V), the guideline conditionally favors triple immunosuppressive therapy using reduced-dose glucocorticoids combined with one of the following strategies: mycophenolic acid analog (MPAA) plus belimumab, MPAA plus a calcineurin inhibitor, Euro-Lupus low dose cyclophosphamide plus belimumab followed by MPAA plus belimumab. The guideline overall prioritizes MPAA-based regimens over cyclophosphamide. The choice of add-on therapy (belimumab or calcineurin inhibitor) is guided by proteinuria burden and extra-renal disease activity, aligning LN management with systemic lupus control. Pure class V LN is treated based on proteinuria severity, with escalation to triple therapy for $\geq$1 g proteinuria. Maintenance therapy is recommended for at least 3-5 years in patients achieving CRR, with a target prednisone dose of $\leq$5 mg/day by six months to reduce long-term toxicity.

Less common lupus-related kidney manifestations, such as thrombotic microangiopathy (TMA), class II LN, and lupus podocytopathy, require individualized evaluation and multidisciplinary care, as management may differ substantially from proliferative LN. TMA represents endothelial injury with heterogeneous etiologies, including antiphospholipid-associated nephropathy and complement-mediated disease, and may require targeted therapies such as anticoagulation, plasma exchange, or complement inhibition. Class II LN is typically managed with RAAS inhibition, with consideration of repeat biopsy in cases of worsening proteinuria to assess for class transformation or podocytopathy. Lupus podocytopathy commonly presents with nephrotic-range proteinuria and is generally treated with glucocorticoids and additional immunosuppressive agents under nephrology co-management.

5. Recommendations on adjunct therapy, monitoring and long-term management

The 2024 ACR LN guideline emphasizes that adjunctive and non-immunologic therapies are essential components of LN management and should accompany immunosuppressive treatment to optimize kidney and overall health. Clinicians should exclude alternative causes of kidney dysfunction, including hypertensive, diabetic, and medication-related nephropathy. Kidney-protective strategies include universal use of RAAS inhibitors when tolerated, dietary sodium restriction, moderation of protein intake in reduced kidney function, and consideration of SGLT2 inhibitors in stable patients. Recent data also suggests a potential role for GLP-1 agonists [34]. The 2024 ACR LN guideline also emphasizes comprehensive care, including cardiovascular risk reduction, bone health, infection screening and vaccination, and reproductive health counseling with age-specific considerations, including glucocorticoid minimization in children, structured transition of care, and regular medication review in older adults.

6. Renal biopsy in lupus nephritis

Ultimately, kidney biopsy remains the gold standard for the diagnosis and classification of LN as the diagnostic and prognostic value of histologic features cannot be accurately predicted at this time by clinical or laboratory parameters alone [35]. Pathologic review of renal tissue evaluates the degree of activity and chronicity of LN, which guides subsequent immunosuppressive therapy. The International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system characterizes LN into six classes based on light microscopy findings: class 1(minimal mesangial), class II (mesangial proliferative), class III (focal proliferative, $<$50% of glomeruli), class IV (diffuse proliferative, $\geq$50% of glomeruli), class V (membranous), and class VI (advanced sclerosing) [36]. Renal biopsies are also classified by the NIH Activity (NIH-AI) and NIH Chronicity (NIH–CI) Indices [37]. Higher chronicity indices predicted worse long-term renal outcomes, while higher activity indices correlated with acute inflammatory injury that may respond to immunosuppressive treatment [38].

As noted above, the 2024 ACR LN guideline recommends that a patient with suspected LN, such as those with proteinuria or otherwise unexplained renal insufficiency, should undergo a kidney biopsy [15]. Additionally, the guideline conditionally recommends considering a repeat renal biopsy for those previously in remission and suspected of having a flare based on clinical parameters or those with persistent or worsening clinical renal disease despite at least 6 months of appropriate therapy. Recently, data presented at the ACR Annual Scientific Meeting in 2025 suggests that a renal biopsy should be considered at a lower proteinuria threshold. Petri and colleagues demonstrated that among patients with SLE and proteinuria (urine protein creatinine ratio 0.25–0.49 g/g), nearly 50% had histologically actionable LN on kidney biopsy, including 21% with proliferative disease (class III/IV $\pm$ V) and 25% with membranous nephritis (class V), despite proteinuria below the conventional 500 mg threshold [39]. While renal biopsy offers notable diagnostic and prognostic benefits, there are risks associated with the procedure that need to be acknowledged. In a large systematic review of 118, 604 percutaneous kidney biopsies, bleeding was the most commonly reported complication, most often related to perirenal hematoma (11%) [40]. Macroscopic hematuria occurred in 3.5% of the cases, with 1.6% requiring erythrocyte transfusion and 0.3% necessitating procedural intervention for bleeding control. Nephrectomy (0.01%) and death (0.06%) were rare. In an Italian study of 5304 percutaneous renal biopsies, a major complication occurred in 5.1% of cases with the more common complications including a drop in

hemoglobin of 2 g/dL (2.2%), blood transfusion (1.1%), invasive intervention (0.5%), and death (0.02%) [41].

There is interest in recent years of per-protocol biopsies for lupus glomerulonephritis (GN). Some clinicians believe that clinical monitoring is sufficient to assess prognosis and make therapeutic decisions while others recommend per-protocol biopsies performed at pre-defined time points, such as at 6 months in clinically stable patients to verify the response to induction therapy, or after one to two years to assess treatment efficacy and optimize the duration of maintenance therapy [35]. This is in part due to a main parameter of clinical remission defined by a urinary protein level less than 500 mg in 24 h. Unfortunately, proteinuria on its own is unable to distinguish between activity and damage in the kidney. In a prospective observational study, DeRosa and colleagues noted that in 44 patients treated for 36 months for LN with proteinuria <500 mg/day, 44% had histologic activity on repeat renal biopsy ranging from an activity index of 1-5 [31]. Additionally, Parodis and colleagues evaluated repeat renal biopsies on 42 patients with class III or IV with or without class V disease 24 months after treatment and found only moderate correlation of urinary protein to creatinine ratio and the activity index score (r 0.48) [43]. Additionally, the study noted 10 patients (23.8%) with UPCR of <1.0 had an activity index of greater than 3 on the repeat biopsy.

Per the 2023 European Alliance of Associations for Rheumatology (EULAR) recommendations for SLE management, a repeat kidney biopsy may be considered in patients in clinical remission when contemplating therapy withdrawal, using the biopsy to assess residual histologic activity that could predict subsequent disease flare. This approach is supported by observational studies [42]; however, it has not yet been formally evaluated in randomized controlled trials [44]. Ongoing efforts to address these gaps include the randomized, prospective clinical trial titled "Per-protocol Repeat Kidney Biopsy in Incident Cases of Lupus Nephritis" [45] which aims to determine whether histology-guided treatment adjustments based on repeat biopsies at 12 months demonstrate improved outcomes compared to standard of care.

7. Disease monitoring in lupus nephritis

Diagnosis of LN and subsequent monitoring is currently performed by checking a combination of serum, urinary, and tissue biomarkers. These are checked at the time of initial SLE diagnosis, monitored serially to assess the development of LN, and monitored during LN treatment to evaluate for treatment response.

Serum biomarkers include autoantibody levels, complement levels, and creatinine clearance. At time of initial diagnosis, serologies often reveal elevated titers of autoantibodies to double-stranded DNA (anti-dsDNA) and C1q, low C3 and/or C4 levels, and either intact or decreased creatinine clearance [46]. High titers of anti-dsDNA have been associated with proliferative LN [47]. Elevated levels of antibodies to C1q at 12 months were associated with recurrence of LN flares [48]. Low C3 can identify patients with "silent" LN where there is active SLE but without abnormal urinalysis or renal impairment [49]. Isolated C3 hypocomplementemia 6 months after kidney biopsy has been identified as an increased risk for development of chronic kidney disease, ESRD, or death [50]. One study demonstrated that the resolution of dsDNA antibody presence and normalization of C3 levels at 6 months predicts therapeutic response at 12 months: C3 normalization had sensitivity of 70% and specificity of 67% and anti-dsDNA resolution had a sensitivity of 70% and specificity of 56% in the validation cohort [51]. Higher baseline serum creatinine has been associated with increased risk for ESRD or decline in eGFR [46]. Higher rate of serum creatinine decrease at 12 weeks was associated with achievement of CRR [52]. However, these serologies are not specific to renal SLE flares and can also be found in non-renal SLE flares.

Traditional urinary biomarkers used in routine LN evaluation include urinalysis with microscopy for proteinuria and cellularity, UPCR, and 24-h urine proteinuria. Using the data from the Euro-Lupus Nephritis Trial, Dall'Era and colleagues found that UPCR <0.8g/day after 12 months of therapy was the best predictor of favorable long-term renal function [53]. Subsequent clinical trials have incorporated UPCR as the measure of primary response outcomes, and both 2024 KDIGO and ACR LN Guidelines refer to CRR as < 500 mg of proteinuria in a 24-h collection. However, others have found that low-grade proteinuria has not been associated with better treatment or renal response [54]. Additionally, proteinuria can be a delayed indicator as it correlates poorly with active disease, and it may manifest only after substantial kidney injury has occurred [46] [55]. Thus, the current use of the UPCR as the primary response biomarker has raised ongoing discussion whether these measures of proteinuria are the best markers for primary response and outcome predictions.

8. Upcoming biomarkers

New strategies with serum and urinary biomarkers are in development. A study using the Accelerating Medicines Partnership (AMP) LN cohort measured 66 serum immune mediators in 268 patients with SLE undergoing clinically indicated biopsy at time of biopsy, and 3-, 6-, and 12- months post-biopsy [56]. The study found elevated levels of serum mediators syndecan-1, TNFRI, TNFRII, and VCAM-1 in patients with proliferative LN (class III/IV ± V on biopsy) compared to non-proliferative LN. The study also revealed that baseline to month 3 decreases in syndecan-1 and VCAM-1 in addition to early improvement in UPCR were predictive of 12-month renal response treatment response. Additionally, models using their panel of serum soluble mediators were better at identifying histologic classes than models using traditional clinical and demographic features alone. They further identified molecular heterogeneity within a given histologic class. Clustering the mediators lead to four groups which had different phenotypes suggesting that molecular profiling could improve LN classification beyond class type alone. The same cohort also demonstrated that immunophenotyping of the peripheral mononuclear cells could differentiate patients into one of three categories that are associated with histology and cellular findings on the biopsy and likelihood of the therapeutic response [57].

There is also momentum to evaluate and monitor disease via urinary biomarkers through cytokines, chemokines, enzymes, injury proteins, vascular molecules, and other molecules – non-exhaustive examples are listed in Table 3. This approach is favorable as urine

Table 3
Types of urinary biomarkers.

Cytokines [58] [64]	Chemokines [65]	Urinary Enzymes [66]	Injury Proteins [58]	Adhesion/Vascular Molecules [58]	Others [62]
TWEAK	**MCP-1(CCL2)**	**NGAL(LCN2)**	**KIM-1**	Angiostatin	C9
IL-16	CCL5/RANTES	NAG	HMGB1	**VCAM-1**	**CD163**
IL-17	CXCL10/IP10			**ICAM-1**	CD206
IL-6	CXCL16			Endothelin	Galectin-1
B-cell activating factor (BAFF)	IL-8			VEGF	Tenascin C
Adiponectin				**ICAM-2(CD102)**	FOXP3
TGF-beta				**L-selectin**	Ceruloplasmin
Osteoprotegrin				**E-selectin**	Transferrin
TNFR1				**ALCAM**	STAT-1
				NCAM-1	HPGDS
					IGFBP2

Bolded = Urinary biomarkers identified in at least 4 studies.

collection is noninvasive, making it easier to serially monitor. Moreover, urine reflects the intrarenal biology more closely than serum [58]. This makes urinary biomarkers conceptually more advantageous than using conventional biomarkers, such as proteinuria, which can be a lagging indicator and a poor discriminator between inflammation and scarring.

A review in 2024 of forty peer-reviewed articles revealed fourteen biomarkers that were repeatedly reported or tested in four or more papers [58]. These included ALCAM, CCL2 (MCP1), CD163, HAVCR1 (KIM-1), HPGDS, ICAM-1 (CD54), ICAM-2 (CD102), IGFBP2, LCN2, NCAM-1 (CD56), SELE (E-selectin), SELL (L-selectin), TNFSF12 (TWEAK), and VCAM-1 [58]. Other examples of urinary biomarkers that have been extensively studied include IL-16, BAFF, and tenascin C, which reflect cytokine signaling, B cell stimulation, and fibrotic remodeling pathways respectively [59]. With the additional insight on intrarenal pathophysiology, urinary biomarkers have been shown to correlate with disease activity via histopathological activity, prognosis, and treatment outcomes. The next sections focus on a few of the more promising urinary biomarkers [58].

9. Urinary biomarkers: pathology and disease activity

Although the field of urinary biomarkers is still in its research phase, a "liquid biopsy" has the potential to further predict histology and stratify disease activity. In a cohort of patients with SLE undergoing kidney biopsy for suspected LN, distinct histologic classes revealed differing proteomic signatures with urine proteomic profiles in proliferative LN differing from membranous LN [60]. Another study of 37 patients with LN who underwent kidney biopsy showed that higher concentrations of urinary ceruloplasmin was associated with patients with cellular crescents, while higher concentrations of urinary MCP-1 was associated with a chronicity index $\geq$4, fibrous crescents, tubular atrophy, and interstitial fibrosis [61]. Urinary epidermal growth factor (EGFR) negatively correlated with the NIH Chronicity Index and positively with the NIH Activity Index [51]. In a study of 30 patients with LN, urinary IL-16, CD163, and transforming growth factor beta (TGF-beta) measured near or at time of diagnostic renal biopsy were found to be associated with intrarenal nephritis activity [62]. Urinary IL-16 showed the strongest positive correlational with biopsy determined histological NIH activity index and was also the most strongly associated with proliferative LN. TGF-beta and CD163 were also associated with histological nephritis activity but to a lesser extent compared to IL-16. Recently, CD-163, IL-16, tenacin –C along with several other biomarkers have been useful in differentiating patients with low grade proteinuria attributed to class III and class V lupus GN versus no renal SLE on biopsy. These protein profiles are unlikely to replace kidney biopsy at diagnosis, but they may serve as a useful risk stratification tool at the time of initial diagnosis or during disease monitoring throughout treatment. [59]).

Given the suboptimal correlation of proteinuria with disease activity, there is interest in using urinary biomarkers to assess disease activity and predict flare. A 12 urinary protein panel implemented by Fava et al. was a better reflector of activity index >2 than dsDNA antibody or proteinuria [55]. Urinary TNF-like weak inducer of apoptosis (TWEAK) levels was higher in patients experiencing a renal flare, as opposed to a non-renal flare, and correlated with the renal SLE disease activity index (rSLEDAI) [63]. TWEAK levels were also associated with longitudinal disease activity, rising during an LN flare compared to measurements at 4 and 6 months before and after the flare, suggesting that monitoring of TWEAK levels may signal upcoming flares [64]. Urinary chemokine MCP-1 and vascular molecule VCAM-1 were measured in 55 patients with LN and 34 healthy controls, and patients with LN had significantly elevated levels of urinary MCP-1 and VCAM-1 [65]. Further analysis showed that MCP-1 and VCAM-1 had a strong correlation with SLEDAI scores, compared with traditional biomarkers.

10. Urinary biomarkers: prognosis/treatment outcome

Urinary biomarkers have also been associated with prognostication of renal function and treatment response. In a longitudinal cohort in the United States and Mexico, urinary CD163 was measured in patients undergoing treatment for LN flares [51]. Persistently elevated CD163 levels correlated to treatment nonresponders, while low urinary CD163 at 6 months predicted complete treatment response at 1 year with >87% sensitivity and 87% specificity. Elevated levels of urinary MCP-1 and urinary NGAL before induction treatment have been associated with poor treatment response [66]. In the AMP cohort, urinary IL-16 levels decreased among patients who achieved treatment response, which was defined by improvement in proteinuria [62]. Tenascin C has recently been reported to

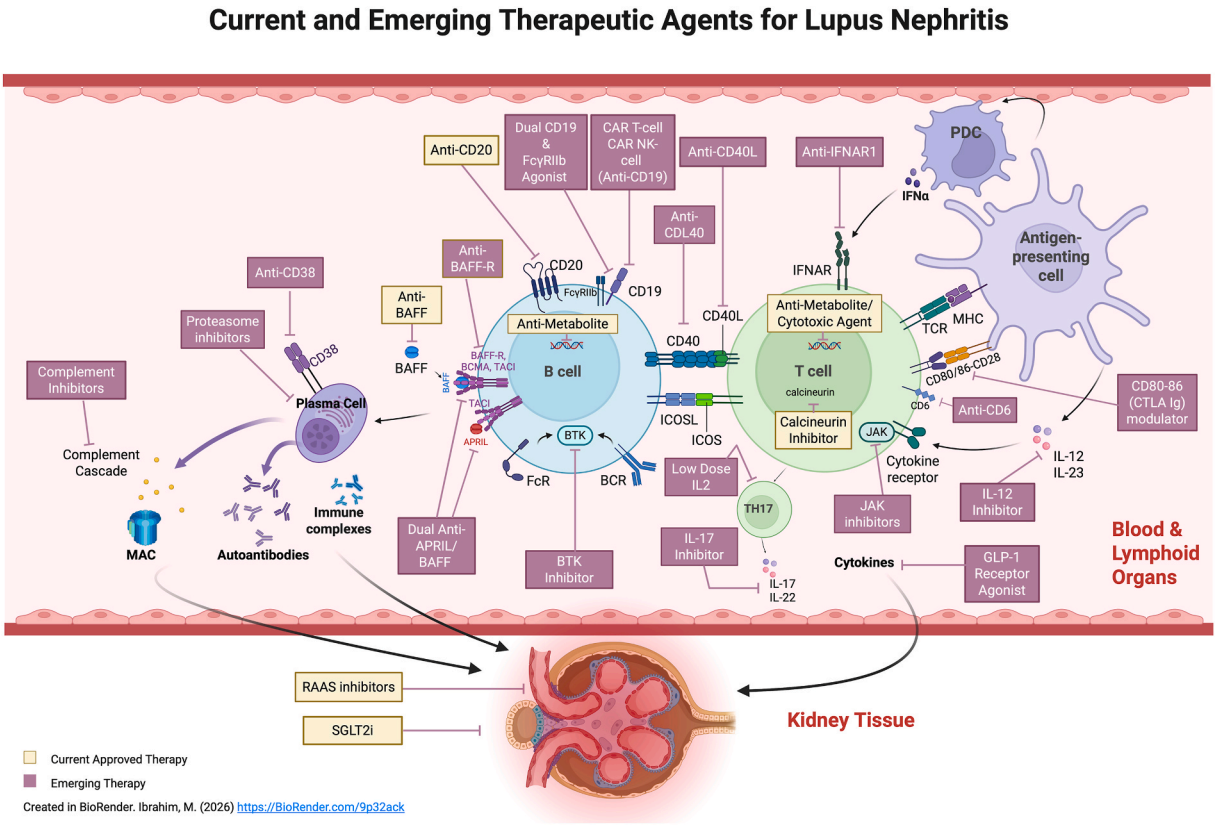


Fig. 1. Current and emerging therapeutic agents for the management of lupus nephritis.
Schematic representation of the mechanisms of action and immunologic targets of conventional immunosuppressive therapies, biologic agents, and emerging targeted therapies in lupus nephritis. Key pathways include B-cell modulation, T-cell co-stimulation, cytokine inhibition, and complement blockade. Created with BioRender.com.

predict decline in glomerular filtration rate in LN at 3 and 12 months [55]. High urinary tenascin C may also predict histological nonresponders on repeat biopsy after 1 year [55]. Furthermore, a combination panel of urinary protein biomarkers correlated with renal function loss and treatment response.

Thus, while there is a great deal of excitement that serum and urinary biomarkers may be used to screen for LN, monitor for renal disease flares, and predict treatment response or failure, further work needs to be done to validate these findings longitudinally and across multiple cohorts. There is not enough data with the available urinary biomarkers to replace the gold standard of renal biopsy. Implementation into clinical practice has yet to be formalized as key questions remain, including whether these urinary biomarkers are to be used individually, in conjunction with others, and the optimal timing frequency.

11. Emerging therapeutic strategies in lupus nephritis

Therapeutic development in LN is rapidly expanding, with increasing focus on targeted modulation of immune pathways that drive renal inflammation and progressive kidney damage. Fig. 1 provides a depiction of the current and emerging treatments and their specific therapeutic targets. Next-generation B-cell directed therapies such as type II anti-CD20 which induce stronger antibody dependent cellular cytotoxicity (ADCC) have been found to produce superior effect on B cell depletion than older anti-CD20 therapies [67]. The FDA recently approved obinutuzumab, a humanized type II anti-CD20 monoclonal antibody, for the treatment of LN. The REGENCY trial demonstrated that obinutuzumab had improved CRR at 46.4% compared to placebo group at 33.1% with both groups on background mycophenolate and prednisone taper [33]. Additionally, anifrolumab, the Anti-IFNAR1 FDA approved SLE therapy, is currently being investigated for LN in an ongoing phase 3 trial, after promising efficacy results in the higher dose arm of a phase II RCT (TULIP-LN) [31,68].

Obexelimab, an investigational bifunctional antibody that binds both the CD19 and FcγRIIb receptors on B cells, acting as an agonist of the inhibitory receptor and thereby silencing without destroying the B cells that cause lupus flares, has shown efficacy in SLE. In a phase 2 “proof of concept” trial, efficacy analysis of primary end point in obexelimab-treated-arm did not reach statistical significance as compared to placebo, however in the secondary analysis, patients who were treated with obexelimab had longer interval to loss of improvement as compared to placebo. Additionally in a subset analysis of obexelimab-treated patients, 2 of 7 gene

expression clusters demonstrated higher clinical response to obexelimab, suggesting a treatment-responsive subpopulation [69].

Telitacicept, a TACI fusion protein dual inhibitor of the cytokines BAFF and APRIL B cell receptors, conditionally approved in China for SLE, has shown efficacy in a recent phase 3 RCT in Chinese patients with SLE including patients with renal involvement (with exclusion of patients with "severe" lupus nephritis) [70]. Supportive data from a large observational real-world study recently published provides further evidence of the drug's efficacy in LN [71]. Further work in targeting of B cell activation in LN is ongoing with phase 3 trial of anti-BAFF-R, ianalumab.

Another target that has gained rapid attention in last few years is anti-CD19 chimeric antigen receptor (CAR) T-cell therapy [72] [73]. Initially reported in the treatment of hematopoietic cancers, CAR T-cell therapy has demonstrated the efficacy of near-complete deep B cell depletion in autoimmune disorders including SLE. In 2021, anti-CD19 CAR T-cell therapy first showed promise when it was used in 20-year-old women with refractory SLE who had notable improvement in serology, renal manifestations, and overall disease activity within weeks of treatment [74]. Since then, further studies supported clinical efficacy of CAR T-cell therapy in autoimmune diseases, especially in SLE. In a landmark study composed of 5 patients with refractory SLE, remission was achieved by DORIS criteria after 3 months in all 5 patients who received anti-CD19 CAR T-cell therapy, and sustained drug-free remission was reported at 8 months follow up without significant CAR T-cell therapy related adverse events [75]. In a follow-up study that included 15 patients with rheumatic autoimmune diseases, anti-CD19 CAR T-cell therapy was administered as a single infusion that resulted in a 2 year sustained remission in all 8 SLE patients, in all 3 patients with idiopathic inflammatory myositis based on ACR-EULAR major clinic response, and the 4 systemic sclerosis patients noted to have a decrease in the EUSTAR activity index [76]. Several global clinical trials are now ongoing to address the efficacy and safety of CAR T-cell therapy in refractive SLE and LN. CAR T-cell therapy has the potential to transform the landscape of current immunosuppression in LN and other rheumatologic diseases. Other forms of cellular therapy are in development for the treatment of SLE. In pre-clinical data, the administration of allogenic cord blood derived NK cell therapy (AlloNK), in combination with B cell depleting monoclonal antibodies, induced cell-specific killing of SLE donor B cells [77]. A Phase 1 study aiming to evaluate the efficacy AlloNK therapy in combination with a monoclonal antibody with class III/IV LN refractory to prior treatments is in process. In parallel, NKX019 is an investigational, off-the-shelf allogeneic CAR NK cell therapy designed to target and deplete CD19-positive B cells for the treatment of refractory LN [78].

There is ongoing work in plasma cell directed therapies such as anti-CD38, a target under investigative development in LN, which was initially discovered for hematologic malignancies [79,80], and aims to achieve deeper and more durable immunologic remission than traditional B-cell depletion. In a case series, 5 of 6 patients with biopsy proven refractory LN who received daratumumab had improved SLEDI, proteinuria, and kidney function as well as seroconversion of dsDNA, supporting its ongoing exploration as a LN therapy [81].

The CD40–CD40 ligand pathway has been described extensively as a culprit in SLE pathogenesis, promoting generation of autoantibodies and immune-complex deposition in the kidneys, which subsequently can lead to LN in some patients [82,83]. Though a phase 2 trial failed to demonstrate a dose-response relationship for the primary CRR endpoint, a post hoc analysis suggested a potential benefit of higher doses of anti-CD40 monoclonal antibody in patients with active LN [84]. A follow-up study of this patient cohort demonstrated that in LN kidney biopsy samples with glomerular monocytes, high-dose anti-CD40 monoclonal antibody treatment improved proteinuria at 52 weeks and resulted in a higher CRR compared to biopsy samples without glomerular monocytes [85]. These results further endorse the potential for utilizing kidney biopsy findings to select targeted therapies. Dapirolizumab Pegol, a PEGylated anti-CD40L, was evaluated in a phase 2 trial with moderate-to-severe active SLE patients, which included stable lupus nephritis, but did not meet its primary endpoint, though notably there was overall improvement in disease activity measures, serum complement and dsDNA levels. Two phase 3 trials of dapirolizumab were conducted in SLE, meeting their primary end points and improvement in outcome measures [86]; however, more studies are needed to predict outcomes in LN.

Complement system activation and immune complex deposition causing kidney inflammation and proliferation in LN has been described for several decades [87,88].Therapeutic agents targeting this pathway have gained attention in last the few years [89]. Pegcetacoplan, a C3 and C3b inhibitor that blocks all three complement pathways, has shown promise in a phase 2 study of patients with complement mediated disease including LN, with reduction proteinuria by 50% and improvement in UPCR ratio [90]. Iptacopan, an oral small molecule selective complement inhibitor of factor B, prevents activation of alternative complement pathway and is currently being investigated in several phase 2 trials globally in patient with active LN [91,92].

Other emerging therapies on the horizon include Zanubrutinib, a BTK inhibitor being investigated for proliferative LN [93] [94]. Itolizumab, a first in class anti-CD6 which binds to T cells, has shown promise with improved UPCR in a phase 1b study, with favorable safety and tolerability profile [95]. Cytokine targeted therapies are not novel therapies. For example, targeting the IL-17/IL-23 axis has been associated with the pathogenesis of LN [96] and is also a target of multiple other autoimmune conditions. A link between IL-2 insufficiency and LN has been studied, with data showing lower levels of serum IL-2 in patients with LN inversely correlated with 24 h urine protein excretion and improved LN outcomes when exogenously replaced [97]. Additionally, low dose IL-2 administration, which selectively promotes regulatory T-cells but inhibits T helper 17 (Th17) cells and follicular helper T cells (Tfh), has shown in a randomized control trial its efficacy with over half of the participants with LN receiving low-dose IL-2 achieved CRR compared to 16.67% of those who received placebo [98]. There was initial interest for IL-17 inhibition, and it was evaluated in a phase 2 clinical trial in patients with LN but the study failed to meet its primary end points [99]. Similarly, Guselkumab, an IL-23 inhibitor, did not meet the primary end point in a phase 2 trail of patients with active LN [100]. Abatacept, a selective co-stimulation modulator that inhibits T cell activation by binding to CD80 and CD86, had been found to have favorable results in case reports of refractory LN [101]. However, it did not meet the primary end point in a randomized controlled trial when compared to placebo in treatment of patients with active LN class III or IV [102]. Lastly, Zetomipzomib, which is a selective inhibitor of the immunoproteasome which blocks multiple pathways involved in inflammatory cytokine production and immune effector cell activity, has demonstrated positive results

Clinical practice points

- 2024 ACR LN Guideline recommends routine screening for proteinuria at least every 6-12 months and during extra-renal disease flares.
- Currently serum creatinine, anti-dsDNA antibodies, complement levels, and urine protein levels are used to monitor LN activity. Research into improved and more specific urinary biomarkers are underway and preliminary results are promising.
- Renal biopsy remains the gold standard of diagnosis of LN.
- Treatment paradigms for proliferative lupus glomerulonephritis and membranous lupus glomerulonephritis with nephrotic range proteinuria have shifted with the recommendation of triple therapy targeting multiple inflammatory pathways that in clinical trials have improved response rates.

Research agenda in lupus nephritis

- **Development and validation of novel urinary biomarkers for lupus nephritis monitoring:** Further research is needed to compare urinary biomarkers across standardized lupus nephritis cohorts, evaluate their role as surrogate markers of intrarenal disease activity beyond proteinuria on UPCR, and define practical strategies for clinical implementation.
- **Define the role of per-protocol renal biopsies in guiding treatment decisions:** Routine per-protocol kidney biopsies remain investigational. The 2024 ACR LN guideline does not recommend scheduled biopsies, but the Voting Panel emphasized that this is a key research priority.
- **Identify more effective targeted therapies in lupus nephritis:** A growing pipeline of novel agents is reshaping the treatment landscape of lupus nephritis. A key research priority is to determine which therapies will be effective, safety profile, and the timing of these treatments alongside stand-of-care regimens.

in a phase 1b/2 trial in LN patients with 11 of the 17 LN patients having a $\geq$50% reduction in UPCR from baseline and 6 of 17 LN patients achieving CRR [103]. Though the initial results were encouraging, further progress in clinical trials with Zetomipzomib in LN has been paused by the FDA due to safety concerns.

12. Summary

The landscape of LN management is shifting, marked by the updated 2024 ACR LN guideline that now endorses triple therapy over traditional dual regimens to improve renal outcomes. Landmark trials established the foundation for current proteinuria-centered framework and treatment regimens. Despite these early advances, this paradigm is increasingly recognized as imperfect, as complete response rates in contemporary LN trials remains under 50%. Building on this, the field is now re-examining long held definitions of proteinuria and pushing toward more precise, individualized care through emerging urinary biomarkers, conversation regarding per-protocol repeat kidney biopsy, and improved approaches to risk stratification and prognostication. These approaches can guide early escalation of therapy. Emerging novel therapeutics are themed toward deeper suppression of pathogenic B cell and plasma cell pathways, inhibition of upstream innate immune and cytokine signaling, and blockade of complement-mediated renal injury, with the goal of improving renal outcomes. Together, these strategies reflect a move toward precision-based, kidney-specific management of LN.

CRediT authorship contribution statement

Malika Ibrahim: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Emily He:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Diana Tran:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft. **Divya Vundamati:** Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft. **Jennifer Grossman:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing.

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Declaration of competing interest

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