

Kidney biopsy in Lupus Nephritis: still essential in clinical practice

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ABSTRACT

Renal involvement in Systemic Lupus Erythematosus is common and its management remains a daily challenge for clinical providers. Percutaneous kidney biopsy remains the gold standard for diagnosis of lupus nephritis. More recently, we have seen the role of the biopsy being challenged, considering the widespread use of corticosteroids and mycophenolate mofetil for all forms of lupus nephritis. We present a review of published evidence regarding first and repeat kidney biopsies for patients with lupus nephritis. Based on the available literature, we recommend a kidney biopsy to guide treatment and determine prognosis and we also suggest an algorithm for kidney rebiopsy in lupus nephritis.

Keywords: Kidney biopsy; Lupus nephritis; Systemic lupus erythematosus

INTRODUCTION

Lupus nephritis (LN) is one of the most common and devastating manifestations of Systemic Lupus Erythematosus (SLE), occurring in over half of patients with this condition. It has been shown that renal involvement is a poor prognostic factor among patients with SLE.¹ The prevalence of SLE and the chances of developing LN vary between world regions, races and ethnicities.² Black and Hispanic SLE patients develop LN earlier and have worse outcomes than the white population.

Percutaneous kidney biopsy, introduced in the 1940s and incorporated into clinical practice since the 1950s, remains the gold standard for diagnosis of LN, and is highly recommended for the recognition and classification of renal involvement, to assess disease activity and thus guide intensity of treatment and also

to predict prognosis.^{3,4} According to the American College of Rheumatology (ACR)/Systemic Lupus International Collaborative Clinics classification criteria (2012), a positive sample for anti-nuclear or anti-double-stranded DNA antibodies with biopsy-confirmed nephritis consistent with LN (following the International Society of Nephrology/Renal Pathology Society 2003 classification of LN – Table 1), is diagnostic of SLE.^{5,6} Kidney biopsy findings in LN have been used to classify and subgroup LN in order to obtain accurate diagnosis, guide treatment decisions and also predict prognosis. The ISN/RPS LN classes have been used to guide treatment (Table 2). Nevertheless, the role of kidney biopsy in SLE when there is clinical evidence of renal involvement seems controversial. The percutaneous kidney biopsy is an invasive procedure, and elicits a “do no harm” response in physicians. Furthermore, it has been suggested that all forms of LN could be treated with corticosteroids and mycophenolate

Table 1

International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2004 classification of lupus nephritis; LM – light microscopy; IF – immunofluorescence; EM – electron microscopy

Class I	Minimal mesangial LN Normal glomeruli by LM, but mesangial immune deposits by IF
Class II	Mesangial proliferative LN Purely mesangial hypercellularity of any degree or mesangial matrix expansion by LM, with mesangial immune deposits. May be a few isolated subepithelial or subendothelial deposits visible by IF or EM, but not by LM
Class III	Focal LN Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative LN
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing LN
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing LN
Class IV	Diffuse LN Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. Divided into diffuse segmental (IV-S): ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G): ≥50% have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative LN
Class IV-G (A)	Active lesions: diffuse global proliferative LN
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing
Class IV-G (A/C)	Active and chronic lesions: diffuse global proliferative and sclerosing
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing
Class V	Membranous LN Global or segmental subepithelial immune deposits or their morphologic sequelae by LM and by IF or EM, with or without mesangial alterations. May occur in combination with class III or IV in which case both will be diagnosed. Class V LN can show advanced sclerosis
Class VI	Advanced sclerosis LN ≥90% of glomeruli globally sclerosed without residual activity

Table 2

Treatment recommendations for LN based on "Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney Inter., Suppl.* 2012; 2: 139–274." CNI – calcineurin inhibitor

Class of LN	Treatment recommended
Class I	Treatment dictated by extrarenal clinical manifestations of lupus
Class II	Treat patients with proteinuria <1g/d as dictated by extrarenal clinical manifestations of lupus Treat patients with proteinuria >3g/d with corticosteroids or CNIs as for minimal change disease
Class III	Initial treatment with corticosteroids combined with either cyclophosphamide or MMF
Class IV	Maintenance therapy after initial therapy with azathioprine or MMF and low-dose oral corticosteroids CNIs with low-dose oral corticosteroids may be used for maintenance treatment in patients intolerant to MMF or azathioprine
Class V	Treat patients with normal kidney function, non-nephrotic-range proteinuria with antiproteinuric and antihypertensive medications; only treat with corticosteroids and immunosuppressive therapy as dictated by extrarenal clinical manifestations of lupus Treat patients with pure class V LN and persistent nephrotic proteinuria with corticosteroids plus an additional immunosuppressive agent: cyclophosphamide, CNI, MMF or azathioprine
Class VI	Treat with corticosteroids or immunosuppressive therapy only as dictated by extrarenal manifestations of systemic lupus

mofetil (MMF)⁷. Having the histologic diagnosis seems not to predict treatment response or long-term kidney outcomes. Although new urine and serum biomarkers are being investigated for LN⁸, and in the future such

markers might be used as assessment tools for personalizing LN treatment and improving outcomes, no novel biomarkers have been approved for clinical testing.

Taken together these considerations raise the question: do we still need a kidney biopsy in LN? This brief review will discuss this subject and propose a possible algorithm for kidney biopsy in LN.

■ REFERENCE BIOPSY

As the clinical manifestations of LN are often subtle, SLE patients should be evaluated for kidney involvement at initial diagnosis and at least yearly thereafter, and if kidney disease is suspected, a kidney biopsy should be considered. The clinical threshold for undertaking a kidney biopsy is not well defined. We suggest performing a biopsy if a SLE patient has proteinuria ≥ 500 mg/d, with or without other clinical abnormalities, or any level of proteinuria or hematuria with impaired kidney function that cannot be attributed to another cause. It has been well established that early diagnosis and treatment of LN improves prognosis.⁹

Regarding proteinuria, there are no specific guidelines as to when to proceed to biopsy; most clinicians use a threshold of $>0.5 - 1.0$ g/day.¹⁰⁻¹² However, patients with low-grade or even absence of proteinuria can have severe LN histology.¹³⁻¹⁵ In a pilot study of 38 lupus patients with glomerular haematuria, proteinuria <500 mg/day and no renal failure, only 5% showed class II LN; the rest had class III, IV or V.¹⁴ In another study designed to evaluate clinical and laboratory predictors of distinct histopathological features of LN, of 297 patients with biopsy-confirmed LN, 19.1% had class III/IV or V with proteinuria <500 mg/day (Table 3).¹⁵

Although immune-complex-mediated GN is the most common histopathological pattern of kidney involvement in SLE, there are other mechanisms of kidney injury which can only be diagnosed by biopsy and require different management strategies, such as thrombotic microangiopathy¹⁶, or rare cases of tubulointerstitial nephritis.¹⁷ Additionally, it is common for LN biopsies to describe vascular and interstitial lesions

and score the activity and chronicity indices, providing additional data for clinical management.

Clinical data commonly obtained in lupus patients are not able to predict the degree of kidney injury in SLE. Based on the available evidence, we believe that a reference kidney biopsy in patients with suspected LN is still a valuable tool since subtle clinical features can mask severe kidney involvement from SLE.

■ REPEAT BIOPSY

Repeat kidney biopsies are even more controversial in LN. Emerging data suggest that serial biopsies may clarify treatment decisions, as in cases with incomplete or no response, or before stopping therapy after a sustained remission has been achieved. This is because there may be considerable discordance between clinical and histological LN activity^{18,19}. The persistence of proteinuria or decline in kidney function does not necessarily reflect current LN activity, and the decline or absence of proteinuria does not necessarily reflect current resolution of kidney inflammation. After long-term immunosuppressive therapy some investigators found persistent histologic activity in patients with sustained clinical remission. Moreover, patients with complete histological recovery may have persistently abnormal clinical findings²⁰, suggesting that repeat biopsies may serve as a guidance tool prior to considering withdrawal of immunosuppressive therapy.

Histologic changes in repeated biopsy can represent risk factors for kidney and patient outcomes. Persistent glomerular and interstitial inflammation, capillary immune complexes and macrophages in tubular lumens found in the kidney biopsy after induction therapy may be risk factors for future decreased kidney function.²¹ Additionally, chronic findings on a repeat biopsy can predict kidney outcomes.^{18,19} The National Institutes of Health Activity and Chronicity indices were measured in repeat biopsies in patients after starting immunosuppression and during follow-up, demonstrating that the probability of decreasing kidney function was significantly associated with the histologic index of activity, and also that renal survival was associated with the index of chronicity.²²

Most of the LN repeat biopsy literature derives from the analysis of clinically indicated biopsies in patients who did not respond to treatment as expected (persistent proteinuria or worsening kidney function); less

Table 3

Proteinuria in 297 consecutive patients with biopsy proven renal involvement with SLE (Mavragani et al, Medicine, 2015)

LN Class	N	Proteinuria ≤ 500 mg/d	Proteinuria <250 mg/d
II	47	38.6%	16%
III/IV	188	24.1%	7.3%
V	62	18.3%	3.3%

evidence comes from clinical trials where a repeat biopsy was done to assess improvement and/or histological versus clinical response.²

LN flares represent a risk for worsening kidney function independent of treatment.²³ It is well known that LN class may change to a different grade during flares.²⁴⁻²⁵ Nevertheless, a repeat biopsy during LN flare remains controversial as some investigations have shown that proliferative LN on the first/reference biopsy does not commonly change to non-proliferative LN during flare. Therefore, treatment adjustments can be initially done based on clinical and laboratory signs.^{24,26} However, it was demonstrated that class change is common, ranging from 40 to 75%, during LN flares if the first/reference biopsy showed a non-proliferative lesion.^{25,27-31} Repeat biopsy in LN classified previously as class II or V may be useful to support the need for intensifying immunosuppression. Several studies⁽²⁴⁻²⁸⁾ have shown that patients re-biopsied because of persistent non-nephrotic proteinuria, nephrotic proteinuria or decreased kidney function commonly display histological transition pattern that may affect their therapy when the reference biopsy was a non-proliferative class (I/II or V). Nonetheless 18-27% of patients with class III/IV LN switched to class V or VI LN and relatively few improved to class I or II.²⁵

Based on all these data, a repeat biopsy at flare would allow identification of patients with proliferative changes who transitioned to a non-proliferative class or *vice versa*. A second biopsy showing chronicity or inactive disease may also help in guiding immunosuppression reduction.

Considering the risks of an invasive procedure, there has been a reluctance to pursue a subsequent biopsy in LN unless there is a strong clinical indication. However, the discordance between clinical features of LN activity and histological remission is becoming increasingly clear. For example, it has been shown in a 77 patient-cohort that only 40% of patients with complete clinical remission had no evidence of histological activity in the repeat biopsy, defined as absence of glomerular and tubulointerstitial inflammation and subendothelial immune deposits.²²

Protocol biopsies have taught us some important lessons. Although very few studies have done a repeat biopsy immediately after induction treatment, findings from such biopsies have been suggested to be more predictive of long-term kidney and patient outcomes than reference biopsies.^{21,32-36} Furthermore, such

biopsies showed that aggressive immunosuppression and rapid control of clinical disease activity did not necessarily prevent chronic damage in LN. Thus, clinical findings after induction therapy may not reflect what is happening in the kidney regarding inflammation and chronic damage.

A recent study of protocol biopsies of proliferative LN after induction showed that one-third of patients with complete clinical response still had high histologic activity on the second biopsy, and that 62% of patients with complete histologic remission on re-biopsy still showed persistent clinical activity.¹⁸ In this study, chronic changes in the second biopsy were associated with CKD. Up to 50% of patients with partial or complete clinical remission still had significant histological activity in the repeat biopsy.^{32,33} While chronic damage on the second biopsy does not seem to predict long-term kidney outcome in these studies, the presence of inflammatory activity – subendothelial deposits and/or glomerular and tubular inflammation – was associated with worse long-term kidney outcomes (doubling of serum creatinine, renal impairment or death).^{22,32}

Repeat kidney biopsy after maintenance treatment is not done routinely at the present time. A few studies described repeat kidney biopsies done one or more years after the initial histologic diagnosis and initiation of therapy³⁶, usually related to kidney deterioration or suspicion of flare, as opposed to per protocol. However, in a study of 77 Middle Eastern patients a repeat protocol biopsy was done in all patients 12–18 months after diagnosis and treatment of LN, including 32 patients in complete clinical remission (defined as urine protein $\leq 0.33\text{g/day}$ and serum creatinine $\leq 125\mu\text{mol/L}$) at the time of the second biopsy.²² Of these, 60% still showed histological activity of LN in the kidney (National Institute of Health Activity Index (AI) ≥ 1). On the other hand, despite persistent proteinuria or an increase in serum creatinine, 16 to 29.4% of patients with no or partial response showed no histological activity in the repeat biopsy (AI = 0). Another study was done with biopsies performed after maintenance treatment and before finalizing the decision to withdraw or continue maintenance in patients with complete or partial clinical remission.²⁰ Despite clinical response, 56% of “complete responders”, defined as $<500\text{mg/day}$ of proteinuria and normal serum creatinine, showed AI ≥ 1 . Once again, the clinical and histological markers of disease activity did not correlate as well as expected. Discontinuing immunosuppression in patients with ongoing marked renal inflammation may put them at risk of renal relapse, while continuing

treatment in patients for signs of clinical activity (proteinuria) with no histological activity may expose patients to the morbidities of immunosuppression unnecessarily. These findings raise the question of what residual features of histological activity are most important for ongoing kidney survival. Looking at this in another way, should we always expect LN treatment to decrease the AI to 0? A repeat kidney biopsy, after patients are stable and in complete or partial remission, may help the decision of whether to continue or taper down or off maintenance treatment.

Repeat biopsies could also have a prognostic value. In a more recent, multivariate survival analysis, it was shown that subsequent biopsy with histopathologic worsening was associated with a significantly greater 15-year risk of ESRD and death, adjusted for age, gender, race, biopsy class, and treatment.³⁷

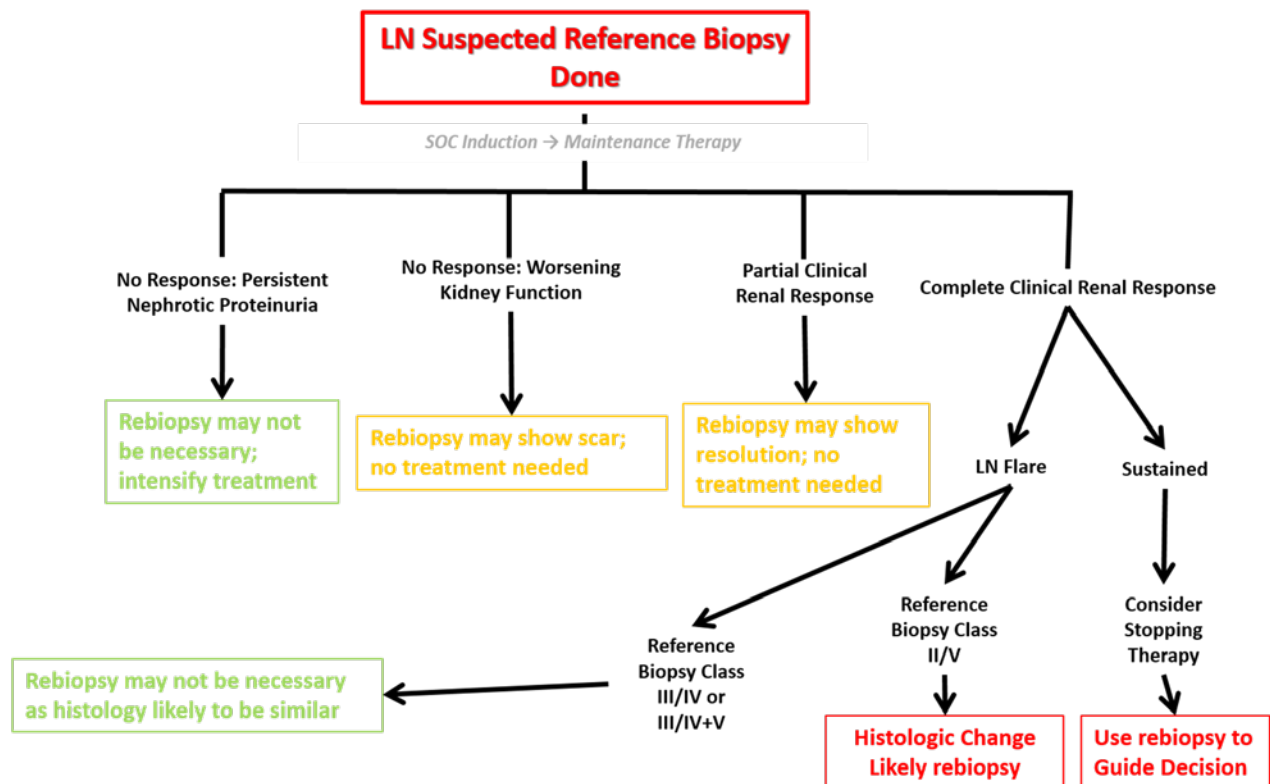
On the basis of the current evidence and considering all the previously presented data, we suggest a kidney

biopsy algorithm for LN as indicated in Figure 1. We recommend performing a “reference” kidney biopsy to confirm diagnosis and classify renal involvement, which will help guide induction treatment. Regarding repeat-biopsies, we suggest doing them in patients with LN flare, especially when the patient’s reference biopsy was ISN/RPS class I/II or class V, as histology changes are likely to impact treatment options. Patients with class III/IV LN on their reference biopsy have less likelihood of switching class at flare, so they may not need a repeat biopsy immediately at flare. Additionally, we suggest considering a repeat biopsy in patients with sustained (>12 months) partial or complete clinical remission as a tool to guide treatment choices, eventually halting or decreasing immunosuppression.

Recently novel urine biomarkers added to traditional laboratory tests, have been proposed to improve the diagnosis and prediction of LN activity and flare³⁸, and seem to accurately reflect histological LN activity but should be validated in different clinical settings.

Figure 1

Kidney biopsy algorithm for LN. SOC – standard of care



SUMMARY

Based on the discussion above, we conclude that current evidence still suggests that in daily practice percutaneous kidney biopsy is a useful tool to guide clinical management of LN. We also consider that both initial and repeat biopsy in LN represent a valuable way of guiding treatment, intensifying immunosuppression when inflammation is evident and avoiding exposure of patients to treatment risk when one does not expect further improvement. However, there is still a need for randomized, prospective studies to confirm this approach.

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Authors' Contributions:

All authors contributed to the article's concept/design, critical revision and approval. Fernando Pereira was responsible for drafting the article.

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