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Update of Lupus Nephritis Overview and Diagnostic Biomarkers

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multi-organ involvement, among which kidney is one of the most commonly affected organs.Systemic lupus erythematosus is a multisystem autoimmune disorder where interplay of environmental and genetic risk factors leads to progressive loss of tolerance to nuclear antigens over time, finally culminating in clinical disease. It is a disease that can affect persons of all ages and ethnic groups and both sexes, but more than 90% of new patients presenting with SLE are women in the childbearing years. SLE is a disease that affects multiple systems. SLE is a complex disease process demonstrating dysregulation of the immune system at multiple levels. Autoantibodies that have been implicated in disease include anti-Ro, La, Sm, nucleosome, NMDA receptor, phospholipid, and α-actinin. Two major theories exist on how these autoantibodies cause tissue damage. The first model suggests that anti-double-stranded DNA antibodies bind to circulating nucleosomes to form immune complexes that then get deposited in end-organ capillary beds such as the renal glomerulus and activate immune/inflammatory responses. The second hypothesizes that these autoantibodies cross-react with normal renal proteins causing tissue destruction. The source of autoantigens that trigger the formation of the aforementioned antibodies is thought to arise from apoptotic cells

Objective: The aim of the present literature is to focus on lupus nephritis and the update of diagnostic biomarkers that reflect disease activity and also being predictors for the complications especially urinary angiostatin.

Conclusion: There are multiple urinary serum and traditional biomarkers for diagnosing lupus nephritis. The novel urinary biomarker angiostatin could be helping for differentiation between active renal from active non-renal disease in patients with SLE.

Key words: Systemic lupus erythematosus (SLE), Lupus nephritis. Urinary angiostatin

1.Introduction:

Systemic lupus erythematosus is associated with a broad spectrum of clinical and immunologic manifestations, of which lupus nephritis is the most common cause of morbidity and mortality. The development of nephritis in patients with SLE involves multiple pathogenic pathways including aberrant apoptosis, autoantibody production, immune complex deposition and complement activation. Some additional lesions that contribute to disease presentation, including glomerular crescents, podocyte injury, tubulointerstitial lesions and vascular injury, should be recognized. Although outcomes for patients with lupus nephritis have improved over the past 30 years, treatment of this disease remains challenging and is best approached on the basis of

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the underlying pathogenesis, which is only partially represented by the various pathological phenotypes defined by the ISN/RPS classification **(1)**.

2. Incidence:

Lupus nephritis (LN) refers to inflammation of the kidney that encompasses diverse patterns of renal disease including glomerular, tubulointerstitial and vascular pathology. Renal involvement in systemic lupus erythematosus may be present in approximately 60 % of adults, with 25–50 % of patients presenting with clinical renal disease at the time of diagnosis. Most patients affected are female, and younger than 50 years of age. However, male patients tend to have more frequent renal involvement and greater severity of disease. The prevalence of SLE ranges from 1.4 to 21.9 %; incidence is estimated to be 7.4–159.4 cases per 100,000 person-years. The incidence varies depending on the studied population. The cumulative incidence of LN is higher in people of Asian (55 %), African (51 %), and Hispanic (43 %) ancestry as compared with Caucasians (14 %) ***(2)***.

3. Classification:

Table 1: International Society of Nephrology/Renal Pathology Society 2003 Classification of Lupus Nephritis (3).

Class I: Minimal Mesangial Lupus Nephritis Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II: Mesangial Proliferative Lupus Nephritis Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III: Focal Lupus Nephritis(a) Active or inactive focal, segmental, or global endocapillary 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 lupus nephritis
Class III (A/C) Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C) Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV: Diffuse Lupus Nephritis(b) Active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft

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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 lupus nephritis
Class IV-G (A) Active lesions: diffuse global proliferative lupus
nephritis
Class IV-S (AC) Active and chronic lesions: diffuse segmental
proliferative sclerosing lupus nephritis
Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C) Chronic inactive lesions with scars: diffuse segmental
sclerosing lupus nephritis
Class IV-G (C) Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V: Membranous Lupus Nephritis
Global or segmental subepithelial immune deposits or
their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
Class V lupus nephritis may occur in combination with class III or class IV, in which case both will be diagnosed
Class V lupus nephritis showing advanced sclerosis
Class VI: Advanced Sclerotic Lupus Nephritis
≥90% of glomeruli globally sclerosed without residual Activity

4. Pathogenesis:

The pathogenesis of systemic lupus erythematosus is rooted in the formation of autoantibodies that target self-DNA or other self-nuclear antigens. The formation of autoantibodies will eventually cause a loss of immune tolerance and further progression of disease. Evidence suggests that nucleosomes from apoptotic cells largely contribute to the immunogenic material targeted by autoantibodies. Usually, the rapid clearance of a dead cell would prevent autoantibody formation. However, in patients with SLE, it is possible that either inappropriate clearance of cellular debris or an abnormal increase in cell death provides ample opportunity for nucleosomes to become antigenic material for autoantibody formation. These autoantibodies can form immune complexes, which deposit in various organ systems, leading to dysfunction ***(2)***.

There is also a lower threshold of immune response to the Type I interferon pathway, which has been identified as a potential factor in SLE. The loss of B-cell tolerance to self-antigens and subsequent autoimmune responses lead to the deposition of circulating immune complexes (CIC). The size of immune complexes, charge, local hemodynamic factors, and clearing mechanisms of the mesangium all influence where the immune complexes localize within the glomerulus. Renal deposition of autoantibodies forms immune complexes, which is the source of renal dysfunction in lupus nephritis. This causes the activation of the complement system and subsequent release of cytokines, leading to renal injury. Studies have also shown that direct binding of anti-DNA antibodies to mesangial cells causes an inflammatory response as well as further cellular proliferation. Autoantibodies against C1q have also been isolated. These autoantibodies have been identified to cause functional C1 deficiency, contributing to defective clearance of cellular debris from apoptosis and immune complexes ***(2)***.

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Genetic factors play a major role in the pathogenesis of lupus nephritis. Predisposing loci include HLA-DR2, HLA-DR3, HLA-DRB1 loci, HLA-DRB*0301, and HLADRB1*1501.

However, multiple genes are involved, including those that regulate immunity and lymphocyte signaling. In short, a single gene polymorphism that leads to SLE has not been identified; rather a combination of susceptibility genes and/or absence of protective genes are necessary to lead to overt disease. Environmental factors have also been implicated in the pathogenesis of SLE. These include viruses such as EBV, ultraviolet light, silica, dust, and allergies to medications ***(2)***.

5. Clinical Manifestations and Complications:

Many patients experience no symptoms at all. Typically, LN is suspected in SLE patients producing abnormal urinalysis results, possibly with an elevated serum creatinine level. Patients may demonstrate persistent proteinuria greater than 0.5 grams per day, random protein/creatinine ratios greater than 0.5 grams, and the production of urine with active sediment consisting of blood cells and/or casts greater than 5 without urinary tract infection. Serum creatinine, blood urea nitrogen, and antiDNA studies may be elevated, while glomerular filtration rates and C3 and C4 complement may be low. Interestingly, IgE is also noted to be elevated with both active SLE and LN. ascertain elevated autoreactive IgE levels to be in significant relationship with active SLE and LN ***(4)***.

The spectrum of manifestations varies from asymptomatic proteinuria or haematuria to overt nephrotic syndrome or acute renal failure ***(5)***.

5.1. Vascular Complications:

Antiphospholipid syndrome-associated nephropathy (APSN) is a vascular nephropathy that can occur in SLE patients and may be associated with the presence of antiphospholipid (aPL) antibodies. The EULAR/ERA-EDTA guideline takes the use of HCQ and/or antiplatelet or anticoagulant treatment into consideration, while the KDIGO and GEAS merely suggest treatment with anticoagulants (INR 2–3). The ACR suggests treating thrombotic microangiopathy (TMA) primarily with plasma exchange. Thrombotic thrombocytopenia (TTP) is a clinical syndrome associated with TMA in the renal biopsy, recommended to be treated promptly with plasma exchange by KDIGO (and other guidelines for idiopathic TTP, as TTP especially in SLE has a high mortality) ***(6)***.

6. Diagnosis:

Definitive diagnosis and classification of LN is made by determining the extent of glomerular injury via renal biopsy, urine, and blood studies. The classification scheme used to stage and type the severity of LN is comprised of six classifications. Hematuria and proteinuria, decreased glomerular filtration rate and hypertension are often seen with class III, while the class IV patient will exhibit hematuria, proteinuria, reduced glomerular filtration rate, hypertension and nephrotic syndrome. The differentiation between class III and class IV is made through the determination of the percentage of glomeruli affected. If involvement of glomeruli tops 50%, class IV LN is diagnosed, while less than 50% involvement is consistent with class III ***(4)***.

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Although renal biopsy is the gold standard reference for lupus nephritis evaluation, it is an invasive operation. Therefore, a noninvasive method as a supplementation for biopsy is highly warranted. This noninvasive approach helps integrating numerous clinical parameters, providing a reliable understanding of lupus nephritis pathology features and prognosis and even select out important clinical indices ***(7)***.

The biopsy is classified according to the system proposed by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) in 2003. A minimum of 10 glomeruli is required to reasonably exclude focal disease, and the biopsy should be examined by light microscopy, immunofluorescence and if possible, electron microscopy. Furthermore, data on activity and chronicity should be quantified (though activity and chronicity indices are not obligatory), and vascular and interstitial lesions described. The histological class plays a fundamental role in the ensuing therapeutic decision process ***(6)***.

A diagnostic kidney biopsy should be performed to guide therapy when a lupus patient presents with clinical evidence of new kidney injury. A repeat biopsy could be considered in patients who have achieved and maintained complete clinical remission for 2 or more years to confirm histologic remission and guide tapering of maintenance immunosuppression. A repeat biopsy should be performed to guide changes in therapy for patients who have responded incompletely. A repeat kidney biopsy could be considered at LN flare, especially in patients who initially had class II or V lupus nephritis because of the risk of acquiring a proliferative component **(8).**

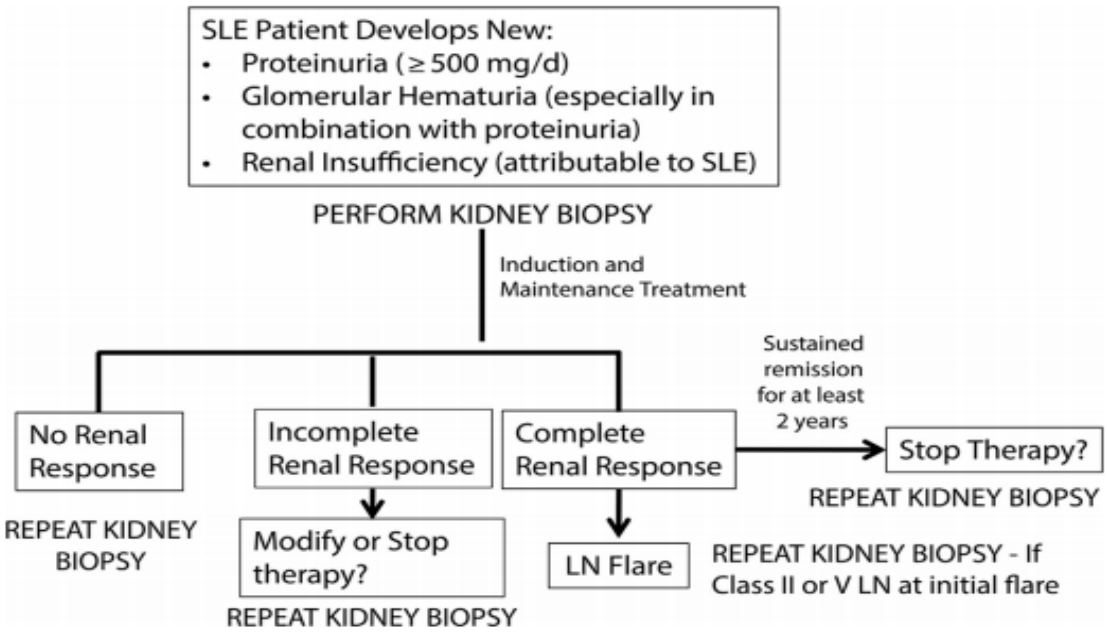

Figure 1: Adapted from **(8).** Algorithm for kidney biopsy in lupus nephritis.

Numerous clinical and laboratory parameters, such as a panel of urinary proteins and autoantibodies, have been explored as indices for lupus nephritis severity assessment and prognosis prediction. However, proper assessment of lupus nephritis depends on comprehensive analysis of multiple parameters rather than a single one, yet clinicians do not always agree on which parameters were important, nor do they have effective ways to evaluate some controversial parameters ***(7)***.

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Although renal biopsy is still the gold standard for diagnosing and classifying the degree of renal inflammation and scarring, its invasiveness as a procedure with potential complications makes it unsuitable for serial monitoring. For these reasons, novel biomarkers are clearly warranted. A biomarker is a biologic, biochemical, or molecular substance that can be detected qualitatively and quantitatively by laboratory techniques, that correlates with disease pathogenesis or activity at various time points ***(9)***.

6. Urinary Angiostatin

A biomarker refers to a biologic, biochemical, or molecular event that can be assayed qualitatively and quantitatively by laboratory techniques. The levels of biomarkers should correlate with disease pathogenesis or activity in different organ systems. An ideal biomarker for lupus nephritis should possess the following properties: (1) good correlation with renal activity as reflected by the degree of proteinuria and urine sediments, (2) ability to predict renal activity/flares before an obvious change in conventional clinical parameters occurs so that early treatment/preventive strategies can be considered, (3) specific to nephritis among patients with SLE, and (4) specific to SLE for aiding early diagnosis of lupus nephritis. In addition, a useful biomarker should be easy to assay, simple to interpret, and readily available in most laboratories with a reasonable cost ***(14)***.

SLE being a rare disease, efforts have to be collaborative in a multi-centric fashion to ensure cost-effective utilization of resources. Conventional serum and urine biomarkers continue to be the most widely used. Renal biopsy is still the gold standard for deciding therapy in LN but its invasive nature prevents it from being used repetitively. What seems achievable and more practical at this point in time is to utilize the most beneficial property of each biomarker and to develop a combination test that could predict the various aspects of treatment of LN, such as chronicity and activity changes, response to treatment and prediction of flare. ***(15)***.

7. Urine Biomarkers for Lupus Nephritis:

Generally, urinary substances are likely to reflect kidney damage better than serum components. Urine is a source of bio-fluid which is easy to harvest and the biomarkers in urine are usually reflecting the renal function directly in various kinds of nephritic diseases. Proteomic approaches, such as two-dimensional gel electrophoresis, mass spectrometric and/ or immunochemical identification of proteins, surface enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF-MS) and capillary electrophoresis-MS, have been used to screen potential urine biomarkers that are associated with renal damages caused by LN. The usual markers of renal disease include urinary protein, creatinine, etc., although the currently recommended spot urinary protein to creatinine ratio may not be sufficiently sensitive to detect early nephritis ***(14)***.

Urine biomarkers have emerged in recent years and have proven effective in reflecting disease activity in lupus nephritis. Potential biomarkers include IL-6, IL-18, MCP-1, VCAM-1, NGAL, and TWEAK. Indeed, urine may be by far the best source for screening biomarkers for kidney diseases for several reasons. First, urine samples are easily obtained and are noninvasive. Second, because urine is a direct product of the kidney, urine biomarkers may be a direct reflection of renal function. Nevertheless, the ideal urine biomarker for monitoring lupus nephritis (LN) remains elusive ***(16)***.

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An unbiased, high-throughput proteomics approach enables simultaneous evaluation of a large number of proteins in an efficient manner. Recent proteomic studies have identified urinary angiostatin, vascular cell adhesion molecule-1 (VCAM-1) and CXC chemokine ligand 4 (CXCL4) as potential urinary biomarkers of LN ***(16)***.

8. Angiostatin in health and diseases other than SLE:

Angiostatin is a naturally occurring protein found in several animal species, including humans. It is an endogenous angiogenesis inhibitor, which blocks the growth of new blood vessels, effecting vascular leakage in any tissue ***(17)***.

Although angiostatin was given a single name, in fact angiostatin refers to several fragments of plasminogen, such as kringle 1 to 3, kringle 1 to 4, kringle 1 to 4.5, and kringle 1 to 5, which all showed anti-angiogenic activities ***(18)***.

9. Angiostatin and malignancy:

Angiostatin has been found to be protective in cancer growth through the blockade of angiogenesis via inhibition of migration and proliferation of endothelial cells. In addition to the murine studies, a second array-based study in human lupus nephritis also indicated that urine angiostatin may be elevated in lupus nephritis ***(Wu et al. 2013)***.

Angiostatin thought to play a crucial role in preventing tumor metastasis, and has also been proposed to inhibit tPA activity ***(19)***.

Angiostatin has been shown to mediate suppression of metastases from Lewis lung carcinoma. Angiostatin specifically inhibits proliferation and induces apoptosis of the vascular endothelial cells, thus inhibiting tumor growth. More recently, angiostatin has been shown to have anti-inflammatory properties by inhibition of activation and migration of neutrophils ***(16)***.

Elevated serum angiostatin levels were detected in patients with Bechet's disease, as well as systemic sclerosis suggesting the possible role of angiogenesis in the pathogenesis of these diseases. Angiostatin was also noted to be a marker of late Systemic Sclerosis disease, where it relates to lung disease severity ***(9)***.

The growth and metastasis of a tumor depend upon the growth of blood vessels. Therefore, inhibition of blood vessel growth is a potential therapy for primary tumors, and it has become an important way to treat tumors by increasing the expression of inhibitory factors of angiogenesis in the tumor area. Angiostatin is one of the endogenous angiogenesis inhibitory factors and has been proved *in vitro* to inhibit the proliferation of endothelial cells. *In vivo* studies also confirmed that angiostatin could inhibit the angiogenesis in solid tumors that could result in the inhibition of tumor growth ***(Wu et al. 2003)***.

Angiogenesis is closely related to gastric cancer as a predictive factor in addition to having prognostic value. The average number of blood vessels is significantly higher in gastric cancer specimens than in normal gastric specimens, higher in advanced disease than in early-stage disease, higher in specimens with metastases or blood vessel invasion than in those without such metastasis or invasion ***(12).***

Thus, angiostatin gene therapy is possibly available for gastric cancer, especially for its simple manipulation, highly specificity, wide-spectrum inhibitory effects on various tumors ***(20).***

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Systemic administration of angiostatin inhibits the growth of transplanted human breast carcinoma, colon carcinoma and prostate carcinoma in mice, without obvious weight loss or other toxicity observed. It causes human primary carcinomas to regress to a dormant state by a net balance of tumor cell proliferation and apoptosis ***(Jung et al. 2003)*** .

Angiostatin has been negatively associated with coronary collateral development in patients with coronary artery disease and type II diabetes. Chronic hyperglycemia was also shown to inhibit coronary collateral growth via an increase in angiostatin (***21)***.

Recent evidence has suggested that decreased angiostatin levels in the vitreous may play a role in the development of proliferative diabetic retinopathy ***(13).***

Moreover, recombinant angiostatin has been shown to block retinal neovascularization in a rat model of oxygen-induced retinopathy. Delivery of a recombinant virus expressing angiostatin has been found to suppress laser-induced choroidal neovascularization. These findings reveal therapeutic potential of angiostatin in the treatment of retinal neovascularization as well as in the treatment of cancer ***(22).***

10. Angiostatin and Diabetes Mellitus:

There is a potential role of decreased angiostatin levels in the development or progression of diabetic nephropathy. the proteolytic release of angiostatin from plasminogen, rather than the expression of the plasminogen gene, is deficient in diabetes. This conclusion is further supported by the observation that both the expression and the activity of matrix metalloproteinase-2 (MMP-2) are suppressed in diabetic kidney, as MMP-2 has been shown to release angiostatin from plasminogen ***(23).***

To investigate the function of angiostatin in the kidney, recombinant angiostatin was delivered *via* an adenovirus-mediated gene. The angiostatin gene delivery indeed reduced urinary albumin excretion in diabetic rats almost to the normal level, suggesting a potent effect of angiostatin on the inhibition of microalbuminuria. As microalbuminuria has been shown to be closely linked with glomerular hypertrophy in the early stage of diabetic nephropathy ***(24).***

11. How to measure Urinary Angiostatin:

Urinary Angiostatin Reflects Renal Chronicity Changes in Lupus Nephritis in Concurrent Biopsy Samples; In order to evaluate precisely how well urinary angiostatin can predict particular changes in renal pathology, Urine samples were collected from the patients on the same day renal biopsies were performed. Then urinary angiostatin levels were measured and compared them with the renal pathology activity index and the renal pathology chronicity index in these paired urine/ biopsy samples collected simultaneously. The activity index is based on evaluation of six histologic parameters (i.e., glomerular endocapillary proliferation, glomerular leukocyte infiltration, glomerular subendothelial hyaline deposits, glomerular fibrinoid necrosis, or karyorrhexis, cellular crescents and interstitial inflammation), each graded on a scale of 0 to 3. A score of 0 absent; 1 ≤ 25% glomeruli affected; 2 = 25–50% glomeruli affected and 3 ≥ 50% glomeruli affected. The scores for glomerular necrosis and cellular crescents were double-weighted because of their more ominous prognostic value. The sum (from 0 to 24) of each individual score represents the activity index. Likewise, chronicity index (from 0 to 12) was graded by summating the individual scores of four histologic features— glomerular sclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis ***(Wu et al. 2013)***.

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Despite the value of urine as a source for proteomic evaluation of kidney disease, there are several considerations that must be made in order for studies to be successful. The urine proteome is highly variable between individuals. Men and women often display variances between levels of specific proteins. Further, there are age differences, especially within the pediatric population. Therefore, when designing urinary proteomic experiments, it is important to match subjects and controls by age and gender. Further, there is marked variation of urine protein content due to hydration status, possibly even diurnal variations, as well as intra-individual variability due to factors such as exercise, diet, and lifestyle ***(25)***.

12. Clinical application of Urinary Angiostatin Biomarker:

Analogous to other renal disease states, urine proteome profiling represents a promising strategy to support the diagnosis, including the findings on kidney biopsy, and to assess the treatment response of LN. Thus, ongoing investigations in subjects with LN have focused on characterization of urinary proteins for (distinguishing histologic classes and kidney biopsy findings, early identification of LN flares, correlation with LN activity and chronicity, assessing prognosis and response to therapy and enabling clinical trials with novel therapeutic agents) ***(25)***.

Studies found that elevated angiostatin expression in the kidney was related to renal capillary density loss and interstitial damage, which resulted in loss of glomerular function. Studies have demonstrated that angiostatin levels were higher in patients with severe tubule-interstitial lesions, and the significant correlation occurred between the biomarker and 24-h urinary protein excretion. The elevated level of angiostatin expression may aggravate tubule-interstitial damage and proteinuria. In addition, angiostatin has anti-inflammatory actions by inhibiting leukocyte recruitment and both neutrophil and macrophage migration ***(26)***.

The proteins in the urine directly reflect renal pathology and indicate SLE disease activity. The ratio of microalbumin to proteinuria has been recommended as a forecaster of renal flare. Urinary sVCAM-1 is enhanced significantly in patients with active LN and is also a potential biomarker for early diagnosis of LN. Urinary angiostatin emerges as a promising marker capable of discriminating patients with active disease from inactive SLE or healthy controls. The cleaved form of urine osteopontin N-half concentration (OPN N-half) is higher in LN patients than in healthy controls, suggesting that urine OPN N-half reflects inflammation of the kidney. Compared with a single marker, the combination of several biomarkers showed higher diagnostic value ***(27)***.
In contrast to a renal biopsy, assessment of urine VCAM-1 or angiostatin is non-invasive and inexpensive, costing less than a dollar to a couple of dollars at most. Routine clinical laboratories can easily do these assays. Given that these assays can readily be converted to point-of-care tests that patients can self-check in the comfort of their home, repeated self-assessment of renal pathology status by LN patients may soon become reality. Clearly, additional urine proteins should be systematically evaluated so that one can identify a panel of different biomarkers that can reliably predict each specific histological feature of renal disease activity and chronicity ***(9)***.

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Table 2: Lupus Nephritis biomarkers (9).

Conventional (traditional) biomarkers	-Anti-dsDNA antibody: Anti-dsDNA antibodies constitute a cardinal diagnostic tool for SLE and have been implicated in the pathogenesis of SLE renal disease as well as other disease manifestations. Anti-dsDNA antibodies are present in higher concentrations in renal tissue compared to systemic circulation. -Complement: Measurements of C3 and C4 have traditionally been used as the best laboratory assessment of SLE disease activity. Reduction of C3/C4 at initial diagnosis is associated with poor prognosis. -Proteinuria, GFR and urine sediments: Until today, proteinuria- measured in 24 h urine samples or as protein:creatinine ratio in the urine- is the principal urinary biomarker for assessing LN.
Urine Biomarkers	-Considerations for the use of urinary molecules as biomarkers: A good biomarker needs to have the ability to predict a "gold standard", which in the case of LN would be the renal biopsy scores or long-term renal outcome. -Urinary Cytokines: (IL-6, IL-17, IL-10, TWEAK, TNFR-1, Adiponectin). -Urinary Chemokines: (MCP-1(CCL2), IL-8, IP-10 (CXCL10) and its receptor CXCR3, CXCL16, RANTES (CCL5)). -Urinary adhesion molecules: (VCAM-1, ICAM-1) -Growth and fibrosis factors: (VEGF, TGF-β) -miRNAs -proteomic Panels -other Biomarkers: (NGAL (neutrophil gelatinase -B associated lipocalin)/ Lipocalin2, Osteoprotegerin (OPG), Kim-1, free light chain)
Serum Biomarkers	-Autoantibodies: (anti- NCS, Anti-C1q antibodies, Anti-α-Actinin antibodies, Perspective on autoantibodies). -Serum chemokines: (CXCL11 [interferon-inducible T-cell a -chemoattractant (I-TAC)], CXCL13 [Blymphocyte chemoattractant (BLC)], CXCL10 (IP-10) and CCL3 (MIP1a) -Serum cytokines: (T cell cytokines such as TNF, IL-6, IL-10, IL-12, IL-17, IL-18 and IL-23, B-lymphocyte stimulator protein (BLyS), also known as B-cell activating factor (BAFF)) -Serum adhesion molecules: Adhesion molecules, ICAM-1 and VCAM-1 in particular. -Serum proteomics.

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13. Treatment:

Despite the use of histopathology to guide therapeutic decisions, the morbidity and mortality of lupus nephritis remains high. The current approach to the management of lupus nephritis is based on steroids and other nonspecific immunosuppressive drugs. Dysregulation of the immune system is fundamental to the pathogenesis of lupus nephritis, and targeting multiple aspects of the immune response through the combined use of multiple immunosuppressants (multitarget therapy) proved superior to a standard regimen of steroids and cyclophosphamide (intravenous or oral) as induction therapy for lupus nephritis in a 2015 Chinese study. Nonselective immunosuppressants are, however, associated with potentially life-threatening complications including an increased risk of infection. In addition, they are often associated with incomplete renal remission and a high rate of renal flares, which might be more prominent in patients with features such as vasculopathy, crescentic glomerulonephritis, and tubulointerstitial lesions. treatment of lupus nephritis remains a challenge and it should target the pathogenesis of the disease, as determined by the assessment of the histopathological disease phenotypes **(1)**.

13.1. Induction and Maintenance Treatment:

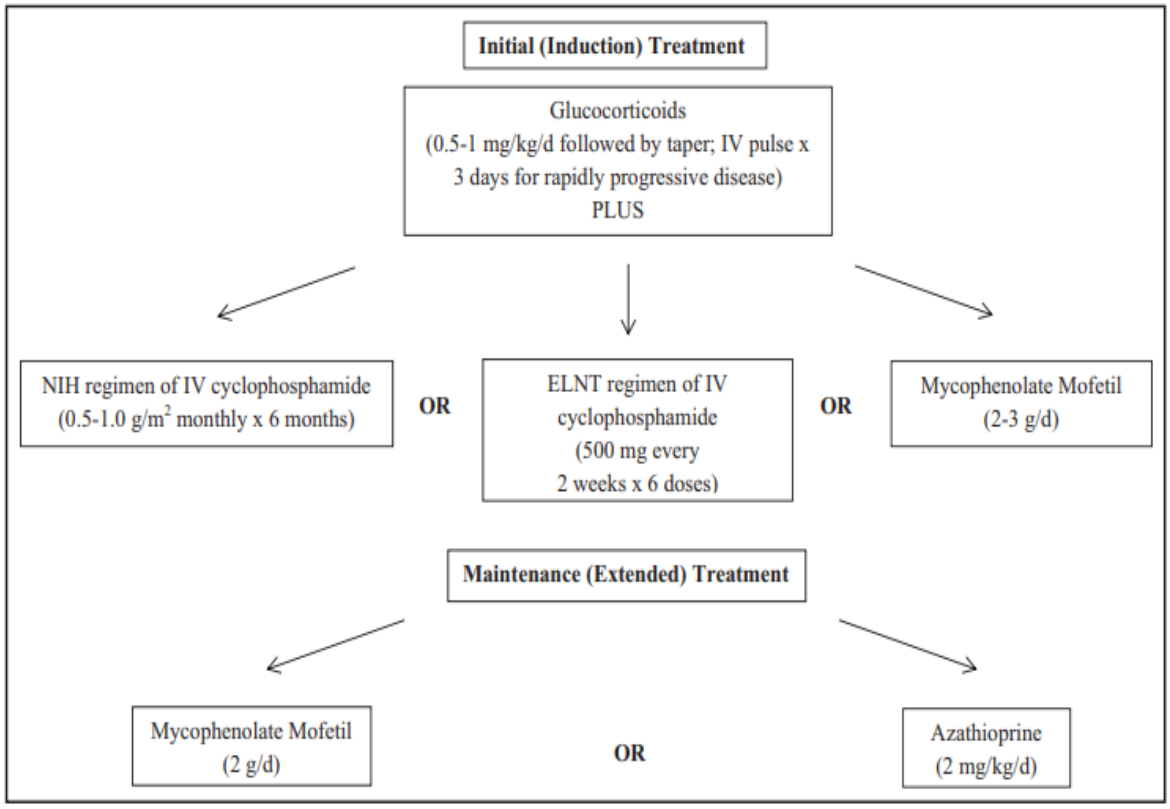

Figure 1: Adapted from **(10).** Contemporary, evidence-based initial (induction) and maintenance (extended) regimens for the treatment of LN. AZA, azathioprine; CYC, cyclophosphamide; ELNT, Euro-Lupus Nephritis; i.e., intravenous, LN, lupus nephritis; MMF, mycophenolate mofetil; NIH, National Institutes of Health**.**

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The treatment of lupus nephritis is largely determined based on the histological class present on the renal biopsy specimen. In most cases, Class I and II of lupus nephritis do not require any specific treatment, but class III and IV lupus nephritis require immunosuppressive therapy. Treatment of Class V and VI remains controversial ***(11)***.

The recommended treatment for biopsy-proved class III and IV LN was the combination use of corticosteroid and cyclophosphamide (CYC) or/and mycophenolate mofetil (MMF) for induction therapy, and the combination use of low-dose corticosteroid and azathioprine (AZA) or/and MMF for maintenance therapy; the recommended therapy for class V was the combination use of corticosteroid + CYC, ± MMF, ± AZA for induction therapy; and the combination use of corticosteroidand CYC, ± MMF, ± calcineurin inhibitors (CNIs, including cyclosporineA, CsA, and tacrolimus, TAC) ± AZA for maintenance therapy in addition to adjunctive therapies (e.g., blood pressure control) ***(12)***.

13.2. Adjuvant Treatment/Treatment of Comorbidities:

All guidelines recommend blood pressure control (target<130/ 80 mmHg), treatment of hyperlipidemia with statins (target LDL<100 mg/dL or 2.6 mmol/L) and treatment of proteinuria with RAAS inhibition. The guidelines agree that all SLE patients should have a background of hydroxychloroquine (HCQ) unless contraindicated, since this is associated with less damage accrual. Patients receiving HCQ have a risk of developing retinopathy and should therefore be screened by the ophthalmologist at baseline and yearly after 5 years. Patients with severe renal or hepatic disease are at higher risk for developing retinopathy, due to less clearance of the drug. In those patients, reducing the dose should be considered to avoid toxicity. There are no clear recommendations from the guidelines on infection prophylaxis, such as for pneumocystis jirovecii pneumonia or surveillance for other pathogens ***(6)***.

13.3. Treatment of Renal Flare:

A renal flare is indicated by an increase in proteinuria and/or serum creatinine concentration, abnormal urine sediment or a reduction in creatinine clearance rate as a result of active disease. The morbidity associated with renal flares is derived from both the kidney damage due to lupus nephritis and treatment-related toxic effects. Current induction treatment protocols achieve remission in the majority of patients with lupus nephritis; however, few studies focus on treatment interventions for renal flares in these patients. The available data, however, suggest that remission can be induced again in a substantial percentage of patients experiencing a lupus nephritis flare. Lupus nephritis flares are independently associated with an increased risk of deterioration in renal function; prevention of renal flares might, therefore, also decrease long-term morbidity and mortality. Appropriate immunosuppressive maintenance therapy might lead to a decrease in the occurrence of renal and extrarenal flares in patients with SLE, and monitoring for the early detection and treatment of renal flares could improve their outcomes ***(13)***.

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13.4. Monitoring of treatment:

The guidelines differ in their approach but agree that patients with active nephritis should have a visit scheduled at least every month, particularly at induction, relapse and withdrawal of treatment. If there is no active nephritis every 3–6 months should suffice, although vigilance is required for prompt identification of disease relapse. At each visit, body weight, blood pressure, serum creatinine (sCr), proteinuria, urinary sediment, complement levels, anti-dsDNA titres , serum albumin and complete blood count should be determined. The ACR states that some of the aforementioned can be determined at larger intervals than others (blood pressure and urinalysis frequent; anti-dsDNA less frequent) and drafted a separate monitoring schedule for pregnancy ***(6)***.

14.Conclusion:

There are multiple urinary serum and traditional biomarkers for diagnosing lupus nephritis. The novel urinary biomarker angiostatin could be helping for differentiation between active renal from active non-renal disease in patients with SLE.

15. Conflict of Interest: No conflict of interest.

18.References

1. **Yu, Feng, Mark Haas, Richard Glassock, and Ming-Hui Zhao. 2017.** "Redefining Lupus Nephritis: Clinical Implications of Pathophysiologic Subtypes." Nature Reviews Nephrology 13 (8): 483–95.
2. **Imran, Tasnim F., Frederick Yick, Suneet Verma, Christopher Estiverne, ChinonyeOgbonnaya-Odor, Srikanth Thiruvarudsothy, Alluru S. Reddi, and Neil Kothari. 2016**."Lupus Nephritis: An Update." Clinical and Experimental Nephrology 20 (1): 1–13.
3. **Fu, Shu Man, Sun-Sang J. Sung, Hongyang Wang, and Felicia Gaskin. 2019.** "Pathogenesis of Lupus Nephritis." In Dubois' Lupus Erythematosus and Related Syndromes, 269–93. Elsevier.
4. **Warren, Nicole G. n.d.** "Lupus Nephritis: A Synopsis of Pathophysiology and Implications for Advanced Nursing Practice," 2.
5. **Mody, P G, G M Mody, and A Assounga. 2018.** "The Clinical Manifestations and Response to Treatment in South Africans with Lupus Nephritis." Lupus 27 (7): 1207–17.
6. **Wilhelmus, Suzanne, Ingeborg M. Bajema, George K. Bertsias, Dimitrios T. Boumpas, Caroline Gordon, Liz Lightstone, Vladimir Tesar, and David R. Jayne. 2016**. "Lupus Nephritis Management Guidelines Compared." Nephrology Dialysis Transplantation 31 (6): 904–13.
7. **Tang, Youzhou, Weiru Zhang, Minfeng Zhu, Li Zheng, LingliXie, Zhijiang Yao, Hao Zhang, Dongsheng Cao, and Ben Lu. 2018.** "Lupus Nephritis Pathology Prediction with Clinical Indices." Scientific Reports 8 (1): 10231.
8. **Parikh, Samir V., Anthony Alvarado, Ana Malvar, and Brad H. Rovin. 2015.** "The Kidney Biopsy in Lupus Nephritis: Past, Present, and Future." Seminars in Nephrology 35 (5): 465–77.
9. **Soliman, Samar, Fatma A. Mohamed, Faten M. Ismail, Samantha Stanley, Ramesh Saxena, and Chandra Mohan. 2017.** "Urine Angiostatin and VCAM-1 Surpass Conventional Metrics in Predicting Elevated Renal Pathology Activity Indices in Lupus Nephritis." International Journal of Rheumatic Diseases 20 (11): 1714–27.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 6656 - 6669
Received 25 April 2021; Accepted 08 May 2021.

10. **Dall'Era, Maria. 2017.** "Treatment of Lupus Nephritis: Current Paradigms and Emerging Strategies." Current Opinion in Rheumatology 29 (3): 241–47.
11. **AzizFahad, and Kunal Chaudhary. 2018.** "Lupus Nephritis: A Treatment Update." Current Clinical Pharmacology 13 (1): 4–13.
12. **Chen, Yuehong, Jianhong Sun, Kun Zou, Yuan Yang, and Gang Liu. 2017.** "Treatment for Lupus Nephritis: An Overview of Systematic Reviews and Meta-Analyses." Rheumatology International 37 (7): 1089–99.
13. **Spranger J, Ben, Marianne Monahan, and Gerald B. Appel. 2012.** "Diagnosis and Treatment of Lupus Nephritis Flares—an Update." Nature Reviews Nephrology 8 (12): 709–17.
14. **Mok, Chi Chiu. 2010.** "Biomarkers for Lupus Nephritis: A Critical Appraisal." Journal of Biomedicine and Biotechnology 2010: 1–11.
15. **Misra, Ramnath, and Ranjan Gupta. 2015.** "Biomarkers in Lupus Nephritis." International Journal of Rheumatic Diseases 18 (2): 219–32.
16. **Mok, Chi Chiu, Samar Soliman, Ling Yin Ho, Fatma A. Mohamed, Faten Ismail Mohamed, and Chandra Mohan. 2018.** "Urinary Angiostatin, CXCL4 and VCAM-1 as Biomarkers of Lupus Nephritis." Arthritis Research & Therapy 20 (1): 6.
17. **Sima J, S.X Zhang, C Shao, J Fant, Y Chen, B Rohrer, G Gao, and J Ma. 2004**. Diabetologia, 47, (2004), 124– 131.
18. **Cao Y, and Xue L. 2004. "Angiostatin." Semin ThrombHaemost 30: 83 –93, 2004.**
19. **Folkman J. 2002.** "Role of angiogenesis in tumor growth and metastasis." Semin Oncol. 2002;29(6 Suppl 16):15–8**.**
20. **Indraccolo S, Morini M, Gola E, Carrozzino F, Habeler W, Minghelli S, Santi L, Chieco-Bianchi L, Cao Y,andAlbini A.** "Effects of angiostatin gene transfer on functional properties and in vivo growth of Kaposi's sarcoma cells." Cancer Res. 2001; 61:5441–5446**.**
21. **Sodha NR, Clements RT, Boodhwani M, Xu SH, Laham RJ, Bianchi C, Selke FW. 2009.** "Endostatin and angiostatin are increased in diabetic patients with coronary artery disease and associated with impaired coronary collateral formation." American Journal of Physiology Heart and Circulatory Physiology. 2009;296:H428–434.
22. **Meneses P, K.A Hajjar, K.I Berns, and R.M Duvoisin. 2001.** Gene Ther., 8, (2001), 646– 648.
23. **Reilly MS, Pirie-Shepherd S, Lane WS, and Folkman J. 1999.** "Antiangiogenic activity of the cleaved conformation of the serpin antithrombin." Science 285: 1926 –1928, 1999
24. **Nakagawa H, Sasahara M, Haneda M, Koya D, Hazama F,andKikkawa R. 2000.** "Immunohistochemical characterization of glomerular PDGF B-chain and PDGF beta-receptor expression in diabetic rats." Diabetes Res Clin Pract 48: 87 –98, 2000.
25. **Aljaberi, Najla, Michael Bennett, Hermine I. Brunner, and Prasad Devarajan. 2019.** "Proteomic Profiling of Urine: Implications for Lupus Nephritis." Expert Review of Proteomics 16 (4): 303–13.
26. **Xia, Yuan-Yuan, Ru Bu, Guang-Yan Cai, Xue-Guang Zhang, Shu-Wei Duan, Jie Wu, Di Wu, and Xiang-Mei Chen. 2019.** "Urinary Angiostatin: A Novel Biomarker of Kidney Disease Associated with Disease Severity and Progression." BMC Nephrology 20 (1): 118.
27. **Qi, S, Q Chen, D Xu, N Xie, and Y Dai. 2018.** "Clinical Application of Protein Biomarkers in Lupus Erythematosus and Lupus Nephritis." Lupus 27 (10): 1582–90.