The management of lupus nephritis

Abstract: Lupus nephritis is one of the most devastating complications of systemic lupus erythematosus. New treatment approaches and recommendations aim to decrease mortality and improve quality of life and outcomes. The role of the primary care provider is essential to help manage complications of treatment and avoid organ damage.

By Monica Richey, MSN, ANP-BC, GNP

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder characterized by multisystem involvement, presence of antinuclear antibodies, and chronic relapsing. The course of the disease is variable, alternating between periods of stable disease (remission) and/or flares with high disease activity. Flares are characterized by generalized symptoms, such as fatigue, fevers, arthralgia, rashes, and alopecia. Chronic, uncontrolled autoimmune response results in organ damage. Major causes of death and morbidity in patients with SLE are infections and cardiovascular disease.

The American College of Rheumatology (ACR) has established 11 criteria for classification of SLE (see 1997 ACR revised criteria for classification of SLE). These criteria are used mostly in clinical trials and population studies rather than for diagnostic purposes. A minimum of four criteria out of 11 are necessary to participate in clinical trials. The 11 criteria are divided into 4 cutaneous, 4 systemic, and 3 lab components.

Epidemiology
The incidence of SLE in the United States ranges from 2.0 to 7.6 cases per 100,000 persons per year; prevalence ranges from 14.6 to 68 cases per 100,000 persons. Survival rates have increased from 50% of patients to 88% to 96% in the first 5 years. Ten-year survival rates range from 95% and 71% for younger and older patients, respectively. SLE affects more females than males with a ratio of 9:1, with a higher incidence among women of childbearing age. SLE disproportionately affects more Black women with a three to four times higher prevalence than Whites. There is also a higher incidence of SLE among the Afro-Caribbean, Asian, American Indian, and Hispanic descent populations as compared to the White population.

Pathophysiology of SLE
Although not completely understood, SLE can be set off by a combination of predisposing genetic traits, hormonal and environmental factors, or infectious agents, which result in an abnormal immune response with dysregulation of B and T cells, resulting in production and formation of autoantibodies, complement fixing, and immune complexes that promote inflammation and tissue damage. There are several mechanisms of tissue injury in SLE. In the kidneys, it may result from autoantibodies binding to circulating antigens, forming preformed immune complexes, or autoantibodies

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binding to antigens deposited from the circulation in the glomerular vessel walls, causing in situ immune complex formation, with initiation of an inflammatory and cytotoxic reaction.9

- **Lupus nephritis**

Kidney disease is one of the most devastating complications of SLE and an important predictor of mortality for patients with SLE. The 5-year survival rate is significantly worse for individuals with lupus nephritis (LN).10 Nearly 50% to 60% of adults and almost 80% of children with SLE develop nephritis within the first 10 years after diagnosis.11 The prevalence is higher in Blacks and Hispanics than in Whites, and higher in men than women.11 LN significantly reduces survival to 88% at 10 years, with Blacks having an even lower survival rate.11 Despite new and aggressive treatment, 10% to 30% of these patients will progress to end-stage renal disease (ESRD). The incidence of ESRD caused by SLE has risen for younger Black patients living in the southern United States.10

- **Diagnosing glomerulonephritis in SLE**

Optimal criterion for the diagnosis of LN is a renal biopsy. LN classification is based on an array of morphologic changes seen in biopsies. It consists of vascular, glomerular, and tubulointerstitial lesions. LN classification is paramount in the treatment decision-making process. It is important to remember that biopsy results alone cannot be used in the diagnosis of LN; they must be combined with the patient’s presentation and serologic findings.9 In addition a diagnosis of LN should be considered valid if based on the opinion of a rheumatologist or nephrologist.11

### Table: 1997 ACR revised criteria for classification of SLE

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>Malar Rash</td>
<td>Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds</td>
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<tr>
<td>Discoid Rash</td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesion</td>
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<tr>
<td>Photosensitivity</td>
<td>Skin rash as a result of unusual reaction to sunlight, by patient history or provider observation</td>
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<tr>
<td>Oral ulcers</td>
<td>Oral or nasopharyngeal ulceration, usually painless, observed by a provider</td>
</tr>
<tr>
<td>Nonerosive arthritis</td>
<td>Involving two or more peripheral joints, characterized by tenderness, swelling, or effusion</td>
</tr>
<tr>
<td>Pleuritis or pericarditis</td>
<td>- Pleuritis—convincing history of pleuritic pain or rubbing heard by a provider or evidence of pleural effusion OR - Pericarditis—documented by ECG or rub or evidence of pericardial effusion</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>- Persistent proteinuria &gt;0.5 g/day or &gt;3+ if quantitation not performed OR - Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>- Seizures—in the absence of offending drugs or known metabolic derangements, for example, uremia, ketoacidosis, or electrolyte imbalance OR - Psychosis—in the absence of offending drugs or known metabolic derangements, for example, uremia, ketoacidosis, or electrolyte imbalance</td>
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</table>

### Immunologic Disorder

- Anti-DNA—antibody to native DNA in abnormal titer OR
- Anti-Sm—presence of antibody to Sm nuclear antigen OR
- Positive finding of antiphospholipid antibodies on: - An abnormal serum level of IgG or IgM anticardiolipin antibodies, - A positive test result for lupus anticoagulant using a standard method, or - A false-positive test result for at least 6 months confirmed by treponema pallidum immobilization or fluorescent treponemal antibody absorption test.

### Positive antinuclear antibody

An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

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Patterns of injury
The patterns of glomerular injury are related to the site of accumulation of immunoglobulins and their ability to evoke a cellular inflammatory response. They can be divided into three groups:

- **Mesangial**, in which hypercellularity and matrix accumulation result from mesangial immune complex accumulation. It is characterized by microscopic hematuria and subnephritic proteinuria with well-preserved or minimally reduced glomerular filtration rate (GFR).

- **Endothelial**, which has an exudative component characterized by leukocyte accumulation, endothelial cell injury, and endocapillary proliferation that is associated with capillary wall destruction, mild to marked immune complex deposition, and crescent formation. It can be divided into diffuse and/or global and focal segment form. It is characterized by acute reduction in GFR, hematuria, and mild-to-moderate proteinuria. Endocapillary changes can occur in connection with mesangial pathology. This membranoproliferative pattern of injury is common in the chronic phase of LN.

- **Epithelial**, in which antibodies and complement cause cytotoxic injury, resulting in nonexudative, nonproliferative capillary wall lesion (membranous glomerulonephropathy). It is associated with significant proteinuria, often with nephritic syndrome and preservation and/or gradual reduction in GFR.

For diagnosis, there are six classifications of LN based on glomerular injury (see Abbreviated International Society of Nephrology/Renal Pathology Society [ISN/RPS] 2003 classification of LN).

### New ACR guidelines for screening, treatment, and management of LN
LN is defined as clinical and lab manifestations that meet ACR criteria: Persistent proteinuria of greater than 0.5 g/day, measured by a spot urine protein/creatinine ratio and/or 24-hour protein urine collection. Urine dipstick of 3+ and/or presence of active urinary sediment, such as: more than 5 RBCs or more than 5 white blood cells (WBCs) in the absence of infection.

All patients with clinical evidence of active but previously untreated LN should undergo renal biopsy (unless contraindicated). The indications for renal biopsy are:
- increase in serum creatinine level without compelling causes (for example, sepsis)
- confirmed proteinuria (≥1.0 g per 24 hours [either 24-hour specimens or spot protein/creatinine ratio])
- combinations of the following, confirmed in at least two tests done in a short period of time and in the absence of alternative cause:
  - proteinuria ≥0.5 g per 24 hours plus hematuria
  - proteinuria ≥0.5 g per 24 hours plus cellular cast

### Most common medications used in the treatment of SLE and LN
**Antimalarials:** Hydroxychloroquine (HCQ) is an FDA approved drug for the treatment of SLE that diminishes the risk of nonorgan dissemination, decreases the rate of flares, and prevents damage accrual. The HCQ weight-based dose begins to work within 6 to 12 weeks but reaches maximum effect after 6 months. It treats synovitis and helps improve some aspects of organ-threatening disease (especially cutaneous manifestations). Recent studies showed that HCQ can help lower cholesterol, inhibits platelet aggregation, reduces the risk of clotting events, and improves sicca (dry eyes and dry mouth) symptoms. Most reported adverse reactions are flulike symptoms and gastrointestinal distress, starting at the lower dose and tapering up can help reduce adverse reactions. Patients taking HCQ for more than 10 years can develop retinopathy. Annual ophthalmology examination with visual fields is advised.

### Abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of LN

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Minimal mesangial lupus nephritis</td>
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<tr>
<td>II</td>
<td>Mesangial proliferative lupus nephritis</td>
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<tr>
<td>III</td>
<td>Focal lupus nephritis</td>
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<tr>
<td>IV</td>
<td>Diffuse segmental (IV-S) or global (IV-G) lupus nephritis</td>
</tr>
<tr>
<td>V</td>
<td>Membranous lupus nephritis</td>
</tr>
<tr>
<td>VI</td>
<td>Advanced sclerosis lupus nephritis</td>
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*Indicates the proportion of glomeruli with active and with sclerotic lesions.

*Indicates the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.

*Indicates the grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

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Glucocorticosteroids: Glucocorticoids are another mainstay in lupus management. Patients with organ-disease require high doses of prednisone equivalent for 4 to 6 weeks followed by taper of 10% per week. Flares presenting with synovitis, fevers, rashes, or serositis are managed with lower doses with quick taper. Long-term therapy with corticosteroids can lead to myopathy, osteoporosis, hypertension, diabetes, cataracts, atherosclerotic vascular disease, avascular necrosis of the bone, and infections.

Mycophenolate Mofetil (MMF): MMF blocks B and T cell proliferation. It is used off-label for the treatment for LN. To date, there is no consistent data on the tapering schedule during maintenance phase. Most common adverse reactions include serious infections and gastrointestinal manifestations (for example, diarrhea/nausea). MMF is contra indicated in pregnancy due to increased risk of birth defects and should be given under cover of reliable contraception. It should be stopped at least 6 weeks before planned pregnancy.

Azathioprine (AZA): AZA is a prodrug that is converted to 6-mercaptopurine, its active metabolite. The use of AZA is off-label for the treatment of SLE and/or LN. Prior to initiation of treatment, patients should be screened for thiopurine S-methyltransferase. It takes 3 to 4 months for complete effectiveness. Blood counts and liver function should be monitored every 1 to 3 months. There is an increased risk of lymphoma after 3 years of therapy.

Rituximab: Rituximab is a chimeric monoclonal antibody that selectively targets CD20 positive B cells but spares stem cells and plasma cells. It is FDA approved for the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, granulomatosis polyangiitis, and rheumatoid arthritis. It can also be used off-label in patients with LN when nephritis fails to improve or worsens after 6 months of induction therapy or after failure of treatment with CYC or MMF.

Cyclophosphamide (CYC): An alkylating agent used to treat severe manifestations of autoimmune inflammatory diseases such as SLE, CYC has a well-established efficacy in LN and is given in lower doses than typically prescribed for cancer chemotherapy. In rheumatic diseases, the drug is often used for extended periods of time, and due to a high rate of clinical relapse, it sometimes requires a repeated course of treatment. Its use carries an increased risk of common and opportunistic infections, teratogenicity, sterility, and secondary hematologic malignancy. It can also cause toxicity to the urinary bladder, including hemorrhagic cystitis and bladder cancer.

One of the most devastating adverse reactions of CYC is infertility; in patients with concern regarding fertility, preservation MMF is preferable to CYC. Gonadal toxicity is an adverse reaction of CYC therapy for both males and females and is dose and age related. Studies have shown that therapy with CYC resulted in ovarian failure in 100% of women over 30 years of age; women between the ages of 20 and 30 and younger are affected to a lesser degree. In males, azoospermia is found in 50% to 90% of patients that are exposed to CYC. Strategies for ovarian and testicular function preservation include cryopreservation of sperm, embryos and oocytes, and in vitro fertilization; suppression of gonadal cycle with testosterone for males and leuprolide for females.

Treatment recommendations
The purpose of LN treatment is to control inflammation and suppress the immune system. Treatment is based on the classification by ISN/RPS criteria and should take into consideration the patient’s ethnicity as well as reproductive concerns:

- Class I (minimal mesangial) and Class II (mesangial proliferative): Generally do not require immunosuppressive treatment.

  Class III (focal) and Class IV (diffuse segmental or global): Aggressive therapy with Glucocorticoids and immunosuppressive agents. Induction therapy for class III and IV consists of MMF 2-3 g daily orally or I.V. CYC along with glucocorticoids. Asian patients may require lower doses of MMF (2 g daily). Evidence suggests that Black and Hispanic patients responded less to I.V. CYC; in that case, MMF may be an initial choice to induce improvement. There are two regimens of I.V. CYC:
  - Euro-Lupus CYC: 500 mg I.V. once every 2 weeks for a total of six doses, followed by maintenance therapy with AZA or daily oral MMF (indicated for persons with western or southern European background).
  - High-dose CYC: 500-1,000 mg I.V. once a month for six doses, followed by maintenance treatment with MMF or AZA.

Class V (membranous) combined with class III or IV: Should be treated in the same manner as class III/IV.

Class V (membranous) combined with class III or IV plus cellular crescents: CYC or MMF along with I.V. pulses of high-dose glucocorticoid and initiation of oral glucocorticoids at the higher dose of 1 mg/kg/day.
Class V (pure membranous): A glucocorticoids (0.5 mg/kg/day) plus MMF 2-3 g daily
Class VI (advanced sclerotic): preparation for renal replacement therapy (for example, dialysis)

All SLE patients with nephritis should be treated with a background of HCQ, plus renin-angiotensin blockade (for patients with proteinuria 0.5 g per 24 hours or greater or equivalent ratio on spot urine samples). Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) reduce proteinuria up to 30% and delay doubling of serum creatinine and progression of ESRD.11

Hypertension should be well controlled with a target of 130/80 mm Hg or less. HMG-CoA reductase inhibitor (statin) therapy is recommended for patient with low-density lipoprotein cholesterol greater than 100 mg/dL.11

Monitoring of patients with LN varies according to severity of disease, additional comorbidities, and the presence of pregnancy. Minimum frequency of visits vary from every 2 weeks at the induction, to every month for the first 6 months, and every 3 months when stable. At each visit, BP, urinalysis with microscopy, protein/creatinine ratio, serum creatinine, complement (C3, C4), and anti-DsDNA should be measured, among others.11

Pregnancy and LN

Given the fact that SLE/LN affects women in their childbearing years, pregnancy can occur at any time before, during, and after treatment. All women with SLE/LN should receive prepregnancy risk counseling, with emphasis on educating women to commence pregnancy during periods of very well-controlled disease activity. Overall, patients with previous/active LN have worse outcomes than the general population, with increased rates of preeclampsia, fetal loss, preterm delivery (higher rates of delivery <34 weeks), fetal growth retardation (FGR), and infants small for gestational age.20 BP control is of utmost importance in managing SLE/LN patients during pregnancy. ACE inhibitors and ARBs are contraindicated during all three trimesters of pregnancy. Therefore, patients should be switched to other agents safer to use (if the potential benefits justify the potential risk to the fetus), such as methyldopa, labetalol, or nifedipine.20 Because of immunosuppressant’s fetal toxicity, only glucocorticoids, AZA, and HCQ can be used safely during pregnancy.21 Several studies have shown that women with SLE/LN can have successful pregnancies; however, they should be managed by a high-risk obstetrician in a tertiary center with a multidisciplinary team approach.20

The role of primary care providers

Primary care providers must be alert to the possible diagnosis of SLE in their patients. Making an early diagnosis is important to avoid organ damage. They can help manage mild and stable patients, make referrals to rheumatologists and other specialists as needed, and collaborate with the whole team to monitor disease activity and therapy.13 It is also important to screen patients for a variety of complications of SLE/LN and its treatment:

Infections: Patients with SLE/LN are at increased risk for infections. They should be encouraged to receive inactivated vaccines, such as pneumonia vaccine and yearly influenza vaccine following CDC recommendations for patients who are immunosuppressed.22

Heart disease: SLE patients have a 7.5-fold increase in coronary artery disease (CAD) that cannot be explained solely by traditional cardiovascular risk factors.22,23 GFR less than 60 mL/min/1.73 m² (equivalent to a serum creatinine level of >1.5 mg/dL) is also a risk factor for accelerated atherosclerosis.11 The combined CAD-promoting effects of SLE and chronic kidney disease lead to an even higher cardiovascular risk.2 Routine care for patients with LN should include screening for cardiovascular risk factor, counseling for lifestyle modification such as smoking cessation, encouraging physical activity and weight loss, and screening for symptoms suggestive of heart disease.3,4

Contraception: Contraceptive options and education should be offered to all women with SLE and LN. Women with severe disease and taking teratogenic medications (for example, mycophenolate) require effective contraception to prevent pregnancy. Studies have shown that women with SLE can use most forms of birth control with benefits of contraception outweighing the risk of adverse reactions.23,24 Intrauterine devices containing levonorgestrel are among the safest and most effective options, also progesterone-only pills are effective in long-term contraception.25 Some studies have shown possible increased risk of thrombosis in women with SLE with positive antiphospholipids antibodies and contraceptive use, therefore, intense screening of risk factors for thrombotic events in women with SLE is important when prescribing contraceptives.21

Osteoporosis: Prevalence of osteoporosis varies from 4% to 24% and from 10% to 20% when including premenopausal patients.22 Fractures (vertebral and nonvertebral) have been reported with glucocorticoid doses as low as 2.5 to 7.5 mg/day. New recommendations made by ACR in 2010 for patients taking glucocorticoid for more than 3 months include smoking cessation, regular exercise, and the administration of calcium (1,200 to 1,500 mg) and
vitamin D (800 to 1,000 international units) for all patients receiving glucocorticoid therapy. All patients starting on chronic treatment with glucocorticoid for more than 5 mg/day should be started on a bisphosphonate if there are no contraindications.

Learning to cope

The diagnosis of SLE and LN can be devastating to patients and their families. Psychological support is an important part of patient care. SLE patients will need the expertise of numerous professionals, including nurses, social workers, physical and occupational therapists, ophthalmologists, dermatologists, nephrologists, and cardiologists (to name just a few) throughout the course of their disease. Through education, patients can learn how to cope with and monitor their disease; partnership with their nurse practitioners and other healthcare providers involved in their care is paramount in avoiding delay in treatment and improving outcomes.

REFERENCES


Monica Richey is a nurse practitioner at the Hospital for Special Surgery in New York, N.Y.

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