

Lupus Guidelines Focus on 12 Recommendations

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The first attempt to develop “comprehensive management guidelines” for systemic lupus erythematosus resulted in 12 recommendations—some potentially controversial—from a European task force.

A European League Against Rheumatism (EULAR) task force composed of 19 rheumatology specialists and one clinical epidemiologist based the guidelines on its review of over 8,000 articles. “These recommendations should facilitate the medical care of lupus patients without restricting the autonomy of the provider physicians,” wrote the authors, adding the “remarkable heterogeneity” of lupus makes it especially challenging to cover all aspects of the disease.

As such, the authors did not cover some systemic lupus erythematosus (SLE) diagnostic criteria, such as the potential usefulness of the American College of Rheumatology 1999 classification criteria for diagnosing SLE at early stages. Nor did they delve into detailed management guidelines for cutaneous lupus. “These issues will be addressed in future sessions,” they wrote.

Dr. Virginia D. Steen, professor of rheumatology at Georgetown University, Washington, noted the lack of differential diagnostic criteria in the guidelines. “Some of the biggest problems in lupus are things like separating infection from active lupus, determining whether ‘CNS’ disease is actually a manifestation of lupus . . . distinguishing drug toxicity from disease manifestations. These may not be things that are apropos to these types of guidelines, but they would be more helpful.”

The members of the EULAR task force noted that in selecting studies to consider, “Retrieved items from electronic searches

were screened for eligibility based on their title, abstract, and/or full content. Animal studies, narrative review articles, commentaries, conference abstracts or statements, expert opinion statements, and guidelines were excluded.”

In assessing the prognosis, diagnosis, etiology, or comorbidities associated with SLE, studies were eligible if they had at least 50 patients. Randomized studies of therapy that included at least five patients were also included (Ann. Rheum. Dis. 2007 July 5 [Epub doi: 10.1136/ard.2007.070367]).

“For nontherapy questions of specific organ manifestations (e.g., nephritis, neuropsychiatric lupus), or specific problems (pregnancy, APS [antiphospholipid syndrome]), studies were eligible if they had studied at least 20 SLE patients with the relevant manifestation,” the authors wrote.

Dr. Robert Lahita, who helped compile the ACR’s SLE classification criteria in 1999, noted that some of the recommendations touch on divisive issues, such as the contention that “pregnancy may increase lupus disease activity, but these flares are usually mild.”

“A lot of people say pregnancy makes lupus worse,” said Dr. Lahita, a professor at Mount Sinai School of Medicine, New York, and chairman of medicine at Jersey City (N.J.) Medical Center.

Another controversial aspect of the EULAR guidelines is the task force’s recommendation that “in patients with SLE and antiphospholipid antibodies, low-dose aspirin may be considered for primary prevention of thrombosis and pregnancy loss.”

The recommendations of the EULAR task force include the following:

► **Prognosis.** In SLE patients, new clinical signs (e.g., rashes, arthritis, serositis); routine laboratory tests (CBC, serum creatinine, proteinuria, and urinary sediment); and immunologic tests (e.g., serum C3, anti-ds DNA) may offer information

about the outcome in general and in potential organ involvement. Confirmation by imaging (brain MRI) and pathology (renal biopsy) may add to this in selected patients.

► **Monitoring.** New manifestations such as number and type of skin lesions, neurologic manifestations (seizures/psychosis), and validated global activity indices may be used to monitor lupus patients.

► **Comorbidities.** SLE patients are at high risk for infections (urinary tract infections, among others), atherosclerosis, hypertension, dyslipidemias, diabetes, osteoporosis, avascular necrosis, and malignancies (especially non-Hodgkin’s lymphoma). Minimize additional risk factors, harbor a high index of suspicion, and practice prompt evaluation and follow-up.

► **Treatment of nonmajor organ involvement.** In SLE without major organ involvement, antimalarials and/or glucocorticoids may be used. NSAIDs may be used judiciously in patients at low risk for complications. In nonresponsive patients or patients unable to cut steroid doses to levels acceptable for chronic use, immunosuppressives (azathioprine, mycophenolate mofetil, methotrexate) may be considered.

► **Adjunctive therapy.** Photoprotection should be considered in patients with skin manifestations. Lifestyle modifications (smoking cessation, weight control, exercise) should be encouraged. On a case-by-case basis, low-dose aspirin, calcium/vitamin D, bisphosphonates, statins, and antihypertensives, including angiotensin-converting enzyme inhibitors, may be considered. Estrogens may be used, but risks must be assessed.

► **Diagnosis of neuropsychiatric lupus.** The diagnostic work-up (clinical, laboratory, neuropsychological, and imaging tests) of neuropsychiatric manifestations should be similar to that of a work-up for someone in the general population presenting with the same symptoms.

► **Treatment of severe, inflammatory neuropsychiatric lupus.** Patients with major neuropsychiatric manifestations of inflammatory origin (optic neuritis, acute confusional state/coma, cranial or peripheral neuropathy, psychosis, and transverse myelitis/myelopathy) may benefit from immunosuppressives.

► **Pregnancy in lupus.** There is no significant difference in fertility in lupus patients. Pregnancy may increase disease activity, but flares are usually mild. Lupus nephritis patients and patients with antiphospholipid antibodies are at increased risk of developing preeclampsia. SLE may affect the fetus, especially if the mother has a history of lupus nephritis and antiphospholipid, anti-Ro, and/or anti-La antibodies. These conditions are associated with an increased risk of miscarriage, stillbirth, premature delivery, intrauterine growth restriction, and fetal heart block. Prednisolone, azathioprine, hydroxychloroquine, and low-dose aspirin may be used in lupus pregnancies. Mycophenolate mofetil, cyclophosphamide, and methotrexate must all be avoided.

► **Antiphospholipid syndrome in lupus.** In patients with SLE and antiphospholipid antibodies, low-dose aspirin may be considered for primary prevention of thrombosis and pregnancy loss. Other risk factors should be assessed; estrogen-con-



New manifestations such as number and type of skin lesions (above), neurologic manifestations, and global activity indices may be used to monitor patients.

taining drugs raise thrombosis risk. In nonpregnant patients with SLE and APS-associated thrombosis, long-term anticoagulation with oral anticoagulants is effective for secondary thrombosis prevention. In pregnant patients with SLE and antiphospholipid syndrome, combined unfractionated or low molecular weight heparin and aspirin cut pregnancy loss and thrombosis.

► **Lupus nephritis: diagnosis and disease monitoring.** Renal biopsy, urine sediment analysis, proteinuria, and kidney function may have independent predictive ability for clinical outcome in therapy of lupus nephritis but need to be interpreted in conjunction with each other. Changes in immunologic tests (anti-ds DNA, serum C3) have only a limited ability to predict patient response to treatment and should be used only supplementally.

► **Lupus nephritis: treatment.** In patients with proliferative lupus nephritis, glucocorticoids plus immunosuppressive agents are effective against progression to end-stage renal disease. Long-term efficacy has been demonstrated only for cyclophosphamide-based regimens, which have considerable adverse effects. In short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy, compared with pulse cyclophosphamide, and has a more favorable toxicity profile. Failure to respond by 6 months should evoke discussions for intensification of therapy. Flares following remission are not uncommon and require diligent follow-up.

► **End-stage renal disease.** Dialysis and transplantation in SLE have comparable rates for long-term patient and graft survival as those observed in nondiabetic non-SLE patients. ■

Additional Lupus Research Is Needed

The EULAR task force that authored the new SLE guidelines has proposed a research agenda to correct for the current dearth of randomized controlled trials establishing optimal management of lupus. Areas that the task force highlighted for future investigation included:

- The validity of renal biopsy, urinary sediment analysis, tests for proteinuria, and immunologic tests as surrogate markers in the treatment of lupus nephritis.
- The relative impact on disease susceptibility and severity of environmental factors like sun exposure, smoking, diet, and genetics.
- Mechanisms by which to identify patients at higher risk for SLE.
- Diagnostic criteria with improved

sensitivity and specificity as well as criteria to identify distinct SLE subpopulations.

- Reliable diagnostic algorithms for neuropsychiatric lupus.
- The indications and optimal targets for autologous stem cell therapy in SLE, as well as the major indications for biologic therapies like B-cell depletion, inhibition of B-cell differentiation, costimulation blockade, and toleragens.
- Treatment options for resistant disease that involve major and nonmajor organs.
- The mechanisms of a lupus flare, along with the best way to manage flares.
- The epidemiology, management, and long-term outcome of geriatric, pediatric, and adolescent SLE.