Systemic Lupus Erythematosus

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Module Updated: 2013-10-15
CME Expiration: 2016-10-15

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1. Screening

Despite a genetic predisposition to SLE, do not screen for the disease in asymptomatic patients.

1.1 Understand the genetic predisposition to SLE and its implications for clinical practice.

Recommendations
- Do not screen asymptomatic people for SLE, whether or not they have a family history of the disease.

Evidence
- A 2008 editorial reviews several genetic studies that implicate specific components of the immune system in the pathogenesis of SLE.
- A review discusses the pathogenesis of SLE.

Rationale
- Over 40 different genes predispose to lupus (or to autoimmune disease in general).
- SLE is a complex autoimmune disease involving a large number of variants, both genetic and environmental.
- Genes that have a role in tolerance or inflammation pathways are likely to be candidates for "autoimmune genes."
- Human leukocyte antigen-DR and -DQ alleles dictate which autoantibodies SLE patients make. Other genes influence apoptosis or immune complex clearance. Fcγ receptor alleles affect clearance of immune complexes.
- Potential biomarkers for susceptibility to SLE include complement deficiency, Fcγ receptor alleles, protein tyrosine phosphatase N22 (PTPN22), and signal transduction and activator of transcription 4 (STAT 4).
- The ANA test, often incorrectly used as a screening test, has poor specificity for SLE.


2. Diagnosis

Consider a diagnosis of SLE in patients with a typical photosensitive rash, polyarthritis, and/or a history of characteristic laboratory abnormalities.  

2.1 Classify the patient as having SLE if four of the eleven American College of Rheumatology criteria are present.

Recommendations

- Document at least four of the following American College of Rheumatology classification criteria:
  - Positive ANA
  - Malar rash
  - Discoid lupus
  - Photosensitivity
  - Oral ulcers
  - Arthritis
  - Serositis
  - Renal disorder
  - Neurologic disorder
  - Hematologic disorder
  - Immunologic disorder

- See table History and Physical Examination Elements for SLE for detailed information.

Evidence

- The American College of Rheumatology classification criteria for SLE have high sensitivity and specificity (3; 4).
- The ACR classification criteria may exclude patients with limited disease. The Boston Weighted Criteria system identifies 7% more patients as having SLE (patients with objective findings of SLE but less than four ACR criteria) (5).

Rationale

- American College of Rheumatology classification criteria, although developed for research purposes, have some utility for diagnosis, because they emphasize objective manifestations of a multisystem disease.

2.2 Consider the possible role of environmental triggers and some drugs in initiating SLE in genetically predisposed individuals.

Recommendations

- Recognize that women who take oral contraceptives or estrogen replacement therapy have a slightly increased risk of developing SLE.
- Recognize that the following may trigger lupus:
  - Ultraviolet light
  - Some drugs (sulfonamide antibiotics, echinacea)
  - Silica
  - Smoking
  - Some infections (Epstein-Barr virus)
  - Stress
Evidence

- In the Nurse's Cohort Study, estrogen replacement therapy was associated with a relative risk of 1.8 to 2.5 of developing lupus, and use of oral contraceptive pills was associated with a relative risk of 1.4 to 1.9 of developing lupus (6; 7).
- Two randomized, placebo-controlled, multicenter studies indicate that HRT (0.625 mg of conjugated estrogen daily plus 5 mg of medroxyprogesterone for 12 days per month) or oral contraceptives (triphasic ethinyl estradiol at a dose of 35 µg plus norethindrone at a dose of 0.5 to 1 mg per day) does not increase the risk of severe flare among women with SLE whose disease is stable. However, the use of HRT in menopausal patients with SLE is associated with a small risk of lupus flares, most of which are mild or moderate (8; 9).
- Ultraviolet light (UV-B more than UV-A) triggers apoptosis in skin keratinocytes, leading to exposure of Ro on nuclear blebs (10). UV-light is a well-recognized trigger of SLE cutaneous flares and, sometimes, systemic flares.
- SLE patients are more likely to be allergic to sulfonamide antibiotics and may have a lupus flare after taking them (11).
- Two population-based, case-control studies, one in the southeastern U.S. and the other in the Boston area, showed an association of silica exposure with SLE (12; 13).
- Smoking is a risk factor for both lupus and rheumatoid arthritis (14; 15; 16), with a significantly higher risk of anti-dsDNA seropositivity in current smokers with lupus than former or nonsmokers with SLE (17).
- Epstein-Barr virus is an associate of SLE in children. Through epitope spreading, an initial immune response against Epstein-Barr virus may lead to an autoimmune response, anti-Sm (anti-Smith, one of the very specific lupus autoantibodies) (18).
- One murine model of autoimmunity, the Lewis rat, is an example of a hypothalamic-pituitary-adrenal axis imbalance leading to autoimmunity (19). Stress, such as surgical procedures, is associated with lupus flares, perhaps through its effect on the neuroendocrine axis.

Rationale

- Estrogen augments immune function at several levels.
- Triggering lupus may be due to perturbation of immune regulation, such as up-regulation, by an infection or changes in the hypothalamic-pituitary-adrenal axis.

Comments

- The benefits of estrogen/progesterone therapy for birth control or hormone replacement in patients with SLE should be balanced against the risks other than disease flare because newer data suggest that hormones do not significantly increase the risk of severe flares when compared to placebo (8; 9).
- HRT was not associated with the occurrence of vascular arterial events in patients in the Lupus in Minorities: Nature vs. Nurture (LUMINA) cohort. HRT use in women with SLE should be individualized but may be safe if antiphospholipid antibodies are not present or vascular arterial events have not occurred previously (20).
- A review of the safety of contraceptives in women with SLE concluded that most contraceptive methods may be considered in women with SLE; however, women who are positive for antiphospholipid antibodies have an increased risk of thrombosis and, therefore, are not good candidates for combined hormonal contraception (21).

2.3 Differentiate a lupus rash from other facial rashes.

Recommendations
• Consider SLE in a patient with a photosensitive rash that usually involves the face and V-area of the neck but spares the nasolabial folds.

• Differentiate the rash from polymorphous light eruption, solar urticaria, and drug eruption.

Evidence
• A review of photosensitive rashes and their differential diagnoses (22).

Rationale
• Many patients with facial rashes and positive ANA are misdiagnosed as having SLE when, in fact, they have another cause of photosensitivity (such as polymorphous light eruption) or a nonphotosensitive rash (such as acne rosacea).

2.4 Consider lupus in a patient with symmetric polyarthritis and/or other systemic manifestations of the disease.

Recommendations
• Consider lupus in patients with polyarthritis persisting >6 weeks and occurring in women <30 years, especially if they are black.

• Consider lupus in patients who exhibit manifestations of the disease in other organ systems.

• See table History and Physical Examination Elements for SLE.

Evidence
• Consensus.

Rationale
• Rheumatoid arthritis is more common than SLE, but both can present with a similar pattern of symmetric polyarthritis.

2.5 Consider SLE in a patient with a history of characteristic laboratory abnormalities.

Recommendations
• Consider lupus:
  • In any patient with a history of proteinuria and an abnormal urine sediment, particularly if urine protein has been quantitated to be >1000 mg per 24 hours.
  • If a CBC has shown lymphopenia, leukopenia, thrombocytopenia
  • If evaluation for anemia reveals a Coombs'-positive hemolytic anemia

Evidence
• Consensus.

Rationale
• Even with current therapy, over 10% of patients with SLE develop renal insufficiency or renal failure. Earlier detection of lupus nephritis may prevent some of these poor outcomes.

• Most cytopenias in patients with SLE are asymptomatic, revealed by routine screening. Often, a cytopenia is the presenting sign of SLE and may be the only sign for many years.

2.6 Obtain appropriate serologic tests to confirm the diagnosis of SLE.

Recommendations
• Obtain an ANA in patients who have clinical evidence of SLE.

• Obtain anti-dsDNA, anti-Sm, anti-RNP, anti-Ro/SSA, anti-La/SSB, and complement levels C3 and C4 to support the diagnosis of SLE.
The criteria for positivity for these tests are laboratory-specific. Each test has different positive ranges. See table Laboratory and Other Studies for SLE.

Evidence

- Anti-dsDNA is found in about 50% of patients with SLE and is highly specific for the disease; anti-Sm (Smith) occurs in 30% of patients with SLE and is also highly specific. (3).
- Low C3 and C4 can occur in other connective tissue diseases, but are frequently found in SLE (27).
- In a multiethnic cohort study, the presence of anti-dsDNA antibodies detected using Crithidia luciliae as a substrate was associated with high levels of disease activity (28).

Rationale

- Serologic tests are helpful in making the diagnosis of SLE.
- The ANA is not very specific for SLE, because it is found so often in normal persons.
- Therefore, to substantiate a diagnosis of SLE, pick autoantibody tests that are more specific for SLE.

Comments

- Other autoantibodies (anti-Ro/SSA, anti-La/SSB, anti-RNP) can be found in SLE but also in other connective tissue diseases, such as Sjögren's syndrome, rheumatoid arthritis, and overlap syndromes. Subtype antibody and complement tests are thus important in the evaluation of the patient with suspected connective tissue disease and may provide supporting data for a more specific diagnosis.
- The immunofluorescence antinuclear antibody assay is the gold standard for ANA testing, with greater sensitivity than solid phase assays.

2.7 Recognize the limited usefulness of an ANA test.

Recommendations

- Do not order an ANA unless there is a high pre-test probability of lupus or another connective tissue disease.
- Recognize, however, that the finding of a negative ANA argues against the diagnosis of lupus.

Evidence

- A positive ANA occurs in 10% to 15% of normal young women (29).
- A positive ANA occurs in 33% of family members of a lupus patient. A positive ANA is very common in patients with localized autoimmune disorders, such as autoimmune thyroid disease (30).

Rationale

- A positive ANA test may occur in 10% to 15% of normal young women, in pregnancy and with increasing age.
- Using the Hep-2 substrate, 95% or more of patients with SLE have a positive ANA, most at high titer (>1:640). The finding of a negative ANA, therefore, argues against the diagnosis of lupus.

2.8 Rely on additional laboratory studies to provide clues to the diagnosis of SLE in a patient with positive lupus serologies.

Recommendations

- Obtain a CBC and other studies to look for hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia.
• Obtain serum creatinine, urinalysis, and additional urinary studies to look for proteinuria with or without hematuria or erythrocyte casts.

• See table Laboratory and Other Studies for SLE.

Evidence

• Hemolytic anemia is an uncommon finding in SLE, although when detected is often at disease onset. Hemolytic anemia in the setting of SLE is associated with black ethnicity, thrombocytopenia, and organ damage accrual (31).

• Over 50% of patients with SLE will have renal involvement during the course of their disease. Cytopenias are equally common (32).

• In a multiethnic cohort study, lymphopenia was found to be positively associated with renal involvement, leukopenia, anti-Ro/SSA antibodies and anti-dsDNA antibodies. Moderate to severe lymphopenia was associated with higher disease activity and organ damage (33).

Rationale

• Cytopenias or nephritis occurring in a young woman, especially a black woman, should suggest SLE.

2.9 Obtain antiphospholipid antibody testing for SLE patients with appropriate clinical history.

Recommendations

• Obtain anticardiolipin antibody (IgG and IgM) and lupus anticoagulant tests in patients with SLE or suspected SLE with a history of venous thrombosis, pulmonary embolus, fetal loss, cerebral ischemia, or livedo reticularis.

Evidence

• A review of the literature suggests that 30% to 50% of patients with SLE have antiphospholipid antibodies, and, among patients with SLE, there is a statistically significant association between antiphospholipid antibodies and a history of or risk for venous or arterial thrombosis (34; 35; 36).

• The international consensus statement of the revised antiphospholipid syndrome classification criteria includes a history of arterial or venous thrombosis, or pregnancy morbidity and lupus anticoagulant or anticardiolipin antibodies (moderate to high titer) on two or more occasions at least 12 weeks apart (37).

Rationale

• Antiphospholipid antibodies are associated with an increased risk of thrombosis.

• Treatment of antiphospholipid antibody syndrome in SLE is associated with a decreased incidence of thrombosis.

2.10 Consider other rheumatic diseases, vasculitides, and chronic infections in the differential diagnosis of SLE.

Recommendations

• Base the laboratory investigation on clinical evidence for or against diseases that may be in the differential diagnosis for lupus.

• Recognize that extensive laboratory investigation is commonly necessary to establish a diagnosis of SLE in a patient who presents with a multisystem disease.

• See table Differential Diagnosis of SLE.

Evidence

• Rheumatoid arthritis is more prevalent than SLE (38).
• Acute viral infection may be present at the onset of a new diagnosis of SLE or may mimic a flare of SLE. Viral serology or molecular studies may improve the detection of viral infection (39).

**Rationale**

• The differential diagnosis of lupus is broad, but characteristic clinical features with confirmatory laboratory studies are usually sufficient for accurate diagnosis.
3. Consultation

Consider rheumatology consultation to confirm the diagnosis of SLE, and consult other specialists for complications of the disease, as needed. Consider consultation with appropriate subspecialists if treatment with first-line agents is unsuccessful, or if the patient becomes or plans to become pregnant.

3.1 Consider rheumatology consultation to confirm the diagnosis of SLE as early as possible.

Recommendations
- Obtain rheumatology consultation if the diagnosis of SLE is uncertain.
- Obtain nephrology consultation when the urinalysis is abnormal and a renal biopsy may be needed.

Evidence
- For other rheumatic conditions, such as rheumatoid arthritis, referral to a rheumatologist leads to better outcome (41).
- Even after a period of inactive disease, the majority of SLE patients required an intervention (most commonly a change in medication) at the next visit with the rheumatologist (42).

Rationale
- An early diagnosis of lupus may lead to the introduction of drugs, such as hydroxychloroquine, which reduces flares and may reduce organ system damage and improve survival.
- A renal biopsy is useful to differentiate lupus nephritis from other causes of renal disease and can identify the WHO lupus nephritis subtype, helping to guide treatment.
- Finding diffuse proliferative glomerulonephritis affects treatment decisions, in addition to confirming the diagnosis of lupus.

3.2 Consult a rheumatologist for help in treating patients with lupus with prednisone and immunosuppressive drugs.

Recommendations
- Obtain rheumatology consultation to institute immunosuppressive drugs in patients who require higher than physiologic doses of prednisone (i.e., ≤7.5 mg) for long-term maintenance therapy.

Evidence
- A prospective COX-proportional hazards analysis has proven that both cumulative and high-dose (>40 mg/d) prednisone lead to later musculoskeletal damage, cataract, and CAD (82).
- Methotrexate therapy can lower daily prednisone dose and decrease lupus disease activity. Methotrexate can be considered a steroid-sparing agent in moderate SLE (83).

Rationale
- Steroids cause more long-term damage than immunosuppressive drugs in SLE.
- Rheumatologists have extensive experience in the management of immunosuppressants and combination therapies.

3.3 Consider consultation with rheumatologist and high-risk obstetrician if the patient becomes or plans to become pregnant since the optimal timing for pregnancy is when SLE is under good control.
**Recommendations**

- Obtain consultation with a rheumatologist and high-risk obstetrician for:
  - Assessment of risk before conception (antiphospholipid antibodies, anti-Ro and La, renal insufficiency, teratogenicity of drug regimen)
  - Monthly visits during pregnancy
  - Advice on use of prednisone, hydroxychloroquine, or azathioprine as appropriate to control disease activity to improve pregnancy outcomes

**Evidence**

- A clinical trial comparing prednisone and aspirin with heparin and aspirin showed that both prevent antiphospholipid-antibody-associated fetal loss (in women without SLE), but that heparin and aspirin was safer (84).
- Multiple studies have shown that patients with SLE are more likely to flare during pregnancy, although this remains controversial (85).
- Patients with SLE and high disease activity (physician global assessment of disease activity) during pregnancy have a high risk of fetal premature birth and fetal loss. These patients must be closely monitored and treated during all trimesters to improve pregnancy outcomes (86).

**Rationale**

- Pregnancy increases lupus flares and is associated with fetal morbidity, preterm birth, intrauterine growth retardation, miscarriage, and congenital heart block.
- Antiphospholipid-antibody-associated fetal loss can be reduced with heparin and aspirin therapy.
- Fetal four-chamber cardiac echocardiography can identify congenital heart block early, at a time when dexamethasone therapy may prevent progression.
4. Hospitalization

Consider hospitalization for patients with unexplained fever, chest pain, CNS symptoms, profound thrombocytopenia, rapidly progressive renal failure, acute pneumonitis, or pulmonary hemorrhage.  

4.1 Consider hospitalizing patients with lupus who are suspected of having serious infection. 

Recommendations

- Consider hospitalizing patients with lupus who require evaluation of temperatures >101°F.
- Obtain appropriate cultures and initiate appropriate antimicrobial therapy.

Evidence

- A major cause of death in SLE is infection, especially opportunistic infections (39; 43; 44).
- Infections are more common in patients with SLE than in controls (45).
- In-hospital mortality is lower in a highly experienced hospital (46).

Rationale

- Patients with SLE are subject to common infections, but also to particular bacterial (Salmonella), viral (cytomegalovirus, Zoster), and fungal pathogens.
- Patients with SLE are immunocompromised by the disease itself and by its treatments (prednisone, immunosuppressives, splenectomy).
- Among patients with SLE, bacteremia is associated with poor long-term outcome. The bacterial species that were detected significantly influenced short-term survival, suggesting that empiric coverage should include S. aureus, Pseudomonas, and Gram-negative organisms (43).

4.2 Consider atherosclerotic cardiovascular disease in patients with SLE who develop chest pain and may require hospitalization. 

Recommendations

- Recognize that chest pain may be due to:
  - Pericarditis
  - Pulmonary embolus
  - CAD
  - Esophageal dysmotility
  - Fibromyalgia
- Hospitalize those patients who are suspected of having had an acute ischemic event, such as myocardial infarction or stroke.

Evidence

- Atherosclerosis is found in 35% of patients with SLE using carotid duplex (47).
- Even without traditional cardiovascular risk factors, one of the earliest steps in atherosclerosis, endothelial dysfunction, is more common in patients with SLE than in controls (48).
- In the LUMINA SLE cohort study, smoking and disease activity as measured by the Systemic Lupus Activity Measure (SLAM) were significantly associated with thrombotic events in multivariable analysis, whereas antiphospholipid antibodies were not (49).
• Prednisone increases traditional CAD risk factors, such as hypertension, hyperlipidemia, and obesity (50).

Rationale
• Chest pain in a patient with SLE might be due to pericarditis, pulmonary embolus, CAD, esophageal dysmotility, or fibromyalgia.
• The major concerns are accelerated atherosclerosis causing angina, myocardial infarction, or stroke, which is the leading cause of death in SLE; accelerated atherosclerosis can also present as peripheral vascular disease.
• Smoking and SLE disease activity are important determinants of thrombotic events in SLE.
• SLE damages endothelial surfaces, but traditional CAD risk factors, which are more common in SLE, might then accelerate atherosclerosis.

4.3 Hospitalize patients with CNS symptoms suggestive of encephalopathy, transient ischemic attack, or stroke.

Recommendations
• Hospitalize patients with neurological signs and symptoms, such as:
  • Altered mental status
  • Coma
  • Seizure
  • Psychosis
  • Stroke
  • Cranial neuropathy
  • Mononeuritis
  • Multiplex or transverse myelitis
• Evaluate such patients rapidly with appropriate tests, such as:
  • Computed tomography or MRI
  • Lumbar puncture (to look for evidence of active CNS lupus or infection)
  • Cardiac echo (if embolic cerebrovascular accident is suspected)
  • Carotid duplex and, possibly, cerebral arteriogram and laboratory tests, for antiphospholipid antibodies

Evidence
• Large series have clearly shown that many CNS presentations in SLE are not always due to active SLE, but rather to comorbid processes (51), including infection, atherosclerosis, hypertension, and medication (i.e., corticosteroid) side effects.
• Monthly intravenous cyclophosphamide after induction with high-dose intravenous methylprednisolone (1 g daily for 3 days) provided a better overall response rate in severe neuropsychiatric SLE compared with bimonthly intravenous methylprednisolone alone (52).

Rationale
• The differential diagnosis of CNS symptoms in SLE includes:
  • SLE
  • Hypertension
  • Atherosclerosis
  • Antiphospholipid-antibody syndrome
  • Infection
• Major CNS-SLE must be treated quickly with intravenous methylprednisolone pulse therapy and, sometimes, intravenous cyclophosphamide, but these treatments would obviously worsen an infection.

4.4 **Consider hospitalizing patients with SLE who have other serious complications of the disease.** [B]

**Recommendations**
- Consider hospitalizing patients with:
  - Profound thrombocytopenia
  - Rapidly progressive renal failure
  - Acute pneumonitis or pulmonary hemorrhage

**Evidence**
- Consensus.

**Rationale**
- These complications seriously affect organ function and require emergent interventions that cannot be accomplished in the outpatient setting.
5. Therapy

Consider diet and lifestyle modification to prevent some of the long-term complications of lupus and its treatment, and treat musculoskeletal lupus, photosensitive cutaneous lupus, and lupus nephritis pharmacologically. [P]

5.1 Institute measures to prevent steroid-induced osteoporosis. [P]

Recommendations
- Institute in all patients with SLE:
  - Vitamin D and calcium supplementation (see module Osteoporosis)
  - Smoking cessation
  - Weight-bearing exercise
  - Bisphosphonates or HRT if taking prednisone ≥7.5 mg daily; unless otherwise contraindicated, alendronate and HRT can both be used

Evidence
- Prednisone is the major factor leading to osteoporosis (53).
- A meta-analysis showed that vitamin D and calcium in SLE help steroid-induced osteoporosis (54).
- Vitamin D deficiency is common in patients with SLE and is associated with sun avoidance (55).

Rationale
- Steroid-induced osteoporosis is a major cause of musculoskeletal morbidity in SLE.
- Osteoporosis in SLE is multifactorial; the same factors operative in postmenopausal osteoporosis are presumed to be important, but osteoporosis is found even in young, premenopausal patients with SLE.
- Alendronate and other bisphosphonates are now approved for treatment of steroid-induced osteoporosis.

Comments
- Alendronate is not appropriate in premenopausal women who become pregnant.

5.2 Institute measures to reduce the risk of atherosclerosis in all patients with SLE. [P]

Recommendations
- Institute in all patients with SLE:
  - Low fat, low cholesterol diet
  - Smoking cessation
  - Weight control
  - Exercise
  - Folate

Evidence
- Cohort studies have demonstrated that hyperlipidemia, hypertension, obesity, smoking, and hyperhomocysteinemia are both common in SLE (56) and are associated later with atherosclerosis (50).

Rationale
• Although the initial damage to the vessel may be due to active SLE, the accelerated atherosclerosis is worsened by traditional risk factors.

5.3 Institute measures to prevent photosensitivity rash.

Recommendations
• Counsel all patients with SLE to avoid sun exposure by:
   • Applying sunscreen
   • Wearing protective clothing

Evidence
• Consensus.

Rationale
• Apoptotic cells accumulate in the skin of patients with cutaneous lupus and may undergo secondary necrosis, leading to an inflammatory response.

5.4 Administer appropriate vaccinations.

Recommendations
• Vaccinate patients with SLE on immunosuppressive therapy against influenza and pneumococcus.
   • Administer influenza vaccine annually
   • Administer pneumococcal vaccine every 5 years
   • Avoid live vaccines

Evidence
• Consensus.

Rationale
• Immunosuppressed patients are more vulnerable to influenza and pneumococcal disease.

5.5 Treat musculoskeletal lupus with NSAIDs and hydroxychloroquine.

Recommendations
• Initially treat lupus arthritis with anti-inflammatory doses of traditional NSAIDs.
• Note that COX-2-specific inhibitors, such as celecoxib, do not have an antiplatelet effect; thus, hypercoagulable patients may be at greater risk for thrombosis with a COX-2-specific inhibitor rather than traditional NSAIDs.
• Consider adding hydroxychloroquine to the treatment plan.
• Schedule yearly eye exams in patients taking hydroxychloroquine because of the rare (1 in 5000) risk of retinopathy.
• Try to avoid use of corticosteroids, but, if necessary, limit use to lower doses (prednisone, ≤10 mg/d) except when higher doses are required for life-threatening disease.
• See table Drug Treatment for SLE.

Evidence
• A randomized, placebo-controlled, double-blind withdrawal study showed that hydroxychloroquine was effective in reducing time to flare-up (57).
• Another randomized study found that hydroxychloroquine use helped reduce major flares (58).
• In a cohort of 518 patients with SLE, those on hydroxychloroquine at the beginning of the study had a reduced risk of organ damage, including renal and CNS disease, after adjustment for other confounding risk factors (59).
A nested case-control study in a cohort of minority patients with SLE found that hydroxychloroquine had a protective effect on survival (adjusted OR, 0.32 [CI, 0.11 to 0.86]) and was well tolerated (60).

NSAIDs have shown benefit for lupus arthritis in open trials (61).

Rationale

- COX-2-specific anti-inflammatory agents, such as celecoxib, have not been tested adequately for safety in SLE, especially regarding hypercoagulability.
- Hydroxychloroquine is a slow-acting immunomodulator, not an immunosuppressive, so its safety profile overall is excellent. Reliance on NSAIDs and hydroxychloroquine will help to avoid corticosteroid toxicity.

Comments

- Beware of generic hydroxychloroquine, which may cause more GI upset.

5.6 Treat photosensitive cutaneous lupus with sunblock, topical corticosteroids, and hydroxychloroquine.

Recommendations

- Treat photosensitive rashes conservatively with sunblock (for UV-A and UV-B), topical corticosteroids (but no fluorinated steroids on the face, because of the risk of skin atrophy), and hydroxychloroquine.
- Consider the necessity of using initial high doses of corticosteroids (i.e., prednisone 40 mg/d) for very severe discoid lesions of the face or scalp for the first month while waiting for hydroxychloroquine to take effect.
- See table Drug Treatment for SLE.

Evidence

- Hydroxychloroquine has been shown to be effective for cutaneous lupus in several clinical trials (57; 62).
- Retinoids have also shown benefit for cutaneous lupus (62).

Rationale

- Reliance on hydroxychloroquine will avoid later corticosteroid toxicity.

5.7 Use the results of renal biopsy to guide treatment of lupus nephritis.

Recommendations

- Treat diffuse proliferative glomerulonephritis (WHO Class IV) with monthly intravenous cyclophosphamide, 500 to 1000 mg/m² body surface area for 6 months, along with high-dose corticosteroids (usually initially pulse methylprednisolone, 1000 mg/d for 3 days, followed by prednisone, 40 to 60 mg/d, for the first month), but also consider prescribing a lower dose of cyclophosphamide given every 2 weeks.
- Treat patients with mild to moderately severe nephritis and intact renal function with mycophenolate mofetil, 1000 to 3000 mg/d.
- Consider azathioprine, 2 mg/kg·d, as an option for treatment of diffuse proliferative glomerulonephritis, but recognize that it is less efficacious than cyclophosphamide.
- Recognize that maintenance therapy is needed after the first 6 months.
- Consider continuing the NIH regimen of quarterly intravenous cyclophosphamide for 2 more years, but maintenance therapy with mycophenolate mofetil, 500 to 1500 mg/d, or azathioprine, 1 to 2 mg/kg·d, may be safer and more efficacious than quarterly cyclophosphamide.
• Taper prednisone quickly as the urinary sediment improves.
• Consider discontinuing maintenance immunosuppressive therapy in a small proportion of patients with lupus nephritis who have stable clinical and serologic remission and have been treated for at least 5 years.
• See table Drug Treatment for SLE.

Evidence
• A series of clinical trials done by the intramural program at NIH has proven that cyclophosphamide is more effective than corticosteroids at preventing renal insufficiency/failure in diffuse proliferative glomerulonephritis (63; 64).
• Mycophenolate mofetil was more effective than intravenous cyclophosphamide in inducing remission of moderately active lupus nephritis with normal or near-normal renal function (serum creatinine, 1.06±0.52 mg/dL) (65). This conclusion is supported by a meta-analysis of four randomized, controlled studies of mycophenolate mofetil vs. cyclophosphamide (66). A 2010 meta-analysis of randomized controlled trials comparing mycophenolate mofetil and cyclophosphamide for the treatment of lupus nephritis concluded that the two groups had similar remission rates, but the mycophenolate mofetil group had less frequent leukopenia (67).
• In a study of patients with proliferative glomerulonephritis, treatment with cyclophosphamide (750 mg/m², 13 pulses in 2 years) and oral prednisone or azathioprine (2 mg/kg·d) plus intravenous pulse methylprednisolone (1000 mg daily for 3 days at day 1, 2 weeks, and 6 weeks) led to equivalent serum creatinine and proteinuria levels after a median follow-up of 5.7 years. There were more frequent renal relapses and herpes zoster infections in the azathioprine group (68).
• A multicenter, open-label trial of induction therapy with mycophenolate mofetil or intravenous cyclophosphamide for patients with lupus nephritis concluded that the two treatments produced similar outcomes (69).
• A lower dose of cyclophosphamide, 500 mg every 2 weeks for 6 doses, followed by azathioprine led to renal remission in 71% of patients with 41.3-month follow-up in a European trial (70).
• Mycophenolate mofetil was equivalent to oral cyclophosphamide in another trial (71).
• Maintenance therapy with mycophenolate mofetil or azathioprine was more efficacious and safer than quarterly intravenous cyclophosphamide (72).
• In a study of 32 patients with biopsy-proven proliferative lupus nephritis in remission, withdrawal of immunosuppressive therapy did not lead to flare in 15 patients after a median follow-up of 203 months. These patients were treated longer and were in remission longer than the 17 patients who had flares. These 17 patients had flares in a median of 34 months. After retreatment, 14 of 17 patients entered complete remission (73).
• The EULAR task force report for the management of SLE recommends that in proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive agents (cyclophosphamide and mycophenolate) are effective against progression to end-stage renal disease (74).

Rationale
• The toxicity of intravenous cyclophosphamide (ovarian failure, infection, cystitis, malignancy) is balanced by the need to avoid renal failure in diffuse proliferative glomerulonephritis.
• Immunosuppressive regimens with less toxicity than cyclophosphamide may be as efficacious when used as maintenance therapy.

5.8 Treat antiphospholipid antibody syndrome in patients with SLE.

Recommendations
• Consider prescribing low-dose aspirin (81 mg/d) for any patient with SLE and antiphospholipid antibodies.

• Treat patients with SLE, antiphospholipid antibodies, and venous thromboembolism with moderate-intensity warfarin (INR range, 2.0 to 3.0) indefinitely.

• Treat patients with SLE, antiphospholipid antibodies, and a first ischemic stroke with aspirin (325 mg/d) or moderate-intensity warfarin to prevent further thromboembolic complications.

Evidence

• Using a decision analysis strategy, the benefit of aspirin therapy outweighs the risk of bleeding and prevents arterial and venous thrombosis (75).

• Based on prospective studies suggesting a high rate of recurrence after warfarin discontinuation, indefinite anticoagulation is recommended (76).

• Warfarin and aspirin prevented recurrent stroke or death equally in the Antiphospholipid Antibodies and Stroke Study (APASS) (77).

Rationale

• Patients with SLE and antiphospholipid antibodies are at high risk for initial and recurrent venous or arterial thromboembolism.

• Treatment with aspirin or warfarin decreases primary or secondary thromboembolic events.
6. Patient Counseling

Inform patients with lupus about their disease and encourage adherence to therapy.  

6.1 Ensure patient understanding of the multisystem nature of their disease, the importance of psychosocial support, and the need for close monitoring.

Recommendations

- Stress the importance of compliance with drug regimen and follow-up visits.
- Immunize according to the CDC immunization guidelines.
- When starting treatment with prednisone, inform patients about weight control, low-fat diet, and exercise.
- Advise patients about proper use and side effect profiles of other medications used in treating SLE.
- Counsel the patient about the importance of developing a social support system that will provide feedback about lupus self-management behaviors, problem solving, and alternate solution planning.

Evidence

- Influenza vaccination is safe in patients with lupus with quiescent disease but is less effective than in controls (78).
- A major factor in poor renal outcomes is patient noncompliance with scheduled visits and taking antihypertensives (79), which is associated with socioeconomic status and race.
- A prospective study identified noncompliance as an independent predictor of poor renal outcome (80).
- Improved self-efficacy and lower fatigue scores were shown in a randomized, controlled trial of education intervention for patients with SLE and a partner (social support choice) (81).

Rationale

- Close follow-up and patient adherence to treatment regimens increases the likelihood of a better outcome.
- Education of the patient and support system improves outcomes.
7. Follow-up

Tailor follow-up to the nature and severity of the disease in patients with SLE.

7.1 Use clinical and laboratory monitoring to detect disease flares early.

Recommendations

- Ask about rash, joint pain, and constitutional symptoms approximately every 3 months.
- Examine face, ears, V-regions of neck, and forearms for photosensitive rash and perform joint exam for polyarthritis approximately every 3 months.
- Order a CBC, creatinine clearance, and urinalysis at routine follow-up visits to look for anemia, leukopenia, thrombocytopenia, or evidence of nephritis.
- Be aware that monitoring serologic tests in following stable patients with SLE is controversial.

Evidence

- By the time the creatinine is 1.0 mg/dL, the average patient has already lost 50% of her glomerular filtration rate (87).
- Technetium-DTPA, iothalamate, and insulin clearances show that creatinine and creatinine clearance are inadequate measures of glomerular filtration rate in SLE (87).
- In a prospective, randomized, double-blind, placebo-controlled trial of lupus patients with clinically stable disease, prednisone therapy for 4 weeks decreased the number of severe flares compared with controls in lupus patients with an elevation of both anti-dsDNA antibodies (25% increase) and C3a levels (50% increase) (88).

Rationale

- Early detection of nephritis allows early treatment before renal sclerosis occurs.
- Early detection of hematologic lupus, especially thrombocytopenia, allows better monitoring and institution of treatment.
- Changes in anti-dsDNA antibody levels may predict clinical flare in patients with SLE and otherwise clinically stable disease.

Comments

- An editorial suggested that changes in anti-dsDNA antibody and C3a levels should lead to an informed decision-making conversation with the patient regarding the following options: no change in follow-up or treatment, or more frequent follow-up or change in therapy for lupus with appropriate follow-up. The long-term implications of corticosteroid therapy in a patient with clinically stable disease in unknown (89).

7.2 Institute lifestyle modifications and pharmacologic therapies to reduce cardiovascular risk factors and to prevent osteoporosis in patients with lupus.

Recommendations

- Consider angiotensin-converting enzyme inhibitors to reduce renal scarring in patients with SLE nephropathy.
- Consider statins in patients with SLE with early atherosclerosis as detected by carotid duplex.
- Advise patients about calcium supplements, vitamin D, exercise, and smoking cessation.

Evidence
• In the LUMINA U.S. cohort study, ACE inhibitor use was associated with a longer time to renal involvement (90).

• A study of 124 women with SLE found that suboptimal 25-hydroxyvitamin D levels (<80 nmol/L) were found in 82 (66.7%) patients, and deficient 25-hydroxyvitamin D levels (<40 nmol/L) in 22 (17.9%) patients (91).

Rationale
• Cardiovascular disease is the major cause of death in SLE.
• ACE inhibitor use delays the development of SLE renal disease.
• Vitamin D deficiency is common in SLE, possibly due in part to avoidance of sun exposure.

7.3 Schedule specific periodic testing to monitor for potential complications of SLE and its treatment. 

Recommendations
• In addition to routine laboratory studies detailed above, consider obtaining the following:
  • Ophthalmology exam yearly (or every 6 to 12 months in patients on hydroxychloroquine)
  • DEXA scanning when starting steroids, then every 2 years
  • Gynecologic exam and Pap smear yearly, especially in patients on immunosuppressants
  • Periodic serum lipids
  • Carotid duplex studies in those with SLE for more than 10 years
  • Hip MRI or bone scan in patients with hip pain to detect early osteonecrosis
  • Antiphospholipid antibodies to assess thrombosis risk and risk for pregnancy loss

Evidence
• Consensus.

Rationale
• Preventive monitoring can detect early complications of lupus and its treatment and decrease morbidity and mortality.
References


27. West CD. The complement profile in clinical medicine. Inherited and acquired conditions lowering the serum concentrations of complement component and control proteins. Complement Inflamm. 1989;6:49-64. (PMID: 2650990)


Systemic Lupus Erythematosus


Glossary

AIDS  acquired immunodeficiency syndrome

ANA  antinuclear antibody

ANCA  antinuclear cytoplasmic antibody

BUN  blood urea nitrogen

CAD  coronary artery disease

CBC  complete blood count

CI  confidence interval

CNS  central nervous system

COX  cyclo-oxygenase

DEXA  dual-energy X-ray absorptiometry

ELISA  enzyme-linked immunosorbent assay

ESR  erythrocyte sedimentation rate

GI  gastrointestinal

HIV  human immunodeficiency virus

HRT  hormone replacement therapy

IgG  immunoglobulin G

IgM  immunoglobulin M

INR  international normalized ratio

MRI  magnetic resonance imaging

NIH  National Institutes of Health

NSAID  nonsteroidal anti-inflammatory drug

OR  odds ratio
Systemic Lupus Erythematosus

**SLE**
systemic lupus erythematosus

**TNF**
tumor necrosis factor

**WHO**
World Health Organization
# Tables

## History and Physical Examination Elements for SLE

<table>
<thead>
<tr>
<th>Category</th>
<th>Element</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Demographics: sex, race, age</td>
<td>SLE is predominantly a disease of women (9:1), and is more common in blacks. Most patients are diagnosed in their 20s or 30s (23)</td>
</tr>
<tr>
<td>History</td>
<td>Family history</td>
<td>Over 10% of patients with SLE have a first- or second-degree family member with some kind of autoimmune disease, with autoimmune thyroid disease being most common</td>
</tr>
<tr>
<td>History</td>
<td>Allergies</td>
<td>Patients with SLE are more likely to be allergic to sulfonamide antibiotics (11)</td>
</tr>
<tr>
<td>History</td>
<td>Constitutional</td>
<td>Fever, fatigue, weight loss, and nausea are common symptoms</td>
</tr>
<tr>
<td>History</td>
<td>HEENT</td>
<td>SLE is associated with secondary Sjögren’s syndrome, which can present with dry eyes and/or dry mouth. Episcleritis and scleritis can occur, but are rare. Nasal or oral ulcers are common</td>
</tr>
<tr>
<td>History</td>
<td>Cutaneous</td>
<td>Patients may report photosensitivity, or hair loss, or scarring from discoid lupus</td>
</tr>
<tr>
<td>History</td>
<td>Serositis</td>
<td>Patients may report classic pleuritic pain, or positional pain consistent with pericarditis</td>
</tr>
<tr>
<td>History</td>
<td>Joints</td>
<td>Polymyalgia or polymyalgia is found in &gt;90% of patients with SLE. Morning stiffness is a classic symptom in inflammatory arthritis</td>
</tr>
<tr>
<td>History</td>
<td>Neuropsychiatric</td>
<td>Memory and other cognitive complaints are common. Seizures and psychosis are more specific for SLE. Headaches are no more common in SLE than controls (24). Commonly available neuropsychological studies are useful for excluding overt neurologic dysfunction in SLE (25)</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Vital signs</td>
<td>Fever, tachycardia (26), and hypertension can occur with SLE</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Skin exam</td>
<td>Discoid lupus occurs commonly on the scalp, in the ears, and on the forearms. Malar rash from SLE must be differentiated from seborrheic dermatitis, acne rosacea, and steroid plethora. Photosensitive rashes spare the nasolabial folds, under the nares, and below the lower lip. Livedo reticularis can be a presenting sign of antiphospholipid-antibody syndrome</td>
</tr>
</tbody>
</table>
**Systemic Lupus Erythematosus**

<table>
<thead>
<tr>
<th>Physical exam</th>
<th>HEENT</th>
<th>Check for eye dryness and lack of a salivary pool, suggestive of secondary Sjögren’s syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam</td>
<td>Neck exam</td>
<td>Lymphadenopathy and thyromegaly can occur</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Chest exam</td>
<td>Auscultate and percuss for pleural effusions. Listen for pleural rubs. Bibasilar dry crackles might indicate lupus pneumonitis</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Cardiac exam</td>
<td>Heart murmurs are common in SLE. An increased P2 may indicate pulmonary hypertension. Pericardial rubs may occur in pericarditis</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Abdominal exam</td>
<td>Hepatomegaly and splenomegaly can occur in SLE</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Musculoskeletal exam</td>
<td>Arthritis in SLE mimics early rheumatoid arthritis: symmetric involvement of PIPs, MCPs, and wrists. SLE arthritis is rarely erosive, but reversible hand deformities (Jaccoud’s arthropathy) do occur</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Neurologic exam</td>
<td>SLE can affect both the central and peripheral nervous system. Foot or wrist drop indicates mononeuritis multiplex. A spinal level can occur with transverse myelitis</td>
</tr>
</tbody>
</table>

SLE = systemic lupus erythematosus.
## Laborotary and Other Studies for SLE

<table>
<thead>
<tr>
<th>Test</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td>The most common anemia in SLE is from chronic disease. Hemolytic anemia will usually have a positive direct Coombs' test, for either IgG or complement, or both. Both leukopenia and lymphopenia are found in SLE. Thrombocytopenia can be due to SLE or to antiphospholipid antibodies.</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>Although the ESR is commonly elevated, it is not specific for SLE</td>
</tr>
<tr>
<td>Comprehensive metabolic panel</td>
<td>An elevated creatinine may be a clue to renal lupus. Mild elevations in liver function tests occur in 30%</td>
</tr>
<tr>
<td>Creatine phosphokinase</td>
<td>SLE myositis presents with proximal muscle weakness. Creatine phosphokinase is usually elevated</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Glomerulonephritis usually presents with proteinuria, with or without hematuria. Erythrocytes or granular casts can be seen</td>
</tr>
<tr>
<td>Serologies</td>
<td>Anti-DNA or anti-Sm are specific for SLE. Low C3 and low C4 are common in SLE, but not specific. A negative ANA argues against SLE. Anti-RNP, anti-Ro/SSA, anti-La/SSB, and antiphospholipid antibodies may be found, but they are not specific for SLE</td>
</tr>
<tr>
<td>Renal biopsy</td>
<td>Indicated in patients with laboratory findings suggestive of lupus nephritis</td>
</tr>
<tr>
<td>Other diagnostic studies</td>
<td>Other diagnostic studies depend upon specific manifestation of the disease</td>
</tr>
</tbody>
</table>

ANA = antinuclear antibody; DNA = deoxyribonucleic acid; ESR = erythrocyte sedimentation rate; IgG = immunoglobulin G; RNP = ribonucleoprotein; SLE = systemic lupus erythematosus.
### Differential Diagnosis of SLE

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Photosensitive rash that usually involves the face and V-area of the neck but spares the nasolabial folds&lt;br&gt;SLE occurs predominantly in women (9:1), and is more common in blacks. Most patients are diagnosed in their 20s or 30s</td>
</tr>
<tr>
<td>Chronic fatigue syndrome; fibromyalgia</td>
<td>Eleven or more characteristic tender points (in fibromyalgia), with chronic pain above and below the waist&lt;br&gt;About 30% of patients with SLE may also have fibromyalgia; most patients with SLE have chronic fatigue syndrome (40)</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Monoarticular (knee) or oligoarticular arthritis&lt;br&gt;A false-positive ELISA for Lyme disease may occur in SLE</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Symmetric polyarthritis, very similar to SLE, but erosions are common&lt;br&gt;Patients with SLE can have a positive rheumatoid factor</td>
</tr>
<tr>
<td>Drug-induced lupus</td>
<td>Fever, serositis, arthritis&lt;br&gt;Minocycline can induce lupus in young women treated for acne; ANCA is usually positive, and hepatitis is common.&lt;br&gt;TNF blockers have been reported to cause drug-induced lupus.&lt;br&gt;Hydralazine, procainamide, and isoniazid are the major drugs that cause drug-induced lupus</td>
</tr>
<tr>
<td>Hepatitis C (essential mixed cryoglobulinemia)</td>
<td>Palpable purpura, nephritis, neuropathy&lt;br&gt;Although mild elevation of liver function tests are found in 30% of patients with SLE, elevated liver function tests should lead to a search for hepatitis B and C</td>
</tr>
<tr>
<td>Granulomatosis with Polyangiitis (Wegener's)</td>
<td>Sinus disease, lung nodules, renal disease&lt;br&gt;ANCA is usually positive</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Vasculitis, renal disease, mononeuritis multiplex&lt;br&gt;Biopsy shows medium-vessel vasculitis. Immunofluorescence will not be floridly positive for immunoglobulin and complement, as it is in SLE</td>
</tr>
<tr>
<td>Parvovirus (fifth disease)</td>
<td>Can cause a symmetric polyarthritis, usually self-limited&lt;br&gt;Ask whether there has been an outbreak of &quot;slapped cheeks&quot; disease in the local school system</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>Can mimic SLE with fever, rash, and complement consumption&lt;br&gt;A detailed drug history is essential</td>
</tr>
<tr>
<td>Atheromatous embolization</td>
<td>May mimic SLE by causing thromboembolic lesions&lt;br&gt;Biopsy should show the characteristic cholesterol clefts</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura</td>
<td>Presents as a systemic illness, and may mimic SLE in terms of fever, CNS changes, thrombocytopenia and renal failure&lt;br&gt;Finding schistocytes on the peripheral smear is a major clue</td>
</tr>
<tr>
<td>Catastrophic antiphospholipid-antibody syndrome</td>
<td>Can present with fever, renal failure, and multiple organ involvement that can mimic SLE; patients with SLE can also develop antiphospholipid-antibody syndrome</td>
</tr>
</tbody>
</table>
### Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticardiolipin</td>
<td>Anticardiolipin in moderate-to-high titer and lupus anticoagulant are the cause of catastrophic antiphospholipid-antibody syndrome, but also can be found in about 50% of patients with SLE.</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Can lead to production of antiphospholipid antibodies (usually not beta-2 glycoprotein I dependent) and a positive Coombs' test, and can cause thrombocytopenia. Some patients with SLE will have false-positive ELISAs for HIV. Western blot confirmation of HIV is essential.</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Positive ANA, anemia, high ESR, polyarthritis, pleural effusions, fever, and other symptoms can occur.</td>
</tr>
<tr>
<td>Viral arthritis, other than parvovirus</td>
<td>Usually self-limited, symmetric polyarthritis, especially joints of the hands and wrists. Community outbreaks may be a clue.</td>
</tr>
</tbody>
</table>

**AIDS** = acquired immunodeficiency syndrome; **ANA** = antinuclear antibody; **ANCA** = antinuclear cytoplasmic antibody; **CNS** = central nervous system; **ELISA** = enzyme-linked immunosorbent assay; **ESR** = erythrocyte sedimentation rate; **HIV** = human immunodeficiency virus; **SLE** = systemic lupus erythematosus; **TNF** = tumor necrosis factor.
## Drug Treatment for SLE

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Dosing</th>
<th>Side Effects</th>
<th>Precautions</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td></td>
<td>Nephrotoxicity, hepatotoxicity, platelet dysfunction, anemia, GI side effects, pruritus, rash, headache, dizziness, tinnitus</td>
<td>CV risk and GI risk. Avoid with: aspirin-sensitive asthma, severe CKD, third trimester pregnancy. Decrease dose with hepatic disease, CKD. Caution with: CV disease, elderly. Drug interactions with CYP2C9 inhibitors or inducers</td>
<td>For musculoskeletal lupus</td>
</tr>
<tr>
<td>Hydroxychloroquine (Plaquenil)</td>
<td>Initially, 400 mg qd or bid. Maintenance is 200-400 mg qd</td>
<td>Ocular toxicity, allergic reactions, AGEP, skeletal muscle myopathy, hearing loss, tinnitus, ECG changes, hypotension, GI side effects, CNS side effects, rare hematologic toxicity</td>
<td>Must be familiar with this agent. Avoid with: pregnancy, ocular disease, G6PD deficiency. Caution with: psoriasis, porphyria, hepatic disease. Do yearly eye exams</td>
<td>For musculoskeletal lupus or photosensitive cutaneous lupus</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td></td>
<td>Long-term use can result in: HPA suppression, immunosuppression, hypertension, adverse neurologic effects, glucose intolerance, weight gain, myopathy, cataracts, glaucoma, osteoporosis</td>
<td>Must be familiar with this agent. Avoid with: pregnancy, ocular disease, G6PD deficiency. Caution with: psoriasis, porphyria, hepatic disease. Do yearly eye exams</td>
<td>For musculoskeletal lupus if NSAIDs and hydroxychloroquine are not adequate. If possible, limit to low dose (&lt;10 mg prednisone daily). High-dose therapy for lupus nephritis</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Moderate illness: 20-40 mg qd. Severe illness: 60-100 mg qd. Maintenance dose: 10-20 mg qd or 20-40 mg qod</td>
<td></td>
<td>Must be familiar with this agent. Avoid with: pregnancy, ocular disease, G6PD deficiency. Caution with: psoriasis, porphyria, hepatic disease. Do yearly eye exams</td>
<td>For musculoskeletal lupus if NSAIDs and hydroxychloroquine are not adequate. If possible, limit to low dose (&lt;10 mg prednisone daily). High-dose therapy for lupus nephritis</td>
</tr>
<tr>
<td>Prednisolone (Prelon, Flo-Pred, Orapred)</td>
<td>5-60 mg total daily dose, dosed qd or in divided doses</td>
<td></td>
<td>Must be familiar with this agent. Avoid with: pregnancy, ocular disease, G6PD deficiency. Caution with: psoriasis, porphyria, hepatic disease. Do yearly eye exams</td>
<td>For musculoskeletal lupus if NSAIDs and hydroxychloroquine are not adequate. If possible, limit to low dose (&lt;10 mg prednisone daily). High-dose therapy for lupus nephritis</td>
</tr>
<tr>
<td>Methylprednisolone (Medrol, A-Methapred, Solu-Medrol)</td>
<td>PO: 1-12 mg qd. IV (methylprednisolone sodium succinate) Pulse: 1000 mg IV qd for 3 days</td>
<td></td>
<td>Must be familiar with this agent. Avoid with: pregnancy, ocular disease, G6PD deficiency. Caution with: psoriasis, porphyria, hepatic disease. Do yearly eye exams</td>
<td>For musculoskeletal lupus if NSAIDs and hydroxychloroquine are not adequate. If possible, limit to low dose (&lt;10 mg prednisone daily). High-dose therapy for lupus nephritis</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td></td>
<td>Hematologic toxicity, risk of: malignancy, infections. Vomiting</td>
<td>Avoid with pregnancy</td>
<td>For lupus nephritis or other organ involvement, or in patients failing other agents</td>
</tr>
<tr>
<td>Methotrexate (Trexall)</td>
<td>7.5-20 mg weekly</td>
<td>Nephrotoxicity, ocular side effects, cardiac arrhythmias</td>
<td>Use only by an experienced physician. Avoid with pregnancy. Risk of malignancy. Monitor therapy carefully. Significant toxicities: hematologic, GI, hepatic, pulmonary, dermatologic. Avoid with hepatic disease. Caution with CKD. Severe bone marrow suppression with concomitant NSAIDs</td>
<td>Used primarily as a steroid-sparing agent in musculoskeletal lupus</td>
</tr>
<tr>
<td>Cyclophosphamide (Cytoxan)</td>
<td>500-1000 mg/m² IV every month for 6 months</td>
<td>Hemorrhagic cystitis, infertility, SIADH syndrome, severe cardiotoxicity, interstitial pneumonitis, anaphylaxis, alopecia</td>
<td>Consider dose reduction if CrCl&lt;55</td>
<td>Combine with high-dose corticosteroids for diffuse proliferative glomerulonephritis</td>
</tr>
<tr>
<td>Azathioprine (Imuran, Azasan)</td>
<td>2 mg/kg qd. Maintenance: 1-2 mg/kg</td>
<td>Hepatotoxicity</td>
<td>Increased risk of malignancy. Caution with: CKD, thiopurine</td>
<td>Alternative for diffuse proliferative</td>
</tr>
</tbody>
</table>

---

**Systemic Lupus Erythematosus**
### Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Side Effects</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mycophenolate mofetil (CellCept)</strong></td>
<td>1-3 g qd. Maintenance: 500-1500 mg qd</td>
<td>GI side effects, nephrotoxicity, abnormal kidney function, respiratory adverse events, ophthalmic adverse events, asthenia, insomnia, paresthesias</td>
<td>■ Administer by experienced personnel in an equipped facility. Immuno-suppression and risk of infection. Risk of pregnancy loss and teratogenicity. Caution with: hepatic disease, CrCl&lt;25</td>
</tr>
<tr>
<td><strong>Rituximab (Rituxan)</strong></td>
<td>375 mg/m² weekly for 2-4 doses</td>
<td>Hypotension, nephrotoxicity</td>
<td>■ Fatal infusion reactions, severe mucocutaneous reactions, PML, HBV reactivation</td>
</tr>
</tbody>
</table>

### Other

**Belimumab (Benlysta)**
- 10 mg/kg IV over 1 hour every 2 weeks for 3 doses, then every 4 weeks. Consider premedication
- Used in patients with active lupus in combination with standard therapy. Limited safety and efficacy data

**Aspirin**
- 81-325 mg qd
- GI side effects, hypersensitivity reactions, minor bleeding
- Avoid with severe hepatic disease or severe CKD. Caution with: asthma, GI disease
- For antiphospholipid antibody syndrome

**Warfarin**
- Initially, 5 mg PO qd. Adjust dose according to INR. Target INR 2-3
- Systemic cholesterol microembolization, uncommon skin necrosis
- Risk of mortality (more deaths than placebo in clinical trials), possible risk of malignancy. Avoid with pregnancy. Caution with: depression, cardiac disease
- Used in patients with active lupus in combination with standard therapy. Limited safety and efficacy data

**Calcium**
- 1000 mg elemental calcium daily. Take calcium carbonate with food; take calcium citrate with or without food
- Caution with CrCl<30
- To prevent steroid-induced osteoporosis. Also take vitamin D

**Vitamin D**
- 20 μg (800 IU) daily
- To prevent steroid-induced osteoporosis. Also take calcium

**Bisphosphonates**
- Take with 8 ounces water, without any other medications. Remain upright for at least 30 min
- GI side effects, musculoskeletal or joint pain, hypocalcemia, hypophosphatemia, jaw osteonecrosis, atypical bone fractures of the femur with long-term use
- Avoid with: CrCl<35, pregnancy. Avoid with esophageal irritation or stricture. Caution with: upper GI disorders, chronic anticoagulation
- For steroid-induced osteoporosis if taking >7.5 mg prednisone daily

**Alendronate (Fosamax)**
- 5 mg qd. Take on an empty stomach 2 hrs prior to breakfast
- Dizziness, peripheral edema
- Caution with: CrCl<30
- To prevent steroid-induced osteoporosis. Also take calcium

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**Notes:**
- = first-line agent; ■ = black box warning; AGEP = acute generalized exanthematous pustulosis; bid = twice daily; CKD = chronic kidney disease; CNS = central nervous system; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P450 isoenzyme; ECG = electrocardiogram; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; HBV = hepatitis B virus; HIT = heparin-induced thrombocytopenia; HPA = hypothalamic-pituitary-adrenal; IM = intramuscular; INR = international normalized ratio; ITP = idiopathic thrombocytopenic purpura; IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs; P-gp = P-glycoprotein; PML = progressive multifocal leukoencephalopathy; PO = oral; prn = as needed; q12hr = every 12 hours; qd = once daily; qid = four times daily; qod = every other day; SC = subcutaneous; SCR = serum creatinine; SIADH = syndrome of inappropriate antidiuretic hormone secretion; SLE = systemic lupus erythematosus; tid = three times daily; VTE = venous thromboembolism.

PIER provides key prescribing information for practitioners but is not intended to be a source of comprehensive drug information.