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Systemic Lupus Erythematosus in Children and Adolescents

Beth S. Gottlieb, MD, MS,* Norman T. Ilowite, MD†

Author Disclosure
Drs Gottlieb and Ilowite did not disclose any financial relationships relevant to this article. All of the medications mentioned in this article for treatment of lupus are off-label, with the exception of aspirin, corticosteroids, and hydroxychloroquine.

Objectives

After completing this article, readers should be able to:

1. List the most common presenting symptoms of systemic lupus erythematosus (SLE) in the pediatric population.
2. Describe the patient who is most likely to have secondary Raynaud phenomenon.
3. Recognize why antinuclear antibody testing lacks specificity.
4. Know the specific serologic markers for SLE.
5. Discuss the treatment for SLE.

Introduction

Systemic lupus erythematosus (SLE) is a multisystem, chronic but often episodic, autoimmune disease that is characterized by the presence of antinuclear antibodies (ANA). Because SLE can present with a number of signs and symptoms, the diagnosis often is considered in children who have prolonged unexplained complaints.

Epidemiology

Approximately 20% of all patients who have SLE are diagnosed in childhood. The onset of SLE is rare in those younger than 5 years of age; most pediatric patients are diagnosed in adolescence. SLE is considered a predominantly female disease, and although most affected patients are female, the ratio changes with age. Prior to puberty, the female-to-male ratio is 3:1; after puberty, the ratio becomes 9:1. Aside from this sex difference, there also are marked racial differences observed in SLE. Native Americans are most susceptible to developing SLE, followed by African-Americans, Hispanics, Chinese, and Filipinos. The disease tends to be more severe in African-Americans and Hispanics.

SLE is a multigenic disease. A patient who has SLE is more likely to have a relative who has either SLE or another autoimmune disease such as thyroiditis or insulin-dependent diabetes. Epidemiologic, twin, and human leukocyte antigen data suggest a strong genetic contribution to the etiology of SLE, but the exact cause is unknown. Multiple factors confer risk, including abnormalities in the metabolism of sex hormones, particular foods that have been found to be immunostimulatory in animals, and infectious agents. Overall, it has been suggested that an environmental trigger is necessary in a genetically predisposed individual to result in the disease.

Clinical Manifestations

The most common presenting symptoms of SLE in teenagers are fever, rash, mucositis, and arthritis. Other common symptoms include constitutional symptoms such as malaise and weight loss. Such symptoms, especially when prolonged in an adolescent female, should prompt evaluation for SLE.

Mucocutaneous

The most recognized sign of SLE is the classic butterfly rash or malar erythema (Fig. 1). This photosensitive, erythematous rash over the cheeks crosses the nasal bridge, but spares the nasolabial folds. Although most commonly associated with SLE, this rash is not unique to the disease; it can occur in dermatomyositis. Unlike rosacea, the malar rash in SLE does

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Figure 1. Typical butterfly rash in a girl who has SLE. Note that the malar erythema crosses the nasal bridge.

not have pustules, papules, or telangiectasia. Vasculitic lesions may be present and frequently are found on the palms, resulting in palmar erythema. Photosensitive discoid lesions on the scalp or extremities and maculopapular lesions that may occur anywhere also may be seen. Subacute cutaneous lesions and bullous lesions are uncommon in children. Subacute lesions appear as papulosquamous erythematous lesions on the trunk and limbs. Alopecia in SLE generally begins in the frontal area and is diffuse. Although a difficult cosmetic issue for adolescents, alopecia rarely is permanent. Mucosal lesions may take the form of ulcers on the hard palate (Fig. 2). Because such ulcers are painless, patients generally do not realize that they are present, but they may be found on physical examination.

Central Nervous System

Neurologic manifestations of SLE are difficult to diagnose because they may be vague and are varied. After renal disease, central nervous system (CNS) disease is the second leading cause of serious morbidity and mortality in SLE. Psychiatric manifestations (including psychosis), seizures, and headaches are the most common CNS symptoms. Headaches, difficulty with concentration or memory, depression, or a decline in school performance all may be due to lupus cerebritis but also may result from coping with a chronic illness or an effect of glucocorticoid treatment. Chorea, neuropathies, and transverse myelitis occur less commonly, but are associated more clearly with active CNS disease. Infection always should be considered, especially in those receiving immunosuppressive therapy. Imaging studies and neurocognitive testing can help determine if other symptoms are due to lupus cerebritis.

Figure 2. Palatal erythema and ulcer.

Cardiovascular

Any layer of the heart may be involved in SLE, although the pericardium is affected most commonly. Patients who have pericarditis may complain of chest pain that is exacerbated when lying down or taking a deep breath. A friction rub may be heard on auscultation. Myocarditis may manifest as congestive heart failure or arrhythmia. Libman-Sacks endocarditis results in sterile verrucous vegetations. Up to 50% of patients who have SLE have Libman-Sacks endocarditis, which places them at risk for subacute bacterial endocarditis (SBE) and suggests the need for SBE prophylaxis.

Raynaud phenomenon is very common in adolescents and most often is primary, although it may be secondary to SLE or other connective tissue diseases. Examination of the nail-bed capillaries often provides a clue to distinguishing primary from secondary Raynaud disease. Dilated or corkscrew-shaped nail-bed capillaries or dropout areas (a large gap between capillaries) is suggestive of vasculopathy and, therefore, secondary Raynaud syndrome. Exposure to cold, emotional stress, caffeine, and cigarette smoke may exacerbate the symptoms. It is

important to advise patients to dress warmly, in multiple layers, and to limit exposure to the cold. Patients who have frequent or prolonged episodes of cyanotic changes in their digits are at risk for infarction of the digits and, therefore, may require treatment with a vasodilator (such as nifedipine) throughout the cold winter months.

Children who have SLE have been found to develop premature atherosclerosis. Multiple factors contribute. Glucocorticoids increase concentrations of cholesterol, very low-density lipoprotein (VLDL) cholesterol, low-density lipoprotein cholesterol, and triglycerides. SLE has been implicated in dyslipoproteinemia in adolescents. High concentrations of VLDL and triglycerides and low concentrations of high-density lipoprotein cholesterol and apoprotein A-I have been demonstrated. Nephrotic syndrome resulting in hypercholesterolemia also may contribute to atherosclerosis in some patients who have SLE. Additionally, there is evidence that increased expression of adhesion molecules by endothelial and inflammatory cells as well as antiphospholipid antibodies play a role in the development of premature atherosclerosis. Prevention of complications should begin in the pediatric age group. Some patients require treatment with statins if diet, exercise, and fish oil capsules fail to result in improvement.

Pulmonary

Pleuropulmonary disease is a frequent manifestation of SLE in childhood. The most common symptom is pleuritic chest pain due to effusion and may be a presenting sign of SLE. Approximately 60% of adolescent patients who have SLE have subclinical pulmonary disease with abnormal pulmonary function tests in the absence of symptoms. (1) Shrinking lung syndrome results from a dysfunction of the diaphragm that elevates this organ, resulting in decreased lung volume. Other less common pulmonary manifestations include pneumonitis, pulmonary hemorrhage, and pulmonary hypertension.

Gastrointestinal

Gastrointestinal symptoms in a patient who has SLE may be difficult to interpret because, like CNS manifestations, symptoms may be due to the disease, an associated adverse effect of therapy, or unrelated to either. Abdominal pain may be related to multiple pathologic processes. Diffuse abdominal pain sometimes accompanied by pain radiating to the shoulder should raise the suspicion of pancreatitis, which may be a manifestation of SLE or a complication of steroid therapy. Mesenteric vasculitis, peritonitis, and hepatitis have been demonstrated.

Renal

Renal involvement occurs in approximately 75% of children who have SLE, most often within the first 2 years of the disease. (2) Renal disease is a major cause of morbidity in SLE. Early evidence of renal disease may be suggested by microscopic hematuria and proteinuria. Patients also may have hypertension, a decreased glomerular filtration rate, and elevated blood urea nitrogen (BUN) and creatinine concentrations.

Renal biopsy provides much useful information that affects treatment. Lupus nephritis is classified by the World Health Organization based on light microscopy:

- Class I: Normal
- Class II: Mesangial proliferation
- Class III: Focal segmental glomerulonephritis
- Class IV: Diffuse proliferative glomerulonephritis
- Class V: Membranous nephritis
- Class VI: Glomerulosclerosis

Histopathology also is helpful in determining the acuity or chronicity of inflammation, which determines responsiveness to treatment. Electron microscopy and immunofluoresence provide details about the location of immune complex deposits, which affect prognosis.

Musculoskeletal

Most children who have SLE experience arthralgias or arthritis. Arthritis in SLE typically is nonerosive and nondeforming. Both small and large joints may be involved. In some cases, arthritis may cause Jaccoud arthropathy, a nonerosive but deforming arthritis that results from joint subluxation. Myalgias and proximal muscle weakness may develop in patients who have SLE. If myositis occurs, it suggests the diagnosis of an overlap syndrome such as mixed connective tissue disease. Fever and arthritis in a child also may be present in systemic-onset juvenile idiopathic arthritis and in acute rheumatic fever. Associated clinical features and laboratory findings (such as an elevated antisteptolysin O titer, as found in rheumatic fever) help to make a definitive diagnosis.

Hematologic

Cytopenias are common at the onset of SLE in children. All cell lines may be affected. Leukopenia may result from either neutropenia or lymphopenia. Anemia occurs in approximately 50% of patients. It most often is a normocytic normochromic anemia consistent with that of chronic disease. In some cases, the anemia is an autoimmune hemolytic anemia. Immune-mediated thrombocytopenia also may occur. SLE should be considered especially in adolescent girls who have chronic idiopathic

Table 1. The 1997 Revised American College of Rheumatology Classification Criteria for SLE

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Nonerosive arthritis
- Serositis: pleuritis or pericarditis
- Renal manifestations: persistent proteinuria or cellular casts
- Neurologic manifestations: seizure or psychosis
- Hematologic manifestations: hemolytic anemia, leukopenia (<4,000/mm^3), lymphopenia (<1,500/mm^3), thrombocytopenia (<100,000/mm^3)
- Immunologic manifestations: positive anti-double-stranded DNA or anti-Sm, false-positive serologic test for syphilis, evidence of antiphospholipid antibodies (elevated anticardiolipin immunoglobulin [Ig]G or IgM Ab or positive lupus anticoagulant test)
- Antinuclear antibody elevation

Reprinted with permission from Hochberg M. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1997;40:1725.

thrombocytopenic purpura or those who have Evans syndrome.

Diagnosis

There is no specific diagnostic test for SLE; the diagnosis is based on clinical manifestations and results of laboratory evaluation. The diagnosis should be considered in an adolescent girl who has multisystem disease and demonstrable autoantibodies. Although there are classification criteria for SLE, these are not meant to be diagnostic criteria in individual patients (Table 1). These criteria serve as an important guide for classifying patients in clinical studies; they have not been validated for the diagnosis of SLE in pediatric patients.

Laboratory Evaluation

Laboratory assessment is helpful for establishing the diagnosis and for monitoring the disease course. The best screening test for SLE is the ANA because it is positive in almost all patients who have active disease. Although the ANA is a sensitive test, it is not specific; it may be positive in up to 33% of the general healthy population. (3) One study reported that 71% of patients referred to a pediatric rheumatology center for a positive ANA did not have any rheumatic disease. (4) This study also reported that only with titers of 1:1,280 or higher was there a higher frequency of rheumatologic disease. Other autoimmune diseases associated with elevated ANA titers include juvenile idiopathic arthritis, dermatomyositis, scleroderma, and thyroid disease. Positive ANA titers also may result from recent infectious illnesses.

Antibodies to double-stranded DNA (anti-ds DNA) are more specific for SLE because they rarely are positive in healthy individuals or in other rheumatologic diseases. These antibodies are helpful for monitoring disease activity because they tend to be present in high titers during active disease. They also may be predictive of disease flares, commonly increasing prior to exacerbation of symptoms, especially in the kidney. Other specific antibodies for SLE include the extractable nuclear antigens anti-Sm (Smith) and -RNP (ribonucleoprotein), anti-Ro (also called SS-A), and anti-La (also called SS-B) (Table 2). Anti-Ro antibodies are most known for their association with neonatal lupus erythematosus (NLE) and the development of congenital heart block. Serologic markers of active disease (reduced levels of C3 or C4, elevated titers of anti-ds DNA antibodies) are important to follow and may indicate a need for more aggressive therapy in patients who have class III or IV nephritis.

Table 2. Significance and Frequency of Autoantibodies in SLE

Antibody	Prevalence	Association
anti-ds DNA	73%	SLE (especially when disease is severe or involves the kidney or central nervous system)
anti-SSA (Ro)	40%	SLE (especially with cutaneous manifestations), Sjögren syndrome, neonatal lupus
anti-SSB (La)	10% to 15%	SLE, Sjögren syndrome, neonatal lupus
anti-Sm	20% to 30%	SLE
anti-RNP	15%	SLE, mixed connective tissue disease
anti-cardiolipin	37%	anti-phospholipid antibody syndrome

Data from: Peng SL, Craft J. Antinuclear antibodies. In: Ruddy S, Harris ED, Sledge CB, eds. *Kelly's Textbook of Rheumatology.* 6th ed. Philadelphia, Pa: WB Saunders Co; 2001:165.
Edworthy SM. Clinical manifestations of systemic lupus erythematosus. In: Ruddy S, Harris ED, Sledge CB, eds. *Kelly's Textbook of Rheumatology.* 6th ed. Philadelphia, Pa: Saunders Co; 2001:1110.
Gedalia A, Molina JF, Garcia CO, et al. Anti-cardiolipin antibodies in childhood rheumatic diseases. *Lupus.* 1998;7:551.

Testing for antiphospholipid antibodies and results of a complete blood count, electrolytes, BUN, creatinine, hepatic enzymes, acute-phase reactants (such as erythrocyte sedimentation rate or C-reactive protein), and urinalysis are helpful in the routine monitoring of affected patients.

Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome may occur as a primary disease or be secondary when associated with SLE. This syndrome places patients at risk for both arterial and venous thrombosis, recurrent fetal loss, Raynaud phenomenon, and thrombocytopenia. Neurologic involvement also may occur and may include chorea and transverse myelitis. Patients also are at risk for Libman-Sacks endocarditis. Laboratory features of this syndrome include the presence of anticardiolipin antibodies, prolonged phospholipid-dependent coagulation tests (such as partial thromboplastin time, abnormal dilute Russell viper-venom time), and circulating lupus anticoagulant, as documented by a failure to correct the prolonged coagulation time with mixing studies. One study revealed that 66% of pediatric patients who had SLE had positive anticardiolipin antibodies, 62% had lupus anticoagulants, and 39% had a false-positive VDRL (a phospholipid-dependent test). (5) In 12% of the patients, only one of these tests was positive. Therefore, no one test can be relied on for the diagnosis.

Neonatal Lupus Erythematosus

NLE is a syndrome in infants of mothers who have SLE that is caused by the transplacental transfer of maternal antibodies. The most common manifestations are hematologic, cutaneous, hepatic, and cardiac abnormalities. Almost all mothers who have affected infants are anti-Ro- or -La-positive. Infants also have positive antibody titers, if tested early. The most common hematologic manifestation is thrombocytopenia, generally without associated bleeding. Cutaneous disease may occur immediately after birth or be delayed for several weeks (Fig. 3). The lesions generally occur on the face and appear similar to subacute cutaneous lupus lesions. They resolve without scarring. Hepatitis may occur in NLE and may be accompanied by hepatomegaly.

Most NLE manifestations resolve without sequelae after an average of 6 months, coinciding with the disappearance of maternal antibodies. Congenital heart block, however, is permanent because the fetal conducting system is damaged during its development. Congenital heart block may be detected early in pregnancy as bradycardia in the fetus. All children require placement of a permanent pacemaker. Despite treatment, mortality still is significant.

Figure 3. Erythematous skin lesions typical of neonatal lupus erythematosus.

Treatment

The long-term prognosis of patients who have SLE has improved in recent years, which may be attributed to better monitoring and treatments. The treatment must be tailored carefully to each patient. The choice of medication depends on the extent of organ system involvement (Fig. 4). Although the disease itself may result in significant morbidity and mortality, much of the emerging morbidity in SLE today results from the medications used to control the disease. Such morbidity includes infections, atherosclerosis, and osteoporosis. Thus, therapy must be monitored closely and decreased whenever possible to diminish iatrogenic sequelae.

All lupus patients are advised to use sunscreen for ultraviolet A and ultraviolet B protection to all skin that is exposed to the light (indoor or sunlight) year-round to prevent exacerbation of skin disease and internal organ disease. Nonsteroidal anti-inflammatory drugs are very

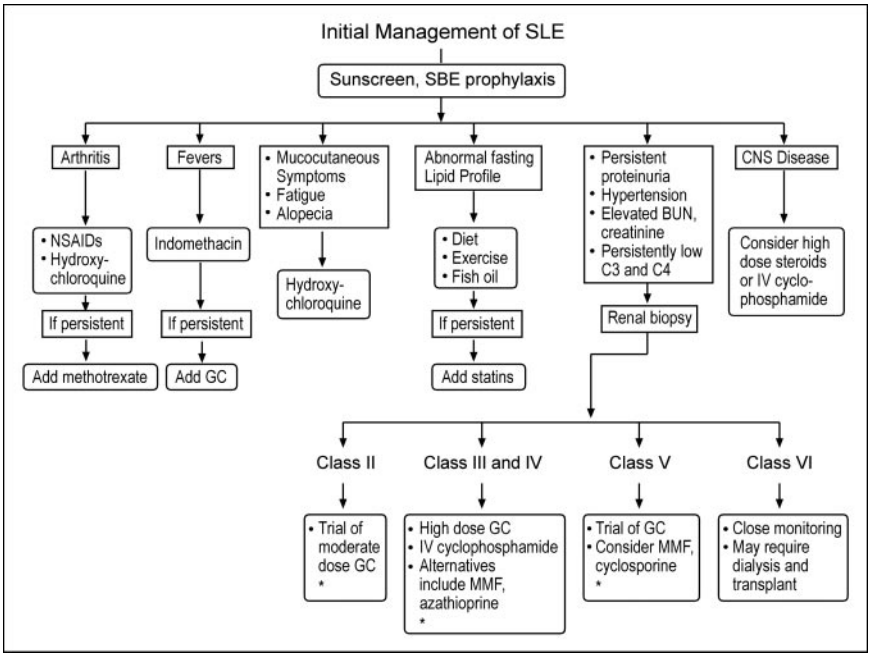

Figure 4. Initial management of SLE. SBE=subacute bacterial endocarditis, NSAID=nonsteroidal anti-inflammatory drug, GC=glucocorticoids, BUN=blood urea nitrogen, CNS=central nervous system, IV=intravenous, MMF=mycophenolate mofetil, *=optimal treatment remains controversial

useful in treating fevers and arthritis. Methotrexate also is used for more extensive arthritis. Hydroxychloroquine is used to reduce fatigue, mucocutaneous symptoms, and alopecia. Due to potential retinal toxicity associated with this medication, patients must have routine ophthalmologic examinations.

Glucocorticoids are required to treat exacerbation of internal organ system disease, especially CNS, renal, and hematologic disease. Glucocorticoids are associated with cushingoid features, cataracts, glaucoma, osteoporosis, hypertension, glucose intolerance, aseptic necrosis of the femoral head, immune suppression, abnormal lipid handling, and myopathy. Therefore, steroid doses are reduced as quickly as clinical improvement allows. Toxicity-sparing strategies include alternate-day or intravenous "pulse" doses of methylprednisolone. Intravenous immunoglobulin may be helpful, primarily for the treatment of chorea and thrombocytopenia.

Immunosuppressive therapy has two important roles: as steroid-sparing agents and in the treatment of steroid-resistant disease. Cyclophosphamide has been considered the therapy of choice for serious organ involvement in SLE. This medication is used especially for focal segmental and diffuse proliferative glomerulonephritis and for CNS disease. Cyclophosphamide has substantial potential toxicity, including infection, bone marrow suppression, nausea, vomiting, alopecia, hemorrhagic cystitis, and bladder malignancy. Administering this drug as monthly intravenous pulse doses instead of daily oral doses may diminish some of the toxicity. Azathioprine and cyclosporine also are used to treat some manifestations of SLE.

Newer therapies aim to target potential pathogenetic processes. Mycophenolate mofetil (MMF) inhibits purine synthesis, lymphocyte proliferation, and T-cell-dependent antibody responses. Studies suggest that MMF may be useful in the treatment of some forms of lupus nephritis (such as class V) with less toxicity. MMF also has been suggested for maintenance therapy after a course of intravenous cyclophosphamide. Many biologic agents currently are being tested for the treatment of SLE. These target specific cytokines (anti-interleukin-10 monoclonal antibody) and costimulatory molecules (anti-CD40 ligand) or attempt to enhance B-cell tolerance (LJP 394). Autologous stem cell transplant is being investigated for severe SLE refractory to available treatments.

The prognosis of children who have SLE has improved due to advances in medical care. According to one study, juvenile-onset SLE has a 92% 5-year survival rate and an 85% 10-year survival rate. (6) The causes of death in affected children have been renal disease, infection, and CNS disease. A multidisciplinary team approach in the care of a child and his or her family is ideal.

References

1. Delgado EA, Malleson PN, Pirie GE, Petty RE. The pulmonary manifestations of childhood onset systemic lupus erythematosus. *Semin Arthritis Rheum.* 1990;19:285–293
2. Cameron JS. Lupus nephritis in childhood and adolescence. *Pediatr Nephrol.* 1994;8:230–249
3. Egner W. The use of laboratory tests in the diagnosis of SLE. *J Clin Pathol.* 2000;53:424–432
4. Malleson PN, Sailer M, Mackinnon MJ. Usefulness of antinuclear antibody testing to screen for rheumatic diseases. *Arch Dis Child.* 1997;77:299–304
5. Seaman DE, Londino V, Kwoh C, Medsger TA Jr, Manzi S.

Antiphospholipid antibodies in pediatric systemic lupus erythematosus. *Pediatrics*. 1995;96:1040–1045

6. Glidden RS, Mantzouranis EC, Borel Y. Systemic lupus erythematosus in childhood: clinical manifestations and improved survival in fifty-five patients. *Clin Immunol Immunopathol*. 1983; 29:196–210

Suggested Reading

Ilowite NT, Copperman N, Leicht T, Kwong T, Jacobson MS. Effects of dietary modification and fish oil supplementation in dyslipoproteinemia in pediatric systemic lupus erythematosus. *J Rheumatol*. 1995;22:1347–1351

Karassa FB, Isenberg DA. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med*. 2001;344:382–383

Klein-Gitelman M, Reiff A, Silverman ED. Systemic lupus erythematosus in childhood. *Rheum Dis Clin North Am*. 2002;28: 561–577

Malleson PN, Sailer M, Mackinnon MJ. Usefulness of antinuclear antibody testing to screen for rheumatic diseases. *Arch Dis Child*. 1997;77:299–304

Silverman ED, Lang B. An overview of the treatment of childhood SLE. *Scand J Rheumatol*. 1997;26:241–246

Steinberg AD, Decker JL. A double-blind controlled trial comparing cyclophosphamide, azathioprine and placebo in the treatment of lupus glomerulonephritis. *Arthritis Rheum*. 1974;17: 923–937

Von Scheven E, Athreya BH, Rose CD, et al. Clinical characteristics of antiphospholipid antibody syndrome in children. *J Pediatr*. 1996;129:339–345

PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. An array of skin and mucous membrane findings have been associated with systemic lupus erythematosis (SLE). One of the vasculitic lesions frequently found with SLE is:

   A. Bullous lesions.
   B. Erythema multiforme major.
   C. Erythema nodosum.
   D. Fissuring of the lips.
   E. Palmar erythema.

2. A 15-year-old girl presents to your office with a 3-month history of facial rash, headaches, swollen knees, and pallor. Urine dipstick analysis shows the presence of protein and blood. You are highly suspicious that she has SLE. Her parents are seeking as much information as possible as you proceed with her evaluation to confirm the diagnosis. The organ system involvement in SLE that is *most* likely to cause the most serious morbidity and mortality is:

   A. Cardiac.
   B. Central nervous system.
   C. Gastrointestinal.
   D. Hematologic.
   E. Renal.

3. An obstetrician is closely monitoring a 25-year-old pregnant woman who has SLE. Her pregnancy, even with the history of SLE, has been stable. You are consulted to advise the woman about the risks for her newborn. You advise her that her infant is *most* likely to develop neonatal lupus erythematosus if the mother has:

   A. A low C4 concentration.
   B. Anti-Ro antibodies.
   C. Anti-Sm (Smith) antibodies.
   D. Proteinuria.
   E. Thrombocytopenia.

4. An 18-year-old girl in whom the diagnosis of SLE was confirmed in the past month has developed increasing signs of altered mental status. You are concerned that she is showing signs of lupus central nervous system (CNS) involvement. Currently, she is receiving corticosteroids for her disease. The additional agent that will be *most* helpful in treating her CNS lupus is:

   A. Cyclophosphamide.
   B. Hydroxychoroquine.
   C. Intravenous immunoglobulin.
   D. Methotrexate.
   E. Mycophenolate mofetil.