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Pediatrics in Review 2012;33;62
DOI: 10.1542/pir.33-2-62

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More Than a Positive Antinuclear Antibody

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Author Disclosure
Drs Weiss has disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gap

For the first time in nearly 50 years, a new medication has been approved by the Food and Drug Administration for treating lupus, and other new medicines are becoming available.

Objectives

After completing this article, readers should be able to:

1. **Describe the common clinical manifestations of systemic lupus erythematosus (SLE).**
2. **Understand the meaning of a positive antinuclear antibody.**
3. **Understand the serologic markers associated with SLE.**
4. **Discuss the treatment and adverse effects of medications used to treat SLE.**
5. **Understand the special needs of a pediatric patient who has SLE.**

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disease characterized by periods of increased disease activity caused by inflammation of blood vessels and connective tissue. The condition is much more than a positive antinuclear antibody (ANA); it is a disease that causes a great deal of morbidity, and patients can be ill at presentation and throughout their disease course.

Pediatric patients with SLE have a more severe clinical course in comparison with their adult counterparts. Patients typically present with rash, fever, and arthritis, although the presentation may be unpredictable. At the time of diagnosis, most patients will fulfill 4 of the 11 American College of Rheumatology criteria for the classification of SLE (Table 1), revised in 1982. (1) These criteria include both clinical and laboratory features of the disease.

The criteria were revised again in 1997 with changes to the immunologic disorder criterion that involve deleting a positive lupus erythematosus preparation and adding a positive finding of antiphospholipid antibodies based on (1) abnormal immunoglobulin G or immunoglobulin M anticardiolipin antibodies, (2) a positive test for lupus anticoagulant (LA), or (3) a false-positive serologic test for syphilis as described.

Abbreviations

ACLA:	anticardiolipin antibody
ANA:	antinuclear antibody
APLS:	antiphospholipid antibody syndrome
ARF:	acute rheumatic fever
DIL:	drug-induced lupus
dsDNA:	double stranded DNA
FDA:	Food and Drug Administration
LA:	systemic lupus erythematosus anticoagulant
LAC:	lupus anticoagulant
MMF:	mycophenolate mofetil
NLE:	neonatal lupus erythematosus
NSAID:	nonsteroidal antiinflammatory drug
pSLE:	pediatric systemic lupus erythematosus
SLE:	systemic lupus erythematosus

Epidemiology

Twenty percent of SLE cases are diagnosed during the first 2 decades of life. Pediatric SLE (pSLE) usually presents in post-pubescent females, with an average age of onset of ~12 years. Before puberty, the male:female ratio is 1:3, but after puberty it increases to 1:9. Ethnicity plays an important role in the incidence of SLE. The incidence of SLE before age 19 years is between 6.0 and 18.9 cases per 100,000 in white girls but is higher in African American (20–30/100,000) and Puerto Rican girls (16.0–36.7/100,000). (2) In addition, the incidence of SLE is higher in Hispanic, Native American, Pacific Islander, and Asian individuals than in white individuals. With more

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Table 1. **1982 Revised Criteria for Classification of SLE***

1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion *OR* Pericarditis: documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	Persistent proteinuria >0.5 g/d or >3+ if quantitation not performed *OR* Cellular casts: may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	Seizures: in the absence of offending drugs or known metabolic derangements; eg, uremia, ketoacidosis, or electrolyte imbalance *OR* Psychosis, in the absence of offending drugs or known metabolic derangements; eg, uremia, ketoacidosis, electrolyte imbalance
9. Hematologic disorder	Hemolytic anemia with reticulocytosis *OR* Leukopenia: <4000/mm^3 total on two or more occasions *OR* Lymphopenia: <1500/mm^3 on two or more occasions *OR* Thrombocytopenia: <100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder	Positive LE cell preparation *OR* Anti-DNA: antibody to native DNA in abnormal titer *OR* anti-Smith antibody: presence of antibody to Sm nuclear antigen *OR* False-positive serologic test for syphilis known to be positive for at least *6* months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

*The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.
(Reprinted with permission from Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982;25:1271–1277.)

aggressive treatment, the 5-year survival rate for pSLE approaches 100% and the 10-year survival rate is 86%.

Pathophysiology

Lupus is thought to result from a combination of hormonal and environmental factors in a genetically predisposed individual. Ten percent of patients with SLE have a first-degree relative who has SLE, and affected patients are more likely to have a family member who has an autoimmune disease. HLA class II alleles DR2 and DR3 contribute to disease susceptibility in some patients, as do inherited complement deficiencies, most commonly homozygous C2 or C4 deficiency. Environmental triggers can be as varied as infection (parvovirus, Epstein-Barr virus), medication (antihypertensives, anticonvulsants), hormonal changes (especially sex hormones), and UV light. Disturbances in B and T cells and abnormalities in apoptosis contribute to the pathogenesis of the disease. Recent studies implicate type I interferon, especially dysregulation of interferon-α, as a prime contributor to loss of tolerance, resulting in autoimmunity.

Clinical Characteristics

Each patient afflicted with SLE presents a different clinical scenario. Common signs and symptoms at disease onset include fatigue, fever, weight loss, lymphadenopathy, and hepatosplenomegaly. Other, more specific, findings aid in diagnosis because most patients express classic SLE findings of malar rash and arthritis at presentation. Because SLE is a periodic illness, depending on the constellation and severity of signs and symptoms, often there is a delay in diagnosis with the time from symptom onset to diagnosis ranging from 1 month to 3.3 years (median, 4 months). (3)

Flares of the illness can involve almost any organ system and common findings are described later in this

article (Table 2). It is important to differentiate SLE from acute rheumatic fever (ARF). Patients with ARF often present with fever and arthritis; however, the rash of ARF, erythema marginatum, can be differentiated from an SLE rash based on its appearance and location. Patients with ARF must have a history of group A *Streptococcus* infection and fulfill the Jones criteria.

Mucocutaneous Involvement

Mucocutaneous features of disease are noted in up to 90% of patients with pSLE. Including photosensitivity, there are three rashes described in the SLE classification criteria. The malar or "butterfly" rash is the most common cutaneous manifestation and is the hallmark of the disease. It develops on the malar eminences and crosses the nasal bridge while sparing the nasolabial folds (Fig 1). The forehead and chin also may be affected. The rash can appear as a blush or a maculopapular eruption with an associated scale and usually is not pruritic. A similar rash may be seen in dermatomyositis; however, Gottron papules on the metacarpophalangeal and interphalangeal joints, elbows, and knees are not seen in SLE, and this feature helps distinguish the two.

Discoid lupus, named after its coin shape, is an erythematous rash that primarily affects the face, ears, and scalp, although the upper extremities and upper chest and back may be affected (Fig 2). The rash may scale or crust. The central area may be hypopigmented, whereas the active border may appear hyperpigmented. The lesions may heal with a scar or atrophy, and discoid patches on the scalp may result in a scarring alopecia if the hair follicle is damaged. Discoid lupus may manifest as a feature of systemic disease or it may be an isolated finding. Fewer than 5% of patients who have isolated discoid SLE will progress to SLE.

It is essential that all patients with pSLE practice sun protection year round with a sun protection factor >30 directed against both UV A and B light to try to prevent development of rash and systemic disease flares. Even if they do not have active rash, it is essential that patients with SLE protect themselves from UV light. Patients should be warned about the risk of rash and disease flares from use of tanning beds. For mild-moderate rash, topical corticosteroids or immunomodulators, such as tacrolimus, also may be used, especially in treating discoid SLE.

Hydroxychloroquine, one of four drugs approved for SLE by the Food and Drug Administration (FDA), is one of the mainstays of treatment for any patient with SLE. Not only does the drug help with control of the rash, but it helps to prevent disease flares. In addition, this medication is well tolerated, although some patients suffer abdominal discomfort.

The major complication of hydroxychloroquine treatment is retinal toxicity; therefore, patients need to be screened by an ophthalmologist at baseline and then every 6 to 12 months. The risk of retinal changes is rare, especially if patients are on a dosage lower than 6.5 mg/kg per day. If retinal changes are seen early they are reversible, but the drug must be discontinued. Between ophthalmology visits patients can monitor themselves with an Amsler grid (a grid of vertical and horizontal lines used to determine a person's central visual field).

For more severe rashes, systemic corticosteroids (also FDA approved for treating SLE) may be needed, usually with the addition of a steroid-sparing agent, such as methotrexate, azathioprine, or mycofenolate mofetil.

For the first time in nearly 50 years, a new medication has been FDA approved for treating SLE. Belimumab, a B-lymphocyte stimulator-specific inhibitor, was approved for the treatment of adult patients with active, autoantibody-positive SLE. Adult patients with SLE with active mucocutaneous symptoms have had the best response in clinical trials. No trials have been performed in patients with pSLE, but trials will likely be under way in the future.

Vasculitic rashes can be part of active SLE. These rashes take on many forms, including palmar erythema and tender skin nodules (Fig 3), purpura, or ulcerations on fingers or toes, pinnae, or nares. Palatal ulceration (Fig 4), as described in the classification criteria, usually is painless and can be detected easily on examination of the oral mucosa. Because the vasculitis is a more systemic process, systemic corticosteroids may be required to treat these lesions.

Raynaud phenomenon can be caused by an underlying connective tissue disease and differs from primary Raynaud disease, in which there is no underlying vasculopathy. Classically, there is a triphasic color change (blue, white, and, on rewarming, red) of the hands or feet, sometimes the ears or nose. Because of vasospasm, the affected area becomes pale and painful, then cyanotic, and on rewarming, erythematous. There may be an associated tingling or burning sensation, especially during the rewarming, erythematous phase. Triggers include exposure to cold, cigarettes, caffeine, and extreme emotion. Patients should avoid triggers and dress warmly, paying attention to keeping the body core, as well as the extremities, warm.

Nail fold capillary changes reflect the vasculopathy that may occur in SLE. Periungal erythema is caused by dilatation of these capillaries. Livedo reticularis occurs in <10% of patients with pSLE. This eruption presents as a reddish-purplish lacy rash, usually on the extremities or torso and often is associated with the presence of antiphospholipid antibodies.

Table 2. Clinical Characteristics of Patients Who Have SLE

Organ System Involvement	At Diagnosis (%) (n = 256)	Within 1 Year After Diagnosis (%) (n = 256)	Ever (%) (n = 256)
Arthritis	157 (61)	159 (62)	171 (67)
Mucocutaneous involvement			
Malar rash	155 (61)	161 (63)	169 (66)
Other rash	96 (38)	106 (41)	111 (43)
Oral ulcers	55 (21)	59 (23)	76 (30)
Alopecia	56 (22)	62 (24)	73 (29)
Photosensitivity	44 (17)	45 (18)	52 (20)
Nasal ulcers	21 (8)	25 (10)	26 (10)
Digital ulcers	9 (4)	10 (4)	13 (5)
Nephritis[a]	95 (37)	117 (46)	141 (55)
Mesangial (class II)	14 (15)	21 (18)	25 (18)
Focal proliferative (class III)	27 (28)	36 (31)	41 (29)
Diffuse proliferative (class IV)	45 (47)	50 (43)	65 (46)
Membranous (class V)	15 (16)	20 (17)	29 (21)
Nephrotic syndrome	20 (22)	22 (19)	25 (18)
Central nervous system	40 (16)	53 (21)	68 (27)
Lupus headache	23 (58)	31 (58)	42 (62)
Psychosis	14 (35)	21 (40)	25 (37)
Cerebrovascular disease	13 (33)	14 (26)	20 (29)
Cognitive dysfunction	9 (23)	13 (25)	15 (22)
Cardiac			
Pericarditis	30 (12)	33 (13)	39 (15)
Myocarditis	3 (1)	5 (2)	6 (2)
Endocarditis	0	0	1 (0.4)
Pulmonary			
Pleuritis	30 (12)	32 (13)	37 (14)
Pneumonitis	1 (0.4)	1 (0.8)	2 (0.8)
Myositis	8 (3)	8 (3)	9 (4)
Diffuse lymphadenopathy	48 (19)	50 (20)	51 (20)
Other			
Raynaud phenomenon	35 (14)	45 (18)	49 (19)
Thrombotic thrombocytopenic purpura	2 (0.8)	2 (0.8)	2 (0.8)
Constitutional symptoms			
Fatigue	129 (50)	136 (53)	142 (55)
Fever	101 (39)	104 (41)	106 (41)
Weight loss	74 (29)	79 (31)	82 (32)
Anorexia	51 (20)	72 (28)	72 (28)
Headache[b]	34 (13)	39 (15)	46 (18)
Autoantibody (%)			
Anti-dsDNA	184 (72)		214 (84)
Anti-Smith antibody	88 (34)		124 (48)
Anti-ribonucleoprotein antibody	68 (27)		95 (37)
Anti-Ro	69 (27)		84 (33)
Anti-La	34 (13)		37 (15)
Antiphospholipid (any)	82 (32)		115 (45)
ACLA[c]	67 (26)		102 (40)
LAC	22 (9)		32 (13)
Rheumatoid factor	28 (11)		35 (14)
Hematologic (any)	141 (55)		161 (63)
Thrombocytopenia	75 (29)		80 (31)
Lymphopenia	73 (29)		93 (36)
Coombs positive hemolytic anemia	58 (23)		63 (25)

[a]Type of nephritis was determined by using the World Health Organization classification system. (5) Two patients did not undergo renal biopsy and are not included in this table.
[b]Not requiring narcotic analgesia.
[c]Total number of patients tested was 254 of the 256.
(Reprinted with permission from Hiraki LT, Benseler SM, Tyrrell PN, Hebert D, Harvey E, Silverman ED. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: a longitudinal study. *J Pediatr*. 2008;152(4):550–556.)

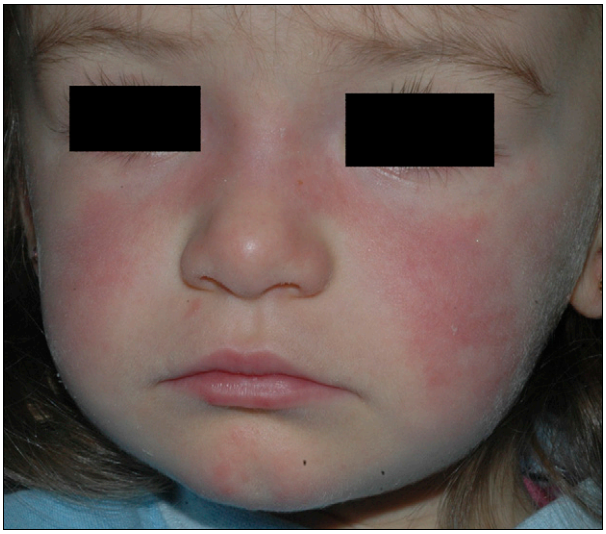

Figure 1. Malar erythema. (Courtesy of H. Shin.)

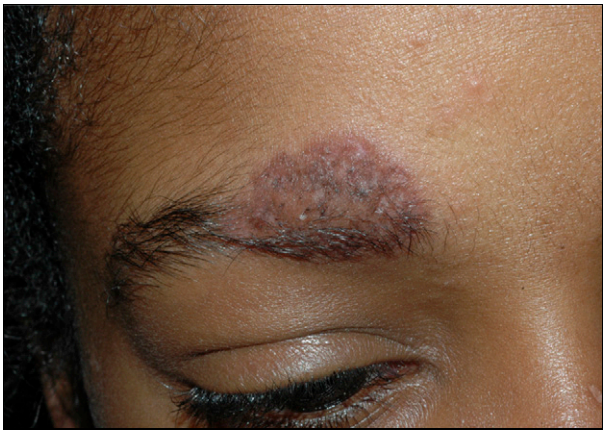

Figure 2. Discoid lupus with follicular plugging and scarring alopecia. (Courtesy of H. Shin.)

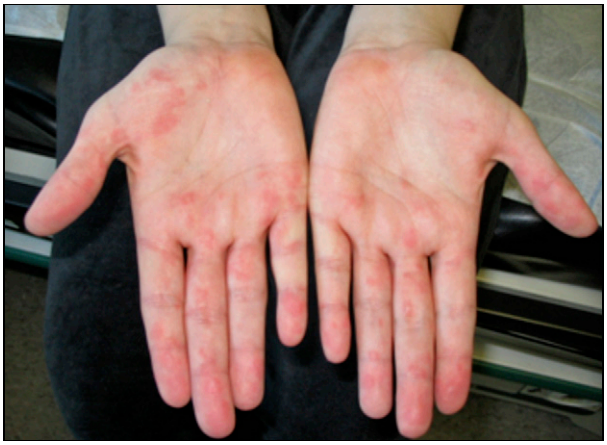

Figure 3. Vasculitic rash with palmar erythema and tender skin nodules. (Courtesy of Y. Kimura.)

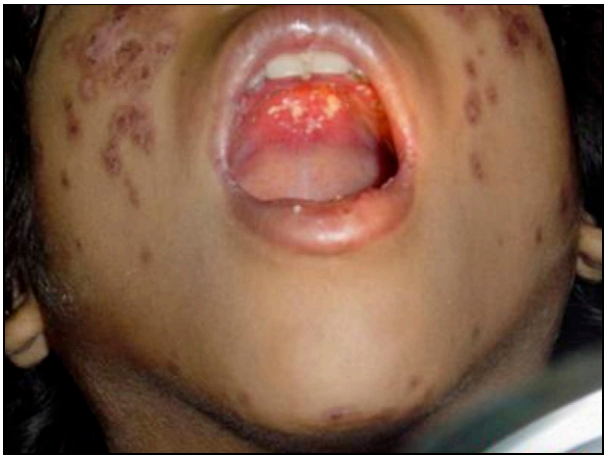

Figure 4. Malar rash and palatal ulcerations. (Courtesy of RheumAtlas.com.)

Alopecia may be one of the presenting manifestations of the disease. It occurs classically in the frontal area but can be diffuse. As the disease activity lessens, patients usually grow new hair.

Musculoskeletal Involvement

Arthralgia and arthritis are very common in pSLE. Unlike the arthritis characteristic of juvenile idiopathic arthritis, SLE arthritis usually is nonerosive. Often there is symmetric involvement of both the large and small joints, primarily the knees, wrists, ankles, and fingers. Patients who have SLE can develop an unusual type of arthritis called Jacoud arthropathy (ulnar deviation of the second to fifth fingers and subluxation of the metacarpophalangeal joints). Myalgia and myositis are less common, but may occur in patients with SLE. Muscle involvement also is common in the so-called "overlap syndrome," in which there are findings common to SLE as well as other rheumatic illnesses.

Nonsteroidal antiinflammatory drugs (NSAIDs) are the usual first-line medications, along with hydroxychloroquine. When there is severe arthritis, particularly when it occurs in parallel with other organ system involvement, corticosteroids may be needed.

Methotrexate also can be used to treat arthritis. It is a disease-modifying agent commonly prescribed for juvenile idiopathic arthritis and works well as a steroid-sparing agent in patients with pSLE who have arthritis. With

severe cases of arthritis, tumor necrosis factor-α inhibitors have been used. Adult patients with SLE with musculoskeletal disease have demonstrated a good response in the belimumab trials.

Renal Involvement

Renal disease is the greatest contributor to morbidity and mortality in the pSLE population. Up to 65% of patients with pSLE are affected, usually within the first year of diagnosis. Renal disease may manifest as proteinuria, microscopic hematuria, hypertension, or elevated blood urea nitrogen and creatinine levels. Eighteen percent of patients may develop nephrotic syndrome. (4) Immune complexes involving DNA and anti-double stranded DNA (dsDNA) deposit in the mesangium and subendothelial space, leading to activation of complement and an influx of inflammatory cells.

These changes manifest histologically as mesangial, focal, or diffuse proliferative glomerulonephritis, and clinically with an active urine sediment (red blood cells, white blood cells, and cellular and granular casts), low complement levels (C3, C4), elevated anti-dsDNA levels, and proteinuria. A spot first-morning urine protein-to-creatinine ratio often is used as an indicator of proteinuria and active renal disease.

A renal biopsy with histologic, immunofluorescent, and electron micrographic analysis is necessary to classify the histologic type of renal disease. Because the class and severity of the renal disease guides treatment, biopsy results play a major role in determining therapy. The International Society of Nephrology and the Renal Pathology Society (5) have revised the original World Health Organization classification of renal biopsy findings in SLE into six different classes (Table 3). Patients may change from one class to another either before or during treatment.

Minimal mesangial lupus nephritis (class I) is the mildest form of nephritis and patients may have a normal urinalysis and creatinine level. This class does not require specific treatment and generally has a good prognosis. Approximately 25% of patients with pSLE will have mesangial proliferative lupus nephritis (class II). These patients may have microscopic hematuria or proteinuria. Treatment consists primarily of a low to moderate dose of corticosteroids over several months. This class of renal disease is considered very mild, but there is always risk of progression.

Focal lupus nephritis (class III) affects 41% of patients with pSLE and often presents with hematuria and proteinuria. Nephrotic syndrome, hypertension, and abnormal blood urea nitrogen and creatinine levels also may be found. Diffuse lupus nephritis (class IV) is the most common and most severe type of lupus nephritis, affecting ~65% of patients. Patients present with hematuria, proteinuria, hypertension, low C3 and C4 levels, and elevated anti-dsDNA levels. This class is similar to class III with the major difference being that more than 50% of glomeruli have evidence of active proliferation.

Most pediatric rheumatologists and nephrologists would treat pSLE patients with class III and IV disease aggressively. This treatment includes high-dose oral corticosteroids (2 mg/kg) or intravenous pulse methylprednisolone (30 mg/kg, max of 1 g) plus potent immunosuppressive agents.

In the adult population with SLE, induction of remission therapy with either cyclophosphamide or mycophenolate mofetil (MMF) routinely is used (6) and the same medications are being used to treat pSLE. Most pediatric rheumatologists probably would start induction therapy with 3 to 6 months of cyclophosphamide and, if the patient has a good response, transition to MMF.

Although cyclophosphamide is effective, risks associated with this medication include bone marrow suppression, alopecia, infection, malignancy, and infertility. The risk of gonadal failure is dose dependent. Some physicians treat post-pubertal girls with luprolide acetate to suppress oogenesis, thus preventing damage caused by cyclophosphamide to dividing cells and lessening the risk of infertility. Because cyclophosphamide also is toxic to spermatogonia and spermatocytes, the best solution for post-pubertal boys to maintain their reproductive capacity would appear to be sperm banking.

MMF inhibits guanosine nucleotides and B- and T-cell proliferation and has antiinflammatory properties. This medication is being used more widely in treating pSLE, especially because the issue regarding fertility is not a concern. Unlike cyclophosphamide, which is given intravenously at monthly intervals, MMF is an oral medication, taken twice daily. Its major adverse effects are abdominal pain and diarrhea; as a result, compliance is of greater concern with MMF. In addition, studies comparing it with traditional treatments, such as cyclophosphamide or azathioprine, have not been done in the pediatric population.

Treatment of major organ system involvement in SLE has taken a page out of the oncologists' book with the aim of achieving remission through intensive therapy at the time of diagnosis, followed by less-intensive medications for the maintenance phase (a step-down rather than a step-up approach).

Newer medicines are becoming available, such as rituximab, a chimeric monoclonal anti-B-cell antibody directed at the CD20 antigen that can lead to the depletion of

Table 3. International Society of Nephrology/Renal Pathology Society 2003 Classification of Lupus Nephritis

Class I	Minimal mesangial lupus nephritis
	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	Mesangial proliferative lupus nephritis
	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits
	May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	Focal lupus nephritis[a]
	Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	Diffuse lupus nephritis[b]
	Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	Membranous lupus nephritis
	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
	Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed
	Class V lupus nephritis show advanced sclerosis
Class VI	Advanced sclerosis lupus nephritis
	≥90% of glomeruli globally sclerosed without residual activity

[a]Indicate the proportion of glomeruli with active and with sclerotic lesions.
[b]Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents. Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.
(Reprinted with permission from Weening JJ, D'Agati VD, Schwartz MM, et al on behalf of the International Society of Nephrology and Renal Pathology Society Working Group on the Classification of Lupus Nephritis. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol.* 2004;15(2):241–250.)

B cells. Its use in nephritis is controversial. Many case reports have demonstrated efficacy, but in a controlled trial of lupus nephritis, the drug did not offer any additional benefit when given as an adjunct to standard therapy. Rituximab can be used alone or with any of the agents mentioned previously. Despite optimal therapy, proteinuria may not resolve completely and an angiotensin-converting enzyme inhibitor can be used to protect the kidney.

Finally, hypertension, if present, must be treated aggressively and maintenance of a normal blood pressure should be the goal. The use of corticosteroids may

exacerbate the hypertension. Overall, if patients are treated early and aggressively, they should go into remission and experience normalization of laboratory parameters.

Patients with membranous lupus nephritis (class V) (29%) commonly present with nephrotic syndrome, which may occur alone or in combination with other types of nephritis. Patients generally are treated with oral corticosteroids for a few months and may require a steroid-sparing agent, such as MMF. Class V nephritis tends to have a better prognosis than class III and IV, but can be refractory to treatment and the proteinuria can be significant, at times >5 g per day. Patients can suffer from severe secondary effects up to and including anasarca.

Advanced sclerosing lupus nephritis (class VI) is characterized by global sclerosis of more than 90% of glomeruli, the result of healing of prior inflammatory injury. Unfortunately, these changes represent end-stage kidney disease and immunosuppression is not helpful for these patients.

Neuropsychiatric Involvement

Neuropsychiatric disease occurs in up to two-thirds of patients with pSLE and often presents within the first year of diagnosis. (3) It is the second leading cause of morbidity and mortality. The highest percentage of neuropsychiatric involvement is manifested as headache. Most other neuropsychiatric manifestations affect fewer than 60% of patients and may present as decreased concentration and cognitive dysfunction, psychosis, seizures, transverse myelitis, central nervous system vasculitis, or stroke. Indeed, SLE can cause almost any neurologic disorder. Headaches are very common in the adolescent population and it may be difficult to determine if the headache should be attributed to SLE. One rule of thumb has been that SLE headaches are not responsive to non-narcotic analgesia.

Treatment of neuropsychiatric disease needs to be directed toward the specific problem, but most patients will require high-dose corticosteroids and immunosuppression with cyclophosphamide, MMF, or azathioprine. Therapy is given in much the same way as for nephritis, by using an induction and maintenance approach.

Hematologic Involvement

More than 60% of patients with pSLE will have cytopenia. Leukopenia, usually secondary to lymphopenia, is found in two-thirds of patients and may provide a clue to the diagnosis. Anemia is seen frequently and although it can be the classic Coombs-positive hemolytic anemia, patients also may have a normocytic normochromic anemia of chronic disease. This latter anemia, however, would not be considered as fulfilling a criterion for diagnosis of SLE. Thrombocytopenia may be found in up to 30% of patients. Patients presenting with idiopathic thrombocytopenia and Evans syndrome (idiopathic thrombocytopenia and hemolytic anemia), especially adolescent girls, should be evaluated for SLE. Cytopenias usually respond to moderate- to high-dose corticosteroids. Intravenous γ-globulin (2 g/kg) often is effective in treating thrombocytopenia, with refractory cases often responding to rituximab. Very rarely is splenectomy required to control the thrombocytopenia.

A more recently described hematologic entity is the antiphospholipid antibody syndrome (APLS). APLS may be primary or secondary to an underlying connective tissue disease, such as SLE. Manifestations can include thrombocytopenia, arterial or venous thrombosis, stroke, transient ischemic attack, chorea, recurrent fetal loss, or avascular necrosis. Laboratory abnormalities include a positive LA, elevated anticardiolipin and antiphospholipid antibodies, or a prolonged partial thromboplastin time. The term LA is a misnomer because patients actually are in hypercoagulable state. Patients with a positive LA are especially at risk for thrombosis, in particular deep vein thrombosis, thromboemboli, and stroke. Patients with lupus who have anticardiolipin antibodies have twice the risk of venous thrombosis, and patients with a positive LA have six times the risk of venous thrombosis compared with patients with SLE without these antibodies. (7)

Patients presenting with any of these complications need to be screened for other disorders of coagulation, such as antithrombin III deficiency or protein S or C deficiency. It is still not entirely clear how best to treat patients who have a positive LA but do not have a history of previous thrombosis or signs and symptoms of APLS because low-level titers can be an incidental finding. Guidelines have been developed to help guide decision-making. Some physicians would treat patients with APLS with low-dose aspirin, although there is no documented evidence of efficacy for preventing a vascular event.

Pulmonary Involvement

Pulmonary involvement may manifest as pleuritis, pleural effusion, pneumonitis, pulmonary hemorrhage, and pulmonary hypertension. Pleuritis is the most common manifestation and patients may complain of dyspnea and sharp, stabbing chest pain during inspiration. Other causes of dyspnea include restrictive lung disease. Pulmonary function tests will be abnormal, demonstrating a restrictive defect and possibly a decreased diffusion capacity. Radiographs may demonstrate interstitial infiltrates, pleural thickening, and elevated hemi-diaphragms. Shrinking lung syndrome results from an impairment of the diaphragm secondary to pleural thickening and fibrosis. A small

effusion can be managed with NSAIDs, although most likely these patients will need corticosteroid therapy.

Pulmonary hemorrhage, although rare, is life-threatening. This complication must be considered in any patient with pSLE who experiences acute shortness of breath and a sudden drop in hemoglobin concentration. Pulse methylprednisolone in combination with cyclophosphamide therapy usually is required to treat pulmonary hemorrhage.

Cardiac Involvement

Patients with lupus are at risk for pericarditis, pericardial effusion, myocarditis, Libman-Sacks endocarditis, bacterial endocarditis, and premature atherosclerosis. The risk of myocardial infarction is low in pSLE, although an infarct must always be considered in the differential diagnosis of chest pain. Pericarditis with pericardial effusion is the most common cardiac complication in pSLE and often is a cause of recurrent chest pain. Pericarditis presents as anterior chest pain and dyspnea that is exacerbated by lying flat. Lupus pericarditis can be treated with NSAIDs alone for mild cases and with the addition of corticosteroids for large effusions or severe pain.

Patients who have both adult and pSLE are at risk for premature atherosclerosis. The Atherosclerosis Prevention in Pediatric Lupus Erythematosus trial, a prospective multicenter study of 221 racially and ethnically diverse patients with pSLE, identified both traditional and nontraditional risk factors for carotid intima-media thickness as a marker for subclinical atherosclerosis. Increased BMI, male gender, increased creatinine clearance, elevated lipoprotein(a) levels, increasing age, weight-adjusted prednisone dose, and azathioprine use all were associated with increased carotid intima-media thickness. (8) Hydroxychloroquine, which most patients are given because of its mild immunosuppressive effect, also has lipid-lowering properties, another reason for using it for treating SLE. All patients should be counseled on proper nutrition and exercise. Limiting the amount and duration of corticosteroid use is extremely important to help minimize atherosclerosis and weight gain, but almost all patients with pSLE will need corticosteroids at times to achieve disease control.

Finally, lupus valvulitis (Libman-Sacks endocarditis) may predispose patients undergoing dental procedures to bacterial endocarditis. Although there is no consensus as to the best medical practice, some physicians, out of concern for an undetected Libman-Sacks endocarditis, will prescribe antibiotic prophylaxis to all patients with SLE before dental procedures.

Gastrointestinal Involvement

Gastrointestinal involvement occurs in approximately one-third of patients and may manifest as serositis, vasculitis, pancreatitis, or enteritis. Abdominal pain is a primary complaint. Vasculitis puts patients at risk for bowel perforation. Pancreatitis may be caused by several factors, including active SLE, infection, or corticosteroid use. Most patients have functional asplenia and are at risk for sepsis from *Streptococcus pneumoniae* and other encapsulated bacteria. These patients should be immunized against pneumococcus, meningococcus, and *Haemophilus influenzae* type B.

Endocrine Involvement

Hypothyroidism is very common in SLE. Hyperthyroidism, on the other hand, has been described rarely. Diabetes mellitus may develop as a result of corticosteroid use and obesity. Delayed puberty is common and studies are under way looking at pubertal development and the role of puberty in affecting pSLE. Irregular menses are common during periods of active disease. The use of estrogen-containing oral contraceptive agents in pSLE is controversial, and other methods of birth control are recommended.

Laboratory Evaluation

Laboratory testing serves two important roles: to aid in diagnosis and to monitor disease activity. A complete blood count is needed to evaluate potential cytopenias. A comprehensive metabolic panel may reveal transaminitis, hypoalbuminemia, or an elevated creatinine level. Because most patients present with constitutional symptoms and inflammation, an elevated erythrocyte sedimentation rate is very common. Despite active inflammation, C-reactive protein levels can remain normal in pSLE; however, often these levels are elevated during active infection. A urinalysis should be performed to screen for proteinuria, hematuria, and other components of active urinary sediment.

In SLE, there is production of myriad autoantibodies that recognize nuclear antigens, as well as many other cellular and tissue components. The ANA is found in 99% of patients with SLE, but also may be positive in other rheumatic diseases, such as mixed connective tissue disease and dermatomyositis. The ANA also may be positive in up to one-third of the healthy population and in family members of patients with SLE. It is helpful that a negative ANA makes the diagnosis of SLE extremely unlikely. ANA is not useful to monitor disease activity. A positive ANA therefore should be interpreted along with the clinical symptoms and having a definite diagnosis in

mind. There is no level of ANA that is diagnostic for SLE, but higher levels, such as a titer of 1:1280 would be suspicious for SLE.

The anti-dsDNA on the other hand is very specific for SLE and may be found in >75% of patients with pSLE. The anti-dsDNA level usually is checked at the time of diagnosis and throughout the disease course to monitor disease activity. A high value in conjunction with other disease activity measures is suggestive of active SLE.

The anti-Smith antibody and anti-ribonucleoprotein antibody often are ordered together as an anti-extractable nuclear antigen panel. The anti-Smith antibody is highly specific for SLE and may be found in up to 50% of patients. This antibody may remain elevated regardless of disease activity and therefore is not useful in monitoring disease activity. The anti-ribonucleoprotein antibody may be found in patients who have classic SLE, but often indicates the patient's diagnosis is a mixed connective tissue disease (SLE with features of systemic sclerosis or dermatomyositis).

Other antibodies can also be seen in SLE, such as SS-A (anti-Ro) and SS-B (anti-La). Complement levels, specifically C3 and C4, are monitored in SLE, and low or undetectable levels are expected in SLE during periods of active disease. The anti-dsDNA and complement levels are important disease markers and help guide medication dosing.

Neonatal Lupus Erythematosus

Neonatal lupus erythematosus (NLE) occurs in 1% of infants who experience transplacental passage of maternal SSA or SSB antibodies. The most common manifestations are rash, cytopenias, and hepatitis with hepatomegaly. Congenital heart block from antibody-mediated damage to the conducting system is the most feared complication, and may be seen in up to 30% of infants born with NLE. As a consequence, all pregnancies in mothers with SLE or known positivity for SSA and SSB antibodies are considered high risk and require close monitoring.

Fetal bradycardia is the first sign of NLE and must be evaluated at 16 weeks' gestation and at continuing intervals throughout pregnancy. Mothers are started on dexamethasone as soon as a fetus is identified as having heart block to decrease maternal antibodies and inflammation of the conducting system and to delay the onset of fibrosis. The rash of NLE is similar to that seen in subacute SLE and is erythematous with a raised border, particularly prominent on sun-exposed areas and around the eyes (Fig 5). The skin may have a fine scale. UV light will worsen the rash and should be avoided as much as possible.

Except for the heart block, all other manifestations will resolve without intervention, usually within 6 months—the time it takes for maternal antibodies to disappear. Approximately 30% to 50% of infants who develop congenital heart block will require pacemaker implantation, usually within the first 24 months. These children need close follow-up; however, it is unlikely that they will go on to develop SLE.

Drug-Induced Lupus

The classic medications that induce drug-induced lupus (DIL) include minocycline, procainimide, hydralazine, penicillamine, isoniazid, quinidine, phenytoin, and carbamazapine. Anti–tumor necrosis factor agents, such as infliximab, adalimumab, and etanercept have also been implicated in DIL. The prevalence of DIL is equal in males and females, although minocycline-induced lupus is usually seen in adolescent girls using the medication

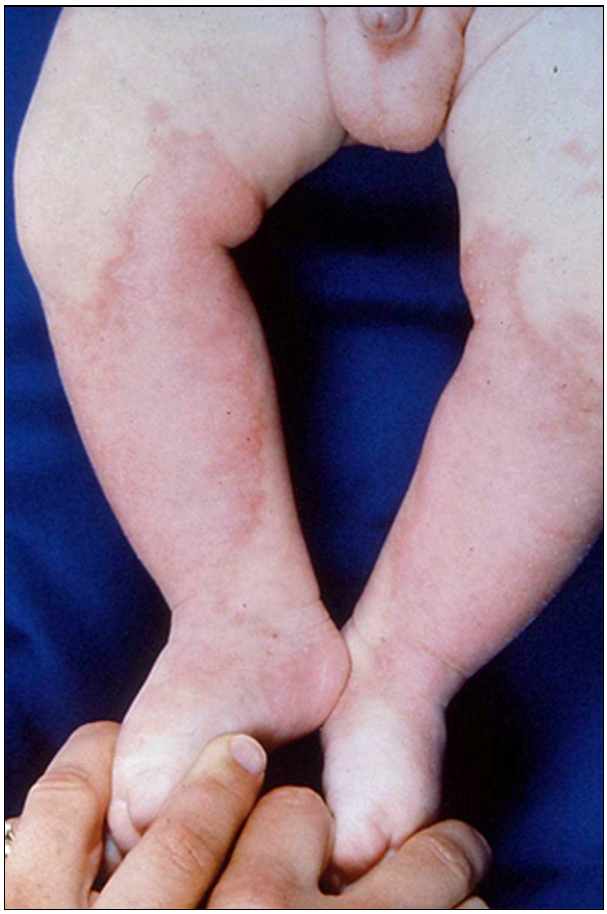

Figure 5. Neonatal lupus rash. (Courtesy of Taunton Southwood.)

for treatment of acne. Chronic use of the medication is required to develop DIL.

Patients often present with constitutional symptoms, photosensitive rash, arthralgia, myalgia, and serositis. Subacute cutaneous lupus also may be present. Positive antihistone antibodies are present in 95% of patients with DIL and help to distinguish these patients from patients with systemic disease, although patients with classic SLE also may test positive for antihistone antibodies. Antineutrophilic cytoplasmic antibodies may be positive. Treatment of DIL requires discontinuing the offending agent. A trial of NSAIDs, hydroxychloroquine, and possibly corticosteroids may be needed. Symptoms usually abate within weeks to months of stopping the medication; however, in some patients DIL will evolve into true SLE.

Complications of Corticosteroids

As stated, corticosteroids are a mainstay of treatment for SLE. Unfortunately, a number of adverse effects can affect the patient not only medically but from a psychosocial standpoint as well. Once corticosteroids are started, patients can gain weight easily, become hirsute, and develop acne, striae, and a cushingoid facies. These effects tempt all patients, but particularly the adolescent girl, to abandon adherence to their medical regimen. Infection, thinning of the skin, short stature, personality changes, sleep disturbance, irregular menses, and mood swings may also occur. Hypertension, glaucoma, and cataracts can develop and should be screened for regularly. Patients may develop avascular necrosis of any bone but this complication is particularly common in the femoral head. Any patient with SLE on corticosteroids suffering from hip pain, with or without limited hip motion, should have imaging studies done to rule out avascular necrosis.

Role of the Pediatrician

Rheumatologists are involved in the care of patients who have SLE; however, the pediatrician's involvement does not need to be peripheral. At each office visit, the patient should be screened for hypertension. It is important that patients are up to date on their vaccinations. Those on immunosuppressive medications cannot receive live virus vaccines, but should be given the 23-valent pneumococcal vaccine and the annual influenza vaccine. If patients have a fever they should be seen in the pediatric office for a thorough evaluation and antibiotics should be used judiciously. Care should be given to try to avoid sulfonamides because their use can result in a disease flare.

In the United States, Section 504 of the Rehabilitation Act and the Americans with Disabilities Act mandate that children with chronic disease have a right to have accommodations made to their educational plans that will allow them to succeed academically. A 504 plan or an individual education plan (IEP) should be put in place if needed. School teachers and guidance counselors should know that patients with pSLE may need assistance with note taking or getting from class to class if they have active arthritis. Patients should not be penalized if they cannot keep up with their peers in physical education class. Patients also may be absent from school because of disease flares or doctors' appointments.

Patients with pSLE do best when care is provided by a team approach that involves the rheumatologist, primary care physician, ophthalmologist, nephrologist, and social worker or child life therapist. These patients need close monitoring, and the patient and family often need extra support. It is important to counsel patients on medication compliance and on healthy diet and exercise, and to ensure proper follow-up with the various subspecialists whom the patient sees.

Summary

- Based on strong research evidence and consensus, the most common disease manifestations at diagnosis of pSLE are constitutional symptoms, arthritis, and malar rash. (4)(5)
- Based on some research evidence and consensus, patients with pSLE tend to have major organ system involvement (renal/central nervous system) and a greater disease burden compared with adults. Despite these findings, mortality is low. (4)(5)
- Based on some research evidence and consensus, the diagnosis of pSLE is unlikely if the ANA is negative, and most patients with SLE have a positive ANA at a titer ≥1:160. (9)
- Based on strong research evidence, both MMF and cyclophosphamide can be used for induction therapy in class III and IV lupus nephritis. (10)
- Based on strong research evidence, patients with SLE and anticardiolipin antibodies or LA have a two and six times greater risk of venous thrombosis, respectively, compared with patients with SLE without antiphospholipid antibodies. (7)
- Based on strong research evidence, patients with pSLE have a higher risk for subclinical atherosclerosis when there is weight-adjusted prednisone use, azathioprine use, increasing age, male gender, high BMI, abnormal creatinine clearance, and elevated lipoprotein(a) levels. (8)

ACKNOWLEDGMENTS The author thanks Drs B. Anne Eberhard and Kathleen A. Haines for critically reviewing this manuscript.

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Suggested Reading

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PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Beginning this past January, learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

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1. The most common skin manifestation of systemic lupus erythematosus is:
   - A. Alopecia
   - B. Discoid lupus
   - C. Gottron papules
   - D. Malar (butterfly rash)
   - E. Psoriasis

2. A patient with discoid lupus is prescribed hydroxychloroquine. Of the following, what intervention should be performed at least annually to monitor for drug toxicity?
   - A. A bone density study (DEXA)
   - B. Opthalmologic examination
   - C. Plasma creatinine
   - D. Prothrombin time
   - E. Pulmonary function testing

3. According to the American Rheumatologic Association, which of the following conditions is a diagnostic criterion for systemic lupus erythematosus?
   - A. Arthralgia
   - B. Hemolytic anemia
   - C. Interstitial pneumonitis
   - D. Splenomegaly
   - E. Vaginal ulcerations

4. The leading cause of morbidity and mortality in systemic lupus erythematosus is:
   - A. Arthritis
   - B. Nephritis
   - C. Neuropsychiatric lupus
   - D. Pericarditis
   - E. Pneumonitis

5. Approximately what percentage of children with SLE will have anti-double-stranded DNA antibodies at the time of diagnosis?
   - A. 1%
   - B. 10%
   - C. 25%
   - D. 50%
   - E. 75%

Pediatric Systemic Lupus Erythematosus : More Than a Positive Antinuclear Antibody

Jennifer E. Weiss

Pediatrics in Review 2012;33;62
DOI: 10.1542/pir.33-2-62