

## Systemic Lupus Erythematosus

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Systemic lupus erythematosus in children and adolescents (pSLE) is a multi-system autoimmune disease with a great variability in disease presentation and course. The diagnosis of systemic lupus erythematosus (SLE) is based on the clinical and laboratory features consistent with this illness in the absence of another autoimmune disease that could explain the findings. At time of diagnosis of pSLE, most but not all patients have at least four of the American College of Rheumatology Classification Criteria for SLE (Table 1) [1]. This article summarizes available epidemiologic data, clinical patterns, approaches to investigation and treatment, and recent outcome data.

### Incidence

The incidence of SLE varies significantly in different ethnic groups and populations, with annual incidence rates in adults ranging from 1.9 to 5.6 per 100,000 [2–6]. Sex-specific incidence rates differ between men and women, with rates between 0.4 and 0.6 for white males, 3.5 and 4.6 for white females, 0.7 for African American males, and 9.2 for African American females [7,8].

Pediatric data suggest the incidence of SLE with onset before age 19 years is probably between 6 and 18.9 cases per 100,000 in white females and higher in black (20–30 per 100,000) and Puerto Rican females (16–36.7 per 100,000) [9].

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Table 1  
The 1982 revised criteria for classification of systemic lupus erythematosus\*

Criterion	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis—convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion or Pericarditis—documented by ECG or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria greater than 0.5 g/day (or > 3+ if quantitation not performed) or Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
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, or electrolyte imbalance)
Hematologic disorder	Hemolytic anemia with reticulocytosis or Leukopenia less than 4000/mm <sup>3</sup> total on two or more occasions or Lymphopenia less than 1500/mm <sup>3</sup> on two or more occasions or Thrombocytopenia less than 100,000/mm <sup>3</sup> in the absence of offending drugs
Immunologic disorder	Positive lupus erythematosus cell preparation or Anti-DNA antibody to native DNA in abnormal titer or Presence of anti-Sm nuclear antigen or False-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by <i>Treponema pallidum</i> immobilization or fluorescent treponemal antibody absorption test
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 SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

Incidence rates are higher in Hispanics, blacks, native Americans, and persons from Southeast and South Asia [10–12].

In the authors' Toronto pSLE cohort, the male:female ratio is 1:4.4, consistent with most larger reviews of white and Asian pediatric populations [13,14]. In African-Caribbean and South American populations, the incidence is higher in girls than in boys, with male:female ratios as low as 1:7 [15,16]. The median age at pSLE diagnosis in the authors' cohort was 12.2 years, comparable with other large pSLE series [14]. The time from onset of symptoms to diagnosis varied from 1 month to 3.3 years (median, 4 months) in the authors' cohort. The overall 10-year survival rate for adult patients with SLE is between 85% and 92%; 5-year survival rates are 3% to 5% higher [17,18]. Thirty years ago, the reported survival rates for pSLE patients were 82.6% at 5 years and 76.1% at 10 years [19]. The recent 5-year survival rate for pSLE has been reported to be as high as 100, with 10-year survival rates as high as 86% [20]. Mortality rates are associated with socioeconomic status and individual access to health care, educational background, racial/ethnic background, endemic infection rates, disease activity, and renal or central nervous system (CNS) involvement [15,16, 20–27].

Earlier diagnosis and rapid introduction of aggressive immunosuppressive treatment lead to an improved outcome.

## Clinical patterns

Children and adolescents with SLE frequently present with systemic, constitutional symptoms such as fever, diffuse hair loss, fatigue, weight loss, and evidence of diffuse inflammation as demonstrated by lymphadenopathy and hepatosplenomegaly, and these manifestations are seen throughout the course of the disease. Skin, musculoskeletal, and renal systems are the most common organ systems involved in pSLE. Important treatment decisions are based mainly on evidence of major organ involvement, including nephritis, neuropsychiatric disease, and severe hematologic disease. Gastrointestinal disease, including significant liver involvement, myositis, and myocarditis, is rare in children. [Table 2](#) summarizes the frequencies of clinical features of SLE at presentation.

## Musculoskeletal disease

Most pSLE patients have musculoskeletal involvement, mainly arthritis, arthralgia, or tenosynovitis. Although myalgia is seen in 20% to 30% of patients, true myositis is seen much less frequently. The arthritis seen in pSLE is commonly a painful, symmetric polyarthritis affecting both large and small joints.

Table 2

Frequencies of clinical features of children and adolescents with SLE at diagnosis and anytime during their disease

Clinical features	At diagnosis		At any time	
	Toronto series (%)	pSLE literature (%)	Toronto series (%)	pSLE literature (%)
Constitutional and generalized symptoms				
Fever	55	60–90	86	80–100
Lymphadenopathy	34	13–45	34	13–45
Hepatosplenomegaly	30	16–42	30	19–43
Organ disease				
Arthritis	78	60–88	80	60–90
Any skin rash	79	60–78	86	60–90
Malar rash	36	22–60	38	30–80
Nephritis	51	20–80	69	48–100
Neuropsychiatric disease	25	5–30	34	26–95
Cardiovascular disease	14	5–30	17	25–60
Pulmonary disease	18	18–40	18	18–81
Gastrointestinal disease	19	14–30	24	24–40

Data from Refs. [16,24,26,28–33].

The affected joints usually have only mild to moderate joint effusions; however, significant joint-line tenderness and painfully reduced ranges of movement are common. The pain is generally more severe than that seen in children with juvenile idiopathic arthritis, and prolonged morning stiffness is common. The arthritis is rarely associated with radiographic changes. Patients with long-standing definite polyarticular or systemic juvenile idiopathic arthritis have been reported to develop pSLE [34–36]. Noninflammatory musculoskeletal pain frequently occurs following treatment and may be the result of a pain amplification syndrome secondary to a sleep disturbance or mood change as a result of the glucocorticoid therapy.

Treatment-induced musculoskeletal complications include avascular necrosis (AVN), osteoporosis (which may be accompanied by fracture or vertebral body collapse), and growth failure. Steroid-induced myopathy is rarely seen.

AVN occurs in approximately 10% of pediatric cases and seems to be more common in children than adults. Typically, the juxta-articular regions of the large, weight-bearing bones are affected; hips and knees are most commonly affected. In general, AVN is associated with long-term, high-dose steroid therapy, but it may occur with standard therapy for significant renal or neuropsychiatric involvement. It may be seen within weeks of the introduction of steroids. Osteoporosis and vertebral fractures are commonly seen and are frequently asymptomatic. Long bone fractures are rare. A reduction in bone mineral density can result from steroid therapy but also can be secondary to lupus per se, low calcium and vitamin D intake, and reduced physical activity. Preventive strategies for

osteoporosis in pSLE include a high calcium intake and adequate doses of vitamin D and exercise. The use of bisphosphonates should be considered after an osteoporosis-induced fracture [37,38].

## Treatment

The arthritis frequently occurs at the time of diagnosis of pSLE or with disease flares and usually responds to the therapy of other organ involvement. Isolated arthritis is usually treated with a nonsteroidal anti-inflammatory drug combined with an antimalarial drug (usually hydroxychloroquine at a dose of 5 mg/kg), but frequently steroids are required. In the authors' experience, methotrexate works well as a steroid-sparing agent. The major side effects of hydroxychloroquine are maculopathy and gastrointestinal distress; rare instances of neuro-myotoxicity and cardiomyopathy have been described [39]. Ophthalmologic examination is required every 6 months [40].

## Mucocutaneous involvement

Skin involvement has been reported in 50% to 80% of patients at the time of diagnosis of pSLE and in up to 85% of patients during the course of the disease. Cutaneous disease may include a malar rash, photosensitive skin rash, vasculitic skin lesions with nodules or ulceration, palmar/plantar erythema, Raynaud's phenomenon, annular erythema, and, less frequently, discoid lupus or lupus profundus (Table 3). Alopecia is common, but scarring alopecia is rare and usually is seen only with discoid lesions.

Table 3  
Mucocutaneous involvement children and adolescents with SLE

Features	Toronto series (%)	pSLE literature (%)
Skin involvement	86	50–90
Malar rash <sup>a</sup>	68	40–80
Photosensitive rash	39	35–50
True vasculitic rash	18	10–20
Raynaud's phenomenon	14	10–20
Hair loss	31	20–40
Digital ulcers	6	5–10
Discoid lesions	5	5–10
Mucous membrane involvement		
Oral/nasal ulcers	29	10–30

<sup>a</sup> The malar or "butterfly" rash is a hallmark of SLE. This is a maculopapular rash over the cheeks (malar eminences) extending over the bridge of the nose and sparing the nasolabial folds (Fig. 1).



Fig. 1. Malar rash in a patient with pediatric SLE.

The malar or butterfly rash is a hallmark of SLE. This is a maculopapular rash over the cheeks (malar eminences) extending over the bridge of the nose sans sparing the nasolabial folds (Fig. 1). In one third of patients, the rash is photosensitive. Other sun-exposed areas may also may a photosensitive rash. Sun exposure may cause a systemic flare as well as exacerbating the skin disease (Fig. 2). Avoidance of sunbathing, and the use of sun-blocking agents with high sun-protecting factor and protective clothing, including long-sleeved shirts and hats, is recommended. A photosensitive rash and, in particular,



Fig. 2. Photosensitive rash on arms following sun exposure.



Fig. 3. Effect of sun-exposure in a patient with a photosensitive malar rash. (A) Before sun exposure. (B) After sun exposure.

annular erythema are frequently associated with anti-Ro and anti-La antibodies (Fig. 3).

Discoid lupus lesions are seen rarely in pSLE but when present tend to heal with a scar (Fig. 4). A true vasculitic skin rash may include ulceration, nodules, or even palpable purpura. These skin lesions are commonly painful, are most frequently located on fingers or toes, and can result in splinter hemorrhages and digital infarcts. These skin lesions may be identical to chil-blains, a common cutaneous lesion seen in children, particularly in countries with cold, damp winters. Severe, ulcerating, lesions may signify more significant disease activity in other organs, whereas the appearance of a malar



Fig. 4. Discoid lupus erythematosus lesion on the forehead.



Fig. 5. Painless oral ulceration.

rash often heralds a disease flare. The pinnae of the ears are frequently involved, and the lesions may range from hyperemia to true vasculitis. Raynaud's phenomenon seems to be less common in pediatric than in adult lupus. Local measures, including avoidance of cold, use of insulated mittens rather than gloves, and the wearing of multiple layers of clothing, hats, and hand/feet warmers, are sufficient for most SLE patients. In more severe disease the use of calcium-channel-blocking agents or other vasodilating medication is required. Involvement of the oral and nasal mucosa ranges from hyperemia, petechial rashes on the hard palate to true ulceration of the oral or nasal mucosa. The ulcers are painless (Fig. 5).

Patients with complement component deficiencies, in particular C4 deficiencies, often present with prominent cutaneous features that are frequently resistant to therapy (Fig. 6) [41].

### Neuropsychiatric disease

Involvement of the CNS and the peripheral nervous system is referred to as neuropsychiatric systemic lupus erythematosus (NP-SLE). NP-SLE occurs in 20% to 70% of pSLE patients [31,42–45]. The large differences in the incidence of NP-SLE among various studies result largely from the differences in the frequency of lupus-associated headaches. In 1999, the American College of Rheumatology classified neuropsychiatric involvement into 19 separate disease entities (Table 4) [46,47]. In the authors' experience, most patients with NP-SLE fulfill criteria for more than one of these entities. As with other major organ involvement, most patients with NP-SLE have the initial neuropsychiatric signs and symptoms within the first year of diagnosis of SLE. Approximately 25% of



Fig. 6. Therapy-refractory skin rash in a pSLE patient with C4 complement deficiency on (A) hands and (B) feet.

patients first demonstrate neuropsychiatric disease later during the course of the disease [42].

### Headaches

Headache is the most common neuropsychiatric manifestation. A true lupus headache is refractory to standard analgesic treatment [48]. Although the significance of headache in the absence of other neurologic symptoms is controversial, a severe, unremitting headache may reflect active CNS vasculitis,

Table 4  
Neuropsychiatric lupus in children and adolescents with pSLE

1999 ACR nomenclature and case definitions for neuropsychiatric SLE	Toronto series (%) N = 56	pSLE literature (%)
Central nervous system		
Aseptic meningitis	NA	NA
Cerebrovascular disease	24	12–30
Demyelinating syndrome	0	4–10
Headache	75	22–95
Isolated headache	27	NA
Movement disorder	11	3–15
Myelopathy	2	1–8
Seizure disorder	18	10–42
Acute confusional state	11	20–40
Anxiety disorder	14	10–28
Cognitive dysfunction	27	20–57
Mood disorder/depression	34	28–57
Psychosis	36	12–50
Peripheral nervous system	NA	3–30
Including Guillain–Barré syndrome, autonomic disorder, mononeuropathy, cranial neuropathy, myasthenia-like syndrome, plexopathy and peripheral neuropathy		

Abbreviation: NA, not available.  
Data from Refs. [28,33,45,48–50].

cerebral vein thrombosis (CVT), or raised intracranial pressure caused by CNS infection or pseudotumor cerebri. Headache in pSLE is frequently seen in association with more severe CNS involvement including organic brain syndrome and psychosis. It also may be secondary to CVT. CVT may present in the absence of other CNS manifestations and is almost universally associated

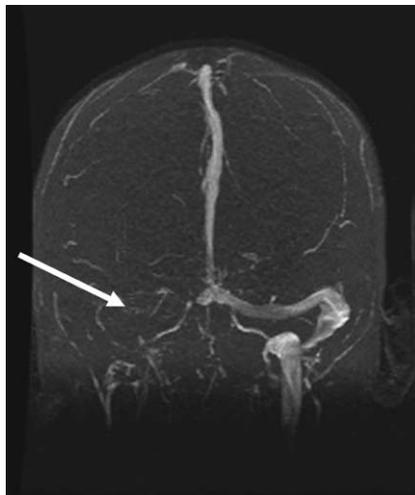


Fig. 7. MR venogram of cerebral vein thrombosis in a patient with pediatric SLE. The arrow shows absence of filling on the right side.

with the presence of the lupus anticoagulant (LAC) [51]. In the authors' series of 56 NP-pSLE patients, 18% developed a CVT. Neuroimaging including either CT or MR venogram (Fig. 7) is required on an urgent basis.

## **Psychosis**

The diagnosis of psychosis is made in 30% to 50% of pediatric patients with neuropsychiatric involvement. Characteristically the hallucinations have features of an organic psychosis including visual or tactile hallucinations. Suicidal ideations are common [42,52]. Frequently headaches, cognitive dysfunction, and confusion are all present. Measures of general disease activity may be normal in approximately one third of patients. Brain parenchymal imaging, including MRI scans, is frequently normal (in up to 67% of patients), making the diagnosis difficult. Although some authors have advocated the use of CNS single photon emission computed tomography (SPECT) imaging, the authors have not found this investigation to be of any benefit in differentiating NP-SLE-associated psychosis from other forms of psychosis, including steroid-induced psychosis. SPECT scans are frequently abnormal in SLE patients in the absence of CNS symptoms and may even be normal in the presence of overt pSLE-associated psychosis [53]. In the authors' experience, steroid-induced psychosis is uncommon and may be differentiated from NP-SLE by the absence of other features of CNS involvement including headache, confusion, and concentration difficulties and the presence of mania, head-banging, and excessive crying (uncommon features of NP-SLE) [54,55].

## **Cognitive dysfunction**

Cognitive impairment, which ranges from concentration difficulties and a decrease in school performance to frank confusion and coma, occurs in 20% to 57% of children with NP-SLE. Inflammatory markers may be normal in one third of patients, and parenchymal imaging may be normal in up to two thirds of patients.

## **Cerebrovascular disease**

Cerebrovascular disease occurs in 12% to 30% of cases. When present, cerebrovascular disease usually involves the microcirculation, and therefore angiographic studies are usually normal except in the presence of a stroke [56]. Headaches and seizures are the most common clinical signs and symptoms of CNS vasculitis. Inflammatory markers are often elevated, and cerebrovascular disease is strongly associated with the presence of antiphospholipid antibodies [57].

## Seizures

Seizures occur in approximately 10% to 40% of pediatric cases, frequently at presentation. Patients with seizures frequently have associated headaches, cerebrovascular disease, and cognitive dysfunction. Generalized seizures are more common than focal seizures. Inflammatory markers are often elevated. Parenchymal lesions are seen in 80% of the authors' cohort. Seizures in pSLE may also develop secondary to uremia, hypertension, or CNS infections.

## Movement disorders

Movement disorders include chorea, cerebellar ataxia, hemiballismus, tremor, and parkinsonian-like movements and occur in 5% to 10% of cases [58]. Chorea is the most common movement disorder and is more common in pSLE than in adult-onset SLE [59]. Antiphospholipid antibodies are almost universally present in patients with chorea, which may be isolated or occur in conjunction with other manifestations of the antiphospholipid antibody syndrome. With the decline in rheumatic fever in developed countries, the diagnosis of SLE or antiphospholipid antibody syndrome should be considered in all patients presenting with chorea [60].

## Peripheral nervous system

Both cranial and peripheral neuropathies occur infrequently in pSLE [61], with cranial nerve involvement being the more common. pSLE patients may present with optic neuropathy [62] and oculomotor palsy [63] and less frequently with facial palsy [64], trigeminal neuropathy, or nystagmus and vertigo [65]. Transverse myelitis may present with acute paraplegia or quadriplegia and may be the presenting sign of SLE [50,66]. Autonomic nerve dysfunction occurs in up to 50% of adults with SLE, and autoantibodies directed against autonomic nervous system tissue may be of etiologic importance [67].

## Investigation

The tools for diagnosing NP-SLE in children include cerebrospinal fluid (CSF) cell count, protein, and CNS imaging apart from systemic inflammatory markers and autoantibodies. There is no good diagnostic test for the presence of NP-SLE, however, and the results of investigations frequently are normal. The major reason for performing investigations in patients with presumed SLE-induced CNS involvement is to exclude other non-SLE causes of CNS diseases, especially infection.

Lumbar puncture may show an elevated CSF protein or white blood cell count, in the absence of infection, with an elevated opening pressure. An altered integrity of the blood–brain barrier and immunoglobulin synthesis in the CSF have been implicated in NP-SLE but are not part of routine investigations [68]. Investigational studies have demonstrated elevated soluble interleukin-2 receptor, tumor necrosis factor- $\alpha$ , interleukin-1- $\beta$ , interleukin-6, matrix metalloproteinase 9, and prolactin levels in the CSF [69–71]. The clinical usefulness of these tests has yet to be proven. Anti-ribosomal P antibodies have been associated with the presence of depression and psychosis but are frequently present in patients without any CNS disease. Similarly, antineuronal antibodies are not specific for cognitive dysfunction. Imaging tools in NP-SLE may include CT, MRI, MR angiogram, MR venogram, conventional angiography, SPECT, and MR spectroscopy. Neuroimaging techniques are best used to demonstrate arterial or venous occlusion and are important investigations in the presence of a stroke, seizures, and to demonstrate CVT. The diagnosis of CVT may be confirmed by the absence of flow on a MR or CT venogram [72]. NP-SLE–related CNS perfusion defects may be assessed by SPECT, but the authors have found this investigation unhelpful in the presence of SLE and no longer use this test [53,73,74]. CNS SPECT scans are more useful in a patient without the diagnosis of SLE to help differentiate an organic psychosis from idiopathic psychosis.

## Treatment

The treatment guidance of NP-SLE mandates an interdisciplinary approach involving psychiatrists, psychologists, neurologists, and rheumatologists. Psychosis, acute confusional state, or organic brain syndrome are potentially life-threatening complications. These patients require combination therapy of high-dose steroids and an additional immunosuppressive agent such as azathioprine or cyclophosphamide. In addition, psychotropic drugs frequently are needed. When depression is severe, antidepressants should be added to the immunosuppressive therapy. Treatment of seizures should be directed at finding their cause in addition to anticonvulsive medications. As previously described, headaches resistant to analgesia are frequently caused by significant underlying CNS disease including CVT, vasculitis, or infection. Therefore, the underlying cause must be identified to direct the treatment.

## Renal disease

Lupus nephritis has been reported in 29% to 80% of pediatric cases, depending on whether the reporting investigators are rheumatologists or nephrologists [16,24,29,33,75–77]. In the authors' combined rheumatology/

nephrology clinic, renal disease is present in 50% to 55% of patients with pSLE. In approximately 90% of patients with renal lupus, the nephritis is manifested within the first year after diagnosis of SLE. The World Health Organization (WHO) has defined a morphologic classification of kidney biopsies in SLE, and this classification was revised in 2003 by the International Society of Nephrology and the Renal Pathology Society (Table 5) [78]. The histologic classes range from normal by light microscopy (class 1) to advanced sclerotic nephritis (class VI). Although it may be easy to predict the histologic classification in patients who present with severe renal failure and significant hypertension, in less severe cases it is difficult to predict the histologic lesion based on clinical and laboratory parameters including the urine sediment and degree of proteinuria. It is well recognized that patients with class IV nephritis can present with a normal serum creatinine levels and blood pressure and with minimally active urine sediment. Because treatment differs for differing forms of SLE nephritis, the authors suggest that a renal biopsy is warranted at the time of initial presentation in patients with an active urine sediment or abnormal renal function.

The most significant lesions are associated with widespread subendothelial immune deposits and proliferation of the mesangial cells. The spectrum of active lupus nephritis ranges from mild mesangial proliferative lupus nephritis (class II) to global diffuse proliferative glomerulonephritis (class IV-G [A] lupus nephritis). Chronic inactive lupus nephritis ranges from focal glomerular scars on kidney biopsy (class III-C lupus nephritis) to diffuse global sclerosing lupus nephritis (class IV-D). Most patients who develop end-stage renal disease have either class III or class IV lupus nephritis. Although activity and chronicity indices initially were thought to have prognostic significance, most pathologists now use the revised WHO classification instead [79,80].

Class II lupus nephritis is relatively mild lesion requiring significantly less therapy than required for class III or class IV lupus nephritis and is associated with an excellent renal and patient long-term survival. In 20% to 30% of patients, however, transformation from mesangial proliferative lupus nephritis to class III or class IV lupus nephritis may occur after months to years. Long-term patient and renal survival rates are then similar to those of patients initially presenting with this lesion.

Isolated membranous nephritis occurs in 10% to 20% of patients with renal disease. The clinical presentation ranges from mild proteinuria with or without hematuria or casts to nephrotic-range proteinuria. Unlike the presentation of patients with idiopathic membranous nephritis, pSLE patients with class V lupus nephritis frequently have hematuria. The possibility of lupus nephritis should always be considered in patients who present during adolescence with what appears to be idiopathic nephrotic syndrome, nephrotic syndrome with hematuria, or resistant nephrotic syndrome. Class V nephritis may be seen in conjunction with another renal lesion.

Renal vasculitis occurs in less than 10% of patients with renal lupus. When present, it is most commonly a thrombotic microangiopathy and less frequently is true renal vasculitis [81,82].

Table 5  
International Society of Nephrology/Renal Pathology Society 2003 classification of lupus nephritis

Lupus nephritis class	Toronto series (%)	Pediatric literature <sup>a</sup> (%)
Class I Minimal mesangial lupus nephritis <sup>b</sup>	NA	NA
Class II Mesangial proliferative lupus nephritis <sup>c</sup>	16	15–25
Class III Focal lupus nephritis <sup>d</sup>	33	12–24
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 <sup>e</sup>	48	44–64
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		
Class IV-G (A/C) Active and chronic lesions, diffuse global proliferative and sclerosing lupus nephritis		
Class IV-S (C) Chronic inactive lesions with glomerular scars: diffuse segmental sclerosing lupus nephritis		
Class IV-G (C) Chronic inactive lesions with glomerular scars: diffuse global sclerosing lupus nephritis		
Class V Membranous lupus nephritis <sup>f</sup>	18	8–20
VI Advanced sclerosing lupus nephritis <sup>g</sup>	NA	NA

*Abbreviation:* NA, not available.

<sup>a</sup> Refs. [14,16,24,29,33,75–77].

<sup>b</sup> Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence.

<sup>c</sup> Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy.

<sup>d</sup> Active or inactive focal, segmental or global endo- or extracapillary glomeronephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations.

<sup>e</sup> Active or inactive diffuse, segmental or global endo- or extracapillary glomeronephritis 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. A segmental lesion 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.

<sup>f</sup> 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 may show advanced sclerosis.

<sup>g</sup> Ninety per cent or more of glomeruli globally sclerosed without residual activity.

*Data from* Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004;15:241–50.

Most patients with lupus nephritis have constitutional symptoms including fever, malaise, anorexia, and weight loss. Hypertension before steroid treatment can be found in one third of pediatric lupus nephritis patients. The presence of hypertension and peripheral edema is usually associated with either class III or class IV lupus nephritis [14]. The hypertension frequently is exacerbated following the introduction of steroid treatment. Laboratory investigations may demonstrate a low serum albumin level, decreased C3 or C4 complement levels, high-titer anti-dsDNA antibodies, or other SLE-associated autoantibodies. Urine analysis may reveal proteinuria or hematuria with an active urine sediment with or without evidence of azotemia. Most patients with impaired renal function have either class III or IV lupus nephritis.

Renal flares are common during the disease course of lupus nephritis and frequently can be detected by increasing proteinuria before the recurrence of constitutional symptoms. The overall renal outcome of children with lupus nephritis has improved significantly during the past decades. The recent 5-year renal survival rates for class IV lupus nephritis are 88% to 93% [14,75]. The reported 10-year renal survival rate is 85% [75]. Factors associated with overall adverse renal outcome include class IV lupus nephritis on biopsy [14], initial evidence of nephrotic syndrome [14], and non-white ethnicity [75].

## Treatment

Therapy of children with lupus nephritis should be based on the renal histology.

### *Class II lupus nephritis*

Patients with mesangial proliferative lupus nephritis require a relatively short course of treatment with low-dose steroids (0.1–0.5 mg/kg prednisone/day) with a rather fast taper over months. The long-term outcome of these patients is excellent, and the side effects of steroid therapy must be weighed against the excellent prognosis.

### *Class III and IV lupus nephritis*

Historically, patients with class III lupus nephritis have been managed with steroids alone. More recently, it has been recognized that active class III nephritis falls within the spectrum of proliferative nephritis, and many investigators therefore advocate the same therapy as for class IV nephritis. The authors agree with this suggestion. The mainstay of therapy of proliferative nephritis is high-dose steroids (initially 2 mg/kg/day, maximum 60–80 mg/day, in divided doses) with a slow taper and the addition of a second agent at the time of confirmation of the histology. Most centers advocate the use of pulse monthly cyclophosphamide, although daily oral azathioprine has been associated with similar long-term

outcome [83,84]. Recent case series suggest that mycophenolate mofetil (MMF) may be as effective as, if not superior to, monthly intravenous pulse cyclophosphamide [85,86]. Large multicentered trials directly comparing MMF and intravenous cyclophosphamide are underway, and the results of these studies will better indicate the role MMF in class III and class IV lupus nephritis [87]. MMF and azathioprine are safer than cyclophosphamide. Based on their published case series and the results of meta-analysis of therapy of class III and class IV lupus nephritis, the authors advocate the use of azathioprine at the time of diagnosis of class III or class IV lupus nephritis [75].

### *Class V nephritis*

Most patients with pure lupus membranous nephritis require only low doses of steroids for a short period. Only a minority of patients requires a prolonged course of steroids or the use of a second immunosuppressive agent. The second agent of choice is cyclosporin, azathioprine, or MMF. Cyclophosphamide is rarely indicated. Many investigators now advocate the use of angiotensin-converting enzyme inhibitors as adjunctive therapy to decrease the proteinuria. In some patients, the renal biopsy shows a mixed lesion with features of class II, III, or IV nephritis in addition to class V nephritis. In these cases, the therapy should be directed by the presence or absence of a proliferative lesion. When class III or IV lesions are present, immunosuppressive agents should be used as outlined in the discussion of therapy for proliferative nephritis.

## **Hematologic involvement**

Anemia, thrombocytopenia, and leukopenia are seen in 50% to 75% of patients. The most common anemia is normochromic normocytic anemia, which, when persistent, usually becomes a microcytic and hypochromic anemia. The Coombs' test is positive in approximately 30% to 40% of patients, but less than 10% of patients have overt hemolysis. Thrombocytopenia is present in 15% to 45% of adults and may be the initial presentation in up to 15% of pediatric cases. Patients with chronic autoimmune idiopathic thrombocytopenic purpura (AITP) should be assessed for the presence of antinuclear antibodies, because they are at high risk developing SLE [88]. In the authors' experience, most, if not all, patients with AITP and Coombs'-positive hemolytic anemia (Evan's syndrome) either have evidence of SLE at presentation of the cytopenia or develop SLE. Many patients with AITP secondary to SLE have resistant thrombocytopenia that usually requires prolonged use of steroids or multiple courses of intravenous immunoglobulin. Splenectomy should be avoided. Case series have suggested that B cell-directed anti-CD20 therapy may be of benefit in patients with resistant AITP or hemolytic anemia [89]. Classic thrombotic thrombocytopenia purpura, presenting with microangiopathic hemolytic anemia and neurologic and renal

disease, is a rare diagnosis in children; when it is present, an underlying diagnosis of SLE should be sought.

Leukopenia is seen in 20% to 40% of cases of pSLE. Both lymphopenia and granulocytopenia can be found, although lymphopenia is more common. Lymphopenia is a sensitive marker of general disease activity and does not require specific therapy. When lymphopenia is profound (an absolute count persistently less than  $500 \times 10^9$  cells/litre), an underlying infection with the herpes family of viruses should be actively sought. Granulocytopenia is usually secondary to a central depression of granulopoiesis, splenic sequestration or to antigranulocyte antibodies.

Coagulation abnormalities are common in pSLE. LAC is positive in 20% to 30% of pediatric cases. These patients have an increased incidence of deep vein thrombosis or CVT and thromboemboli but rarely have arterial thrombosis [51]. Most patients with an arterial thrombosis have a true vasculitis in addition to the LAC. Treatment with heparin followed by low molecular weight heparin or warfarin is required if a thrombosis occurs. Antiphospholipid antibodies in SLE are common, but in pediatric patients the risk of thrombosis is related to the presence of the LAC and not other currently measured antiphospholipid antibodies [90,91]. A complication of antiphospholipid antibodies is the development of the catastrophic antiphospholipid antibody syndrome characterized by severe microangiopathic thrombotic changes with thrombosis in multiple organs. Other coagulation abnormalities in SLE include prothrombin deficiency and, rarely, an acquired von Willebrand's-factor deficiency [92]. The antiphospholipid syndrome is discussed elsewhere in this issue.

### **Cardiac involvement**

The most common form of cardiac involvement is pericarditis with pericardial effusion. Less commonly, endo- or myocarditis or valvular disease is found, and, rarely, ischemic heart disease may result secondary to coronary artery vasculitis. Valvular heart disease may be associated with the presence of antiphospholipid antibodies or with noninfective or Libman-Sacks endocarditis [93]. Symptomatic pericarditis is the most common cardiac manifestation, occurring in approximately 15% to 25% of patients and in up to 68% of patients with echocardiographic abnormalities [94]. Pericarditis rapidly responds to non-steroidal anti-inflammatory medication alone or to a low to moderate dose of corticosteroids.

The major cardiac morbidity associated with SLE is premature atherosclerosis. A number of traditional and nontraditional atherosclerotic risk factors, including lipid abnormalities, altered endothelial function, nephritis, and proteinuria, have been implicated in the development of premature atherosclerosis in patients with pSLE [95,96]. Reports of myocardial perfusion deficits, altered vascular reactivity, and carotid intima-media thickness in pSLE patients suggest that even during adolescence pediatric patients are at risk for premature atherosclerosis,

myocardial infarction, and cerebral vascular events [95]. It is likely that the major risk factor for premature atherosclerosis is the chronic inflammatory process of pSLE itself. This risk is likely to increase with the use of corticosteroids as the main line of pSLE treatment. One of the added benefits of the use of antimalarial agents in SLE is their lipid-lowering effect. Interdisciplinary approaches involving dieticians and physiotherapists to control classic Framingham risk factors such as obesity, reduced physical exercise, and high blood lipid levels are mandatory for the management of pSLE patients.

### **Pulmonary involvement**

Pulmonary involvement is common in pSLE and occurs in 25% to 75% of cases. The clinical spectrum includes pleuritis, pneumonitis, infectious pneumonia, pulmonary hemorrhage, pulmonary hypertension, and pneumothorax. Uncommon manifestations are diaphragm involvement (including shrinking lung syndrome), vasculitis, and pulmonary embolus.

Severity of pulmonary involvement ranges from asymptomatic abnormalities of pulmonary function tests to severe life-threatening pulmonary hemorrhage. The most common manifestation is pleuritis with or without pericarditis. These patients commonly have respiratory symptoms or chest pain, and the pleuritis may be unilateral. When the pleuritis is mild, treatment can consist of anti-inflammatory doses of nonsteroidal drugs, but prednisone, at a low to moderate dose, may be required.

When patients present with acute respiratory failure and fever, treatment with broad-spectrum antibiotics and high-dose steroids, including pulse therapy, may be required. The use of bronchial washings obtained by bronchoscopy should be considered early, but frequently patients require an open-lung biopsy to determine whether lung involvement is related directly to the SLE or to determine accurately the organism leading to the respiratory failure. Patients with SLE receiving immunosuppressive therapy are at high risk for infection with opportunistic organisms including Herpes viruses, *Pneumocystis carinii*, Legionella, and fungal infections. These infections must be ruled out before the introduction of significant immunosuppressive therapy.

### **Gastrointestinal and liver disease**

Gastrointestinal involvement occurs in 20% to 40% of patients. Abdominal pain can result from peritoneal inflammation (serositis), vasculitis, pancreatitis, malabsorption, pseudo-obstruction, paralytic ileus, or direct bowel wall involvement (enteritis).

Lupus enteropathy may present as acute ischemic enteritis or a protein-losing enteropathy [97]. Bowel wall inflammation presenting as cramping abdominal pain and diarrhea can reflect enteritis or can develop secondary to a mesenteric

vasculitis or thrombosis. Patients with gastrointestinal vasculitis are at risk for perforation, and the signs and symptoms may be masked by the use of high-dose steroids.

Pancreatitis is uncommon, with an overall incidence of less than 5%, and may reflect active disease, an infectious complication, or be secondary to drug therapy, in particular steroids or azathioprine [98–100].

Splenomegaly, occurring in 20% to 30% of pediatric cases, usually reflects the generalized inflammatory state. Functional asplenia is common and increases the risk of sepsis. Hepatomegaly occurs in 40% to 50% of patients, and up to 25% have abnormal liver function tests. Markedly elevated liver function tests can be seen in lupoid hepatitis.

### **Endocrine involvement**

The thyroid is the endocrine organ most commonly involved in SLE. Both hypothyroidism and hyperthyroidism are seen, but hypothyroidism is the more common abnormality. Up to 35% of pSLE patients have antithyroid antibodies, with 10% to 15% of patients developing overt hypothyroidism [101]. Steroid-induced diabetes mellitus occurs in 5% to 10% of patients and frequently requires insulin treatment. Delayed puberty and menstrual abnormalities are common. Irregular menses frequently are related to active disease and usually resolve when the disease is controlled. Ovarian failure is a significant complication of cyclophosphamide therapy and is dose dependant [102,103].

### **Autoantibodies**

The hallmark of SLE is the production of autoantibodies directed against histone, non-histone, RNA-binding, cytoplasmic, and nuclear proteins. Antinuclear autoantibodies are seen in up to 100% of patients, and anti-DNA antibodies are seen in 60% to 70% of cases. Antibodies against the RNA-binding proteins, anti-U1 RNP and anti-Sm antibodies, occur in 70% to 90% and in 40% to 50% of patients, respectively. Antibodies against Ro and La occur in 30% to 40% and in 15% to 20% of patients, respectively. The most commonly measured antiphospholipid antibodies are anti-anticardiolipin antibodies, found in approximately 50% of patients, and LAC, present in 20% of cases. Antiphospholipid antibodies are associated with an increased risk of thrombosis, development of chorea, avascular necrosis, epilepsy, migraine headache, and livedo reticularis [104]. Antiribosomal P antibodies are present in approximately 15% of patients; a higher percentage of patients with psychosis have these autoantibodies. Aside from the lupus anticoagulant and the antinuclear autoantibodies, most laboratories use ELISA to detect specific autoantibodies. When anti-Sm antibodies are detected by immunodiffusion, a less sensitive assay than ELISA, these autoanti-

bodies have a specificity of 100% for SLE. This specificity is higher than that for anti-DNA antibodies. Rheumatoid factor is seen in 12% to 29% of patients and frequently is seen in association with anti-Ro and anti-La antibodies.

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