Childhood-Onset Systemic Lupus Erythematosus: A Review and Update

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Lupus is a chronic, autoimmune multisystem inflammatory disease that is associated with sizable morbidity and mortality.[1] When lupus commences in an individual less than 18 years of age,[2] it is commonly referred to as childhood-onset systemic lupus erythematosus (cSLE). With a reported incidence of 0.3-0.9 per 100 000 children per year, and a prevalence of 3.3-24 per 100 000 children,[3] cSLE is rare. About 10%-20% of all patients with SLE are diagnosed during childhood. Typically, cSLE has a more severe clinical course than that seen in adults, with a higher prevalence of lupus nephritis, hematologic anomalies, photosensitivity, neuropsychiatric, and mucocutaneous involvement.[3-5]

As with adult-onset SLE, a higher frequency of cSLE has been described in African Americans, Asians, Hispanics, and Native Americans compared with whites.[6,7] The median age at presentation is around 11-12 years, with cSLE rarely reported under the age of 5 years.[8] Consistent with adult-onset disease, cSLE has a strong female preponderance; the female to male ratio is at 4:3 and 4:1 for disease onset in the first and second decades of life, respectively.[9]

In this review, we provide an update on cSLE, focusing on information deemed especially relevant to general pediatricians in their role of caring for children and adolescents with this disease. Neonatal and drug-induced lupus are not discussed.

Pathogenesis of Lupus

The etiology of cSLE is multifactorial, involving genetic risk factors, epigenetic mechanisms, and environmental triggers.[10-13] Systemic Lupus Erythematosus (SLE) is thought to constitute a loss of tolerance in a genetically susceptible individual with progression to autoimmunity that is triggered by various environmental factors and infections[14] (**Figure 1**).

ACR	American College of Rheumatology
ANA	Antinuclear antibody
AZA	Azathioprine
cSLE	Childhood-onset systemic lupus erythematosus
CYC	Cyclophosphamide
EBV	Epstein-Barr virus
GC	Glucocorticoid
HCQ	Hydroxychloroquine
Ig	Immunoglobulin
MMF	Mycophenolate mofetil
NPSLE	Neuropsychiatric manifestations of SLE
PJP	*Pneumocystis jirovecii* pneumonia
QI	Quality indicator
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinic

Genetic Factors

There is a 10-fold increase in SLE risk among monozygotic as compared to dizygotic twins.[15,16] Further, siblings of a patient with SLE carry an 8- to 20-fold higher risk of developing SLE as compared with a healthy general population.[16,17]

SLE is considered a polygenic disease, although rare monogenic causes have been described recently.[18] Genetic variants that are well-established include very rare mutations in genes coding for select complement factors. Indeed, a single gene mutation that results in a complete deficiency of C1q increases the risk of SLE, or lupus-like symptoms, to more than 90%. C4 deficiency is also a well-established risk factor for the disease and a lower number of copies of the C4 gene increases the risk of cSLE.[19] Genome-wide association studies have identified a series of additional risk alleles that have the potential to influence the function of both the innate and the adaptive immune systems.[20] However, genetic predisposition alone does not account sufficiently for the risk of developing SLE, given that the concordance rate among monozygotic twins is approximately 40%.[17,20]

Environmental/Epigenetic Factors

Epigenetic factors also contribute to the development and manifestations of SLE.[20,21] Ultraviolet light, especially ultraviolet B,[22] infections,[23] and toxins are all suspected to promote the onset and exacerbation of SLE.[6,16] There is an increasing body of evidence suggesting that at least some environmental triggers exert their influence through epigenetics. These triggers seem to alter the degree of DNA methylation and the phosphorylation of histones, leading to a change in gene transcription rates without modifying the gross genetic structure of the DNA itself.[21,24] SLE has been associated with reduced DNA methylation in gene regions that can promote loss of B- and T-cell tolerance.[21,25,26] Prolonged exposure to ultraviolet light increases the amount of self-antigen presented to the immune system via free DNA in the blood owing to destruction of dermal cells; abnormal apoptosis and/or structural alterations in DNA of dermal cells increase their immunogenicity.[27,28]

Epstein-Barr virus (EBV) is another proposed inducer and enhancer of tolerance loss. In individuals with a genetic susceptibility for SLE, EBV infections lead to marked B-cell activation that results in the production of large amounts of
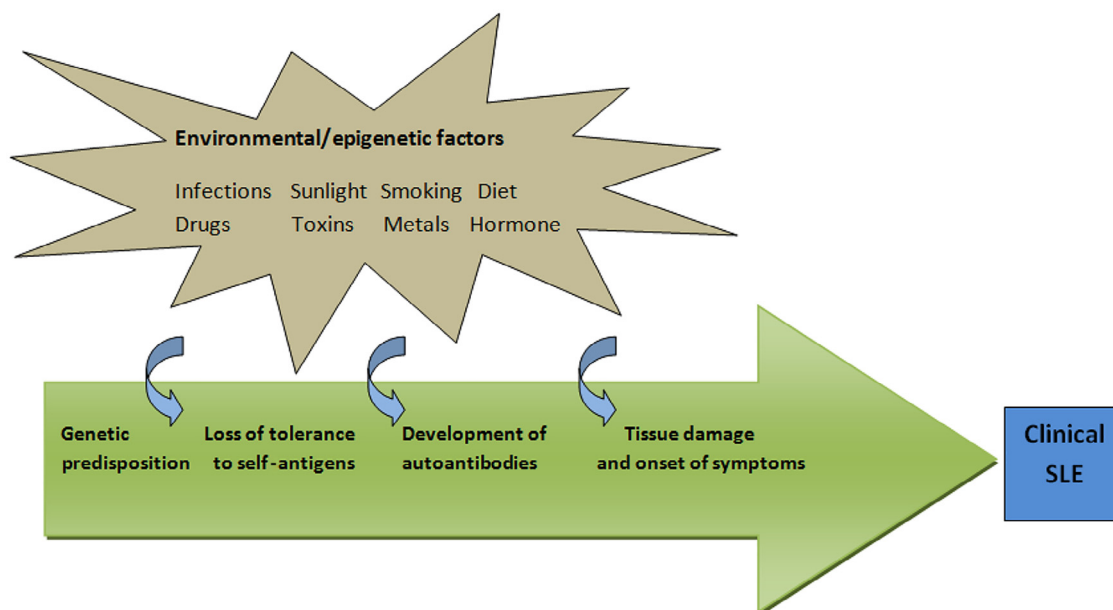
Figure 1. Loss of self-tolerance causing the production of autoantibodies in a genetically susceptible individual causing clinical SLE.

autoantibodies, which in turn can further a loss of tolerance.[23,29-31] Given the high frequency of EBV infections in the population as compared with the relative rarity of SLE, EBV infections alone are unlikely the only infectious trigger of SLE.[16,23,32]

As such, silica, allergens, and certain cosmetics all have been associated with SLE in certain ethnic groups.[16] However, strong scientific evidence regarding the mechanisms that result in SLE upon exposure to these toxins is lacking at present.

Hormones

Compared with age-matched males, SLE is 8-15 times more common in females in their reproductive years.[33] The higher prevalence of SLE in females suggests that genes on the X chromosomes, estrogen, or other sex hormones may promote SLE manifestations.[6,17] Indeed, estrogen prolongs the lifespan of autoreactive lymphocytes,[34-36] and mutations on the X chromosome have been associated with SLE.[37,38]

Immune Dysfunction in SLE

SLE is characterized by the production of antibodies against self-antigens, many years before the onset of overt signs or symptoms of SLE in adults. In up to 85% of patients with SLE, autoantibodies precede initial clinical symptoms by an average of 2-3 years, with prodromal periods as long as 9 years described in some individuals.[16,17,39]

Antinuclear antibodies (ANAs) are formed first, followed by anti–double-stranded DNA, antiphospholipid antibodies, and anti-Smith and anti-ribonucleoprotein.[16,40] The respective autoantigens escape the regulatory mechanisms of the immune system, resulting in the production of these autoantibodies and resultant overproduction of proinflammatory cytokines.[16,17,39,41] Further, autoantibodies lead to dysregulation

of both the innate and adaptive immune systems, including the formation of immune complexes that are associated with the development of tissue damage.[6,17,20,22,23]

Clinical Presentation of Disease

There is often a delay in diagnosis ranging from 1 month to 3.3 years, given the nonspecific and highly variable initial presentations with cSLE.[42] At disease onset, there is often a combination of fever, weight loss, arthralgia or arthritis, a photosensitive and/or malar rash, and renal disease.[43] Presenting features of cSLE are acute, commonly involving many organs at diagnosis. Compared to adults, children often experience a more severe clinical course of cSLE.[4,5,44,45] **Table I** provides a summary of the frequency of clinical signs and symptoms at initial presentation in cSLE.

Constitutional Symptoms

Fever, weight loss, malaise, fatigue, and lymphadenopathy are the most frequent constitutional symptoms with cSLE, both at presentation and over time.[43] Understandably, none of these symptoms are specific to cSLE; other disease processes including infections and malignancy need to be excluded.

Mucocutaneous Symptoms

Skin involvement is exceedingly common with cSLE both at diagnosis and during the course of the disease. The most typical cutaneous manifestation is the fixed eruption of the so-called butterfly rash or malar rash (**Figure 2**). Besides often painless oral and nasal ulcers, nonscarring alopecia also is often observed, typically in the frontal area.[8,9,46,47] Different from adults, an isolated discoid lupus rash is rare in children.

Table I. General frequencies of clinical features of childhood-onset SLE at presentation

Clinical features	Frequency of occurrence in cSLE (%)
Constitutional symptoms	47-92
Fever	36-84
Mucocutaneous	79-97
Malar	44-61
Photosensitivity	17-34
Musculoskeletal	68-71
Arthritis	61-71
Hematologic	20-63
Anemia	9-23
Renal	41-53
Nephritis	20-53
Cardiopulmonary	24-36
Serositis	12-30
Neuropsychiatric	16-36
Headache	5-22
Gastrointestinal	14-30

Created from information contained in references.[1-4]

Isolated discoid lupus and lupus erythematosus panniculitis have been described in 4.0% and 0.7% of patients with cSLE,[46-48] respectively. Discoid lupus rash will heal with scarring (**Figure 3**; available at www.jpeds.com), and almost all children with such a rash ultimately develop cSLE.

Musculoskeletal Abnormalities

The majority of patients with cSLE have arthritis, defined as joint swelling combined with pain and/or limitation in the range of motion. Joint stiffness in the morning or after prolonged inactivity is typical. Arthralgia or arthritis is mild to severe, often involving the small joints of the hands and feet.[13,46,47] Chronic arthritis occurs in fewer than 5% of patients with cSLE[46] and may lead to ulnar deviation of the hands, which is called Jaccoud arthropathy.[49] Muscle pain and myositis can also occur with cSLE. Despite mild overt weakness, inflammatory myositis can result in high muscle enzymes (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatinine phosphokinase, and aldolase).[47]

Hematology/Lymphatic Abnormalities

Leukopenia, thrombocytopenia, and/or anemia are especially frequent, with Coombs-positive hemolytic anemia recognized as the most common hematologic manifestation of cSLE.[50] Other hematologic abnormalities in cSLE include myelodysplasia, secondary hemophagocytosis, macrophage activation syndrome, and coagulation disorders, such as antiphospholipid antibody syndrome, that increase the risk of thrombotic events.[13,16,50]

Renal Abnormalities

Lupus nephritis is an important predictor of long-term survival with cSLE, especially if not controlled early.[13,46,51,52] Lupus nephritis is more common among patients of African, Asian, or Mediterranean descent.[16,53] The gold standard for the diagnosis of lupus nephritis is a kidney biopsy, which is indicated in patients with proteinuria and abnormal urine sediment not explained otherwise. There are 6 classes of lupus nephritis: class I, minimal mesangial lupus nephritis; class II, mesangial proliferative lupus nephritis; class III, focal lupus nephritis (active and chronic; proliferative and sclerosing); class IV, diffuse lupus nephritis (active and chronic; proliferative and sclerosing; segmental and global); class V, membranous lupus nephritis; and class VI, advanced sclerosing lupus nephritis.[54] In particular, class IV lupus nephritis has a poor prognosis and requires rapid initiation of steroids and immunosuppressive therapy.

Cardiorespiratory Abnormalities

Chest pain owing to pleurisy and pericarditis are typical cardiorespiratory manifestations in cSLE.[16,55,56] Pulmonary findings with cSLE are manifold, but hemoptysis, the hallmark of pulmonary hemorrhage, and dyspnea, possibly owing to a pulmonary embolus, must both be considered medical emergencies. Dyspnea may also be due to cardiac pathologies such as inflammatory endocarditis and myocarditis.[43,55,56]

Neurologic Abnormalities

Central nervous system abnormalities commence most commonly during the first year after diagnosis and may even be a presenting manifestation of cSLE.[47] Common central nervous system presentations are headache, mood disorders, new-onset seizures, psychosis, cerebrovascular disease, and chorea.[57] The diagnosis of neuropsychiatric lupus is exclusionary; other etiologies, such as acute/chronic infections, recreational drugs, primary psychiatric disease, malignancy, trauma, and metabolic abnormalities, must be excluded.[58] Neurocognitive testing and magnetic resonance imaging of the brain are now widely used for evaluation.[35,36] Despite the presence of neuropsychiatric manifestations of SLE (NPSLE), normal standard imaging is often indicated.

Figure 2. Malar rash in pediatric patient showing sparing of the nasolabial folds. (*Source*: Rheumatology Image Bank.)

Gastrointestinal Abnormalities

Abdominal pain and anorexia are among the more common gastrointestinal symptom reported in cSLE.[16,59] Besides

autoimmune pancreatitis, the presence of bowel vasculitis must be considered, especially in the setting of severe abdominal symptoms. Vomiting and nausea owing to cSLE treatment (steroids, nonsteroidal anti-inflammatory medications) occur more frequently than from the underlying disease.[60]

Approach to Diagnosis

There are no specific clinical or laboratory diagnostic criteria for cSLE. In fact, the widely applied Classification Criteria for Systemic Lupus Erythematosus by the American College of Rheumatology (ACR), often used to aid diagnosis, are meant for use in research studies. **Table II** (available at www.jpeds.com) lists the revised ACR criteria from 1997. For a patient to be classified as having cSLE, at least 4 of the 11 criteria have to be present at time of diagnosis or cumulatively before diagnosis. More recently, the Systemic Lupus International Collaborating Clinics Classification Criteria (SLICC criteria) have been developed. Compared with the ACR criteria, the SLICC criteria seem to be more sensitive but are less specific in capturing patients who are diagnosed with SLE by lupus experts.[61-63]

Laboratory Evaluations

Laboratory assessment can be helpful when establishing the diagnosis of cSLE, monitoring disease activity, that is, the degree of active inflammatory changes from cSLE, and detecting disease exacerbations (flares). The most helpful laboratory tests in support of a diagnosis of cSLE are summarized in **Table III** (available at www.jpeds.com).

Autoantibodies in cSLE
Almost all patients with cSLE test positive for ANA at disease onset[41,42]; in fact, the absence of ANA makes the diagnosis of SLE highly unlikely.[64] However, ANA are not specific to cSLE, and low-titer ANA can be present in 10%-33% of the general healthy population.[42,65,66] ANA also occur in conjunction with other rheumatologic diseases, such as juvenile idiopathic arthritis and juvenile dermatomyositis. Malignancies and infections can result in transient ANA positivity.[42,65] In cSLE, ANA titers do not correlate with disease activity, but high-titer ANA are a hallmark of cSLE at the time of diagnosis.[42,64]

Anti–double-stranded DNA positivity is very specific for SLE and present in up to 75% of patients with cSLE.[42,64] These antibodies occur especially in the setting of active inflammation from cSLE, including lupus nephritis.[67,68] Antibodies against extractable nuclear antigens, that is, anti-Smith, anti-ribonucleoprotein, anti-Ro (also called SS-A), and anti-La (also called SS-B) are other autoantibodies often encountered in cSLE.[69,70] Positive in up to 80% of patients, antihistone antibodies do not differentiate cSLE from drug-induced lupus, but can reflect disease activity.[64]

Novel Diagnostic Tools Used by Pediatric Subspecialists
The need for early diagnosis of potentially life-threatening organ involvement and better tools to predict cSLE disease course

prompted research in novel SLE biomarkers. These include serum C1q, urinary neutrophil gelatinase-associated lipocalin, and urinary monocyte chemoattractant protein 1 for the detection and monitoring of lupus nephritis.[28,69,71-74] Serum adiponectin is a promising biomarker used in assessing atherosclerotic risk in patients with cSLE.[75]

Antiribosomal P antibodies, antineuronal antibodies, and plasma levels of anti-NR2A/B antibodies are considered the most established new biomarkers of NPSLE and have been associated with neurocognitive dysfunction, depression, anxiety, and psychosis from NPSLE.[34,37,76,77]

Assessment of cSLE Disease Control and Permanent Tissue Damage
Disease activity can be defined as the reversible manifestations of the underlying inflammatory disease process.[38] Increase in disease activity, more commonly known as a disease flare, is defined as a "measurable worsening of SLE disease activity" in at least 1 organ system, causing new or worsening clinical signs that may be associated with new or worsening SLE symptoms; depending on the severity of flare, more intensive therapy may be required.[60,76,78] Disease damage, in contrast, refers to irreversible degenerative tissue and organ changes from disease activity or SLE treatment.

The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) is commonly used to measures the activity of cSLE. SLEDAI scores range from 0 to 104, with higher scores indicating more pronounced inflammatory changes from cSLE. Sometimes, a SLEDAI score of less than 5 is considered a measure of sufficient cSLE control, although a score of 0 is highly desirable. The SLICC/ACR Damage Index is used to measure cSLE damage.[79] Patients with any cSLE damage, that is, with a damage score of greater than 0, have a higher risk of dying and an increased risk for accumulating additional tissue damage from cSLE.[79]

Treatment

A multidisciplinary approach is essential for the proper management of cSLE. Collaboration among rheumatologists, general pediatricians, and other specialists like nephrologists and psychologists is often needed, with therapies tailored to organ involvement. Treatment goals include control of cSLE activity, avoidance of flares, damage prevention, and minimizing the iatrogenic effects of medications while maximizing patient quality of life.[42,80]

Hydroxychloroquine
Hydroxychloroquine (HCQ) is an antimalarial agent given to patients with cSLE as first-line therapy with accumulating evidence on its role in reducing mortality and morbidity.[80] HCQ is known to aleviate cSLE skin and muscloskeletal disease, along with decreasing disease activity and flares.[81] HCQ may promote cardiovascular health, and have a beneficial effect on bone density and glucose metabolism in cSLE.[80,81] HCQ is generally well-tolerated; although abdominal discomfort is the most

common complaint, retinal toxicity remains the most serious complication. Irreversible HCQ-related retinopathy occurs in 0.5%-1.0% of patients after 5 years of use, with increasing prevalence when HCQ is used at high doses and over a longer duration. Therefore, a funduscopic examination, including optical coherence tomography is recommended at baseline and annually thereafter.[42,58,80,81]

Immunosuppressive Medications

Systemic glucocorticoids (GCs) remain the mainstay in treatment of cSLE.[82] Dosing of oral or intravenous formulations of GC is based on the type and degree of organ involvement with cSLE.[80,82] Chronic GC therapy is associated with substantial iatrogenic complications,[80,81] including abnormal glucose metabolism, adrenal insufficiency requiring stress dosing, cataracts, glaucoma, avascular necrosis of the bones, osteoporosis, poor growth, and premature atherosclerosis.[42,82,83] GC therapy also constitutes an important risk factor for infections. Thus, cSLE management includes constantly striving to minimize GC to the absolute lowest necessary dose to control cSLE activity.

Cyclophosphamide (CYC) is an alkylating agent, used primarily for the management of severe organ involvement, including lupus nephritis and NPSLE. CYC is a relatively well-established and tested[81] agent that, despite its benefits in controlling cSLE, comes with many side effects. CYC is associated with an increased risk of infections, especially *Pneumocystis jirovecii* pneumonia (PJP); thus, patients receiving CYC therapy generally receive PJP prophylaxis, like cotrimoxazole or pentamidine. Rare CYC side effects include hemorrhagic cystitis and malignancies, particularly a small increased risk of bladder cancer.[80] Premature ovarian failure and gonadal toxicity are widely reported with CYC therapy in adults and much less commonly in cSLE. The use of triptorelin, a gonadotropin-releasing hormone agonist, at high doses every 28 days may provide ovarian protection for girls with cSLE who have entered puberty (Tanner stages 2-5) during CYC therapy.[84]

Mycophenolate mofetil (MMF) inhibits the de novo synthesis of guanosine nucleotides and, therefore, has a cytostatic effect on B and T lymphocytes. MMF has been studied extensively, particularly in the treatment of lupus nephritis and as a GC-sparing agent for the dermatologic manifestations of cSLE. Owing to notable individual variability in pharmacokinetics, personalized pharmacokinetic-based dosing of MMF is favored over weight-based dosing in support of achieving improved therapeutic benefits from MMF use.[85] The principal side effects of MMF include mild gastrointestinal symptoms, cytopenias, and teratogenicity.[81]

Azathioprine (AZA), a purine analogue, is another commonly used GC-sparing agent.[81] Thiopurine methyltransferase is the principal enzyme responsible for AZA metabolism. Certain thiopurine methyltransferase polymorphisms lead to decreased degradation of AZA and, if present, are associated with an increased drug toxicity risk. Laboratory tests are available to determine thiopurine methyltransferase activity and help to guide the use and dosing of AZA. Common side effects of AZA include gastrointestinal complaints, leukopenia, and hepa-

totoxicity; an increased risk of cancers, particularly melanoma and lymphomas, has been described with use of AZA.[42]

Biologic Agents in SLE

Increased understanding of the etiology and pathogenesis have led to the study and use of a number of biologic agents that specifically target disease pathways involved with lupus.[80]

Belimumab is a human immunoglobulin (Ig)G1 monoclonal antibody that binds to soluble B-lymphocyte stimulator protein and inhibits its biological activity. Belimumab was approved for the treatment of adults with autoantibody-positive SLE in the US and Europe in 2011. Thus far, it has not been specifically indicated in lupus nephritis or NPLSE.[86] There is an ongoing trial of belimumab in cSLE, but off-label use of belimumab in cSLE occurs. B-lymphocyte stimulator protein levels are elevated with SLE and are associated with greater disease activity. Studies in adults show that belimumab is generally well-tolerated, can improve disease control, and helps to reduce GC use. There is, however, a mildly increased risk of infections associated with belimumab treatment.[38,86]

Rituximab is an anti-CD20 monoclonal antibody that targets B cells and their ability to produce antibodies toward autoantigens. Studies in children suggest that rituximab is particularly effective in treating cSLE-associated cytopenias,[87,88] lupus nephritis,[89,90] refractory cSLE manifestations,[91,92] NPSLE,[93] and cutaneous disease.[80,87] Immunosuppression with an increased risk of opportunistic infections is a significant concern for patients with cSLE receiving rituximab; therefore, PJP prophylaxis is often used. Profound neutropenia may occur within 4 weeks of initiating therapy with rituximab[38] and monitoring for B-cell depletion, hypogammaglobinemia, and infusion reactions is important in patients with cSLE receiving rituximab.[87] Progressive multifocal leukoencephalopathy, albeit very rare, is associated with rituximab use.[93]

Medical Emergencies with cSLE

There are several cSLE complications that require prompt recognition for appropriate, timely therapy to be initiated. Summarized in Table IV are medical situations that, if present in patients with cSLE, require prompt interventions by a health care provider. The increased risk of infections, including sepsis, generally necessitates a comprehensive workup of every febrile patient with cSLE.

Childhood SLE and Health Quality Indicators: Role of the General Pediatrician

Childhood SLE therapy is complex and health quality indicators (QIs) based on scientific evidence and expert opinion have been developed recently.[58] QIs describe minimal standards of medical practice targeted at improving the quality of medical care.[58] The role of the general pediatrician in accomplishing these QIs cannot be overstated. The most important QIs for cSLE where the oversight of the general pediatrician is critical are summarized herein.

Table IV. A summary of signs and symptoms indicative of lupus emergencies

Signs/symptoms	Differential considerations
Fever	Evaluate for infection.
	Consider disease flare.
	Consider macrophage activation syndrome.
Thrombosis/hemoptysis	May be arterial or venous.
	Evaluate for antiphospholipid syndrome.
Chest pain	Pleurisy, pericarditis, pulmonary infarction/embolus.
Dyspnea	Pneumonitis, alveolar hemorrhage, pleural effusions, congestive heart failure.
Headache	Vascular headaches, meningitis, thrombus, cerebrovascular accident, hypertensive crisis.
Altered mental status	Cerebritis, hypertensive crisis.
Rash	Vasculitis lesions, palpable purpura, infarction.
	Consider macrophage activation syndrome.
Icterus	Autoimmune hemolysis.
	Autoimmune hepatitis.
Petechiae	Thrombotic thrombocytopenia.
	Thrombocytopenia.
Seizure	Cerebritis, infection, metabolic causes, hypertensive crisis.

Vaccinations/Infections

Given their immunosuppressed and/or immunocompromised state, patients with cSLE are at higher risk for infection from viruses, bacteria, atypical bacteria, or fungi. Risk can greatly be reduced with reinforcement of vaccination and universal precaution such as hand washing. In a patient with cSLE, vaccination against influenza and encapsulated organisms, such as *Pneumococcus*, *Meningococcus*, and *Haemophilus influenzae* should be administered before and after treatment is initiated, in the absence of contraindications.[58,94] The administration of outstanding vaccines before initiating immunosuppressive therapies such as high-dose steroids, rituximab, or CYC is desirable, but may not be possible. Live or attenuated live vaccines may be contraindicated in children with cSLE receiving immunosuppressant medications.

Bone Health/Vitamin D and Calcium

In cSLE, bone density loss is believed to be due to the effects of chronic inflammation, vitamin D deficiency, decreased physical activity, and the impact of GC therapy.[95-97] Bone loss and vitamin D deficiency is often exacerbated by chronic GC use, which decreases the serum vitamin D level and enhances the activity of osteoclasts.[98] The preferred method for assessing status and interval change of bone mineral density and bone mass is dual x-ray absorptiometry, although computed tomography may be more accurate. For any child with cSLE on chronic GC therapy, that is, prescribed a prednisone dose of 0.15 mg/kg/d or greater for 3 months or longer, bone mineral density evaluation should be considered.[58] Because sun exposure can trigger a cSLE flare, sun avoidance and sunscreen use are recommended, but this likely contribute to vitamin D deficiency in cSLE. Calcium and vitamin D supplementation is recommended with chronic GC use in cSLE.

Mental Health in cSLE

The impact of mental health on the well-being of patients with cSLE cannot be overemphasized. Childhood SLE is often as-

sociated with a poor quality of life, suboptimal disease control owing to problems with medication adherence, and low readiness to transition to adult care.[99] Compared with healthy peers, mental health problems occur more frequently among patients with cSLE.[100,101] Depression and anxiety, owing to NPSLE or the general burden of the disease, are often under-recognized. Patients with cSLE with mental health disorders will most likely be identified in the pediatrician's office because of the recommended yearly depression and anxiety screenings.[99] As with their peers with depression and/or anxiety only, referral to mental health services is invaluable to their medical care.

Cardiovascular Health in cSLE

There is an increased risk of premature atherosclerosis owing to the effects of SLE on blood vessels, the presence of systemic inflammation, and the need of GC therapies.[102,103] Therefore, atherosclerosis prevention activities are recommended for individuals diagnosed with cSLE.[53] Specifically, patients with cSLE should receive routine cardiovascular risk assessments, and regular counseling about modifiable risk factors of cardiovascular disease such as sedentary lifestyle, dyslipidemia, hypertension, obesity, and smoking are advisable.[104,105] The routine use of statins in cSLE is currently not recommended.[105]

Morbidity/Mortality in cSLE

The diagnosis of SLE during childhood constitutes an important risk factor for morbidity and mortality in adulthood.[6,106] The increased morbidity and mortality seen in cSLE is attributable to disease-related organ damage and medication side effects, particularly long-term steroid use. Renal disease, infections (opportunistic or otherwise), myocardial infarction, and coronary artery disease remain important causes of morbidity and mortality in adulthood for patients with cSLE.[107,108] Malignancies are more frequent in cSLE than in the age-matched population. There is a risk of 1.6 cancers per 1000 person-years and, hence, an increased standardized incidence ration of 4.13 (95% CI, 2.26-6.93).[109] ■

References

1. Petty RE, Lindsley CB, Laxer RM, Wedderburn L, eds. Cassidy's textbook of pediatric rheumatology. 7th ed. Philadelphia (PA): Elsevier; 2016. p. xiv [Chapter 24].
2. Silva CA, Avcin T, Brunner HI. Taxonomy for systemic lupus erythematosus with onset before adulthood. Arthritis Care Res (Hoboken) 2012;64:1787-93.
3. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol 2010;6:538-46.
4. Malattia C, Martini A. Paediatric-onset systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2013;27:351-62.
5. Tarr T, Dérfalvi B, Győri N, Szántó A, Siminszky Z, Malik A, et al. Similarities and differences between pediatric and adult patients with systemic lupus erythematosus. Lupus 2015;24:796-803.

6. Brunner HI, Gladman DD, Ibanez D, Urowitz MD, Silverman ED. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis Rheum 2008;58:556-62.

7. Hiraki LT, Benseler SM, Tyrrell PN, Harvey E, Hebert D, Silverman ED. Ethnic differences in pediatric systemic lupus erythematosus. J Rheumatol 2009;36:2539-46.

8. Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. Pediatr Clin North Am 2012;59:345-64.

9. Mina R, Brunner HI. Pediatric lupus—are there differences in presentation, genetics, response to therapy, and damage accrual compared with adult lupus? Rheum Dis Clin North Am 2010;36:53-80, vii-viii.

10. Rekvig OP, Van der Vlag J. The pathogenesis and diagnosis of systemic lupus erythematosus: still not resolved. Semin Immunopathol 2014;36:301-11.

11. J de A, C A, P SG, S C. Systemic lupus erythematosus: old and new susceptibility genes versus clinical manifestations. Curr Genomics 2014;15:52-65.

12. Schiffer L, Worthmann K, Haller H, Schiffer M. CXCL13 as a new biomarker of systemic lupus erythematosus and lupus nephritis — from bench to bedside? Clin Exp Immunol 2015;179:85-9.

13. Lehman T, Nuruzzaman F, Taber S. Systemic lupus erythematosus: etiology, pathogenesis, clinical manifestations, and management. In: Sarzi-Puttini F, ed. Handbook in systemic autoimmune diseases. pediatrics in systemic autoimmune diseases. Oxford, UK: Elsevier; 2016. p. 173-89.

14. Schwartz N, Goilav B, Putterman C. The pathogenesis, diagnosis and treatment of lupus nephritis. Curr Opin Rheumatol 2014;26:502-9.

15. Lewandowski L, Scott C, Gomez-Martin D, Silverman ED, Aksentijevich I, Deng Z, et al. GG-10 Imagine SLE: international multi-site assessment of genetics and inflammation in early onset and familial systemic lupus erythematosus. Lupus Sci Med 2016;3.

16. Wallace DJ, Hahn B, Dubois EL. Dubois' lupus erythematosus and related syndromes. 8th ed. Philadelphia (PA): Elsevier/Saunders; 2013. p. xv.

17. Lloyd P, Doaty S, Hahn B. Aetiopathogenesis of systemic lupus erythematosus. In: Gordon C, Isenberg D, eds. Systemic lupus erythematosus. Oxford Rheumatology Library, Oxford, UK: Oxford University Press; 2016.

18. Belot A, Cimaz R. Monogenic forms of systemic lupus erythematosus: new insights into SLE pathogenesis. Pediatr Rheumatol Online J 2012;10:21.

19. Pereira KM, Faria AG, Liphaus BL, Jesus AA, Silva CA, Carneiro-Sampaio M, et al. Low C4, C4A and C4B gene copy numbers are stronger risk factors for juvenile-onset than for adult-onset systemic lupus erythematosus. Rheumatology (Oxford) 2016;55:869-73.

20. Deng Y, Tsao BP. Advances in lupus genetics and epigenetics. Curr Opin Rheumatol 2014;26:482-92.

21. Hedrich CM, Tsokos GC. Epigenetic mechanisms in systemic lupus erythematosus and other autoimmune diseases. Trends Mol Med 2011;17:714-24.

22. Lehmann P, Hölzle E, Kind P, Goerz G, Plewig G. Experimental reproduction of skin lesions in lupus erythematosus by UVA and UVB radiation. J Am Acad Dermatol 1990;22(2 Pt 1):181-7.

23. James JA, Harley JB, Scofield RH. Epstein-Barr virus and systemic lupus erythematosus. Curr Opin Rheumatol 2006;18:462-7.

24. Hedrich CM, Bream JH. Cell type-specific regulation of IL-10 expression in inflammation and disease. Immunol Res 2010;47:185-206.

25. Renaudineau Y, Youinou P. Epigenetics and autoimmunity, with special emphasis on methylation. Keio J Med 2011;60:10-6.

26. Zouali M. Epigenetics in lupus. Ann N Y Acad Sci 2011;1217:154-65.

27. Hejazi EZ, Werth VP. Cutaneous lupus erythematosus: an update on pathogenesis, diagnosis and treatment. Am J Clin Dermatol 2016;17:135-46.

28. Yu C, Chang C, Zhang J. Immunologic and genetic considerations of cutaneous lupus erythematosus: a comprehensive review. J Autoimmun 2013;41:34-45.

29. Doaty S, Agrawal H, Bauer E, Furst DE. Infection and lupus: which causes which? Curr Rheumatol Rep 2016;18:13.

30. Pasoto SG, Ribeiro AC, Bonfa E. Update on infections and vaccinations in systemic lupus erythematosus and Sjögren's syndrome. Curr Opin Rheumatol 2014;26:528-37.

31. Hanlon P, Avenell A, Aucott L, Vickers MA. Systematic review and meta-analysis of the sero-epidemiological association between Epstein-Barr virus and systemic lupus erythematosus. Arthritis Res Ther 2014;16:R3.

32. Caza T, Oaks Z, Perl A. Interplay of infections, autoimmunity, and immunosuppression in systemic lupus erythematosus. Int Rev Immunol 2014;33:330-63.

33. Lu LJ, Wallace DJ, Ishimori ML, Scofield RH, Weisman MH. Review: male systemic lupus erythematosus: a review of sex disparities in this disease. Lupus 2010;19:119-29.

34. Khan D, Dai R, Ansar Ahmed S. Sex differences and estrogen regulation of miRNAs in lupus, a prototypical autoimmune disease. Cell Immunol 2015;294:70-9.

35. Lee MH, Sriram U, Chakhtoura M, Chain RW, Caricchio R, Gallucci S. The effects of estrogen on the IFN signature in lupus. J Immunol 2016;196:118.

36. Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum 2010;39:257-68.

37. Slae M, Heshin-Bekenstein M, Simckes A, Heimer G, Engelhard D, Eisenstein EM. Female polysomy-X and systemic lupus erythematosus. Semin Arthritis Rheum 2014;43:508-12.

38. Borgia RE, Silverman ED. Childhood-onset systemic lupus erythematosus: an update. Curr Opin Rheumatol 2015;27:483-92.

39. Munroe ME, Lu R, Zhao YD, Fife DA, Robertson JM, Guthridge JM, et al. Altered type II interferon precedes autoantibody accrual and elevated type I interferon activity prior to systemic lupus erythematosus classification. Ann Rheum Dis 2016;75:2014-21.

40. Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003;349:1526-33.

41. Devarapu S, Anders H, Rupanagudi K. Update on immune mechanisms in systemic lupus and lupus nephritis. Lupus Open Access 2016;1:2.

42. Weiss JE. Pediatric systemic lupus erythematosus: more than a positive antinuclear antibody. Pediatr Rev 2012;33:62-73, quiz 4.

43. Huggins JL, Holland MJ, Brunner HI. Organ involvement other than lupus nephritis in childhood-onset systemic lupus erythematosus. Lupus 2016;25:857-63.

44. Peschken CA, Katz SJ, Silverman E, Pope JE, Fortin PR, Pineau C, et al. The 1000 Canadian faces of lupus: determinants of disease outcome in a large multiethnic cohort. J Rheumatol 2009;36:1200-8.

45. Klein-Gitelman M, Reiff A, Silverman ED. Systemic lupus erythematosus in childhood. Rheum Dis Clin North Am 2002;28:561-77, vi-vii.

46. Silva CA. Childhood-onset systemic lupus erythematosus: early disease manifestations that the paediatrician must know. Expert Rev Clin Immunol 2016;12:907-10.

47. Gomes RC, Silva MF, Kozu K, Bonfá E, Pereira RM, Terreri MT, et al. Features of 847 childhood-onset systemic lupus erythematosus patients in three age groups at diagnosis: a Brazilian multicenter study. Arthritis Care Res (Hoboken) 2016;68:1736-41.

48. Guissa VR, Trudes G, Jesus AA, Aikawa NE, Romiti R, Silva CA. Lupus erythematosus panniculitis in children and adolescents. Acta Reumatol Port 2012;37:82-5.

49. Ruano CA, Malheiro R, Oliveira JF, Pinheiro S, Vieira LS, Moraes-Fontes MF. Ultrasound detects subclinical joint inflammation in the hands and wrists of patients with systemic lupus erythematosus without musculoskeletal symptoms. Lupus Sci Med 2017;4:e000184.

50. Gokce M, Bilginer Y, Besbas N, Ozaltin F, Cetin M, Gumruk F, et al. Hematological features of pediatric systemic lupus erythematosus: suggesting management strategies in children. Lupus 2012;21:878-84.

51. Chaigne B, Chizzolini C, Perneger T, Trendelenburg M, Huynh-Do U, Dayer E, et al. Impact of disease activity on health-related quality of life in systemic lupus erythematosus - a cross-sectional analysis of the Swiss Systemic Lupus Erythematosus Cohort Study (SSCS). BMC Immunol 2017;18:17.

52. Sule SD, Moodalbail DG, Burnham J, Fivush B, Furth SL. Predictors of kidney disease in a cohort of pediatric patients with lupus. Lupus 2015;24:862-8.

53. Barsalou J, Levy DM, Silverman ED. An update on childhood-onset systemic lupus erythematosus. Curr Opin Rheumatol 2013;25:616-22.

54. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004;15:241-50.

55. Couture J, Silverman ED. Update on the pathogenesis and treatment of childhood-onset systemic lupus erythematosus. Curr Opin Rheumatol 2016;28:488-96.

56. Beresford MW, Cleary AG, Sills JA, Couriel J, Davidson JE. Cardiopulmonary involvement in juvenile systemic lupus erythematosus. Lupus 2005;14:152-8.

57. Bader-Meunier B, Armengaud JB, Haddad E, Salomon R, Deschênes G, Koné-Paut I, et al. Initial presentation of childhood-onset systemic lupus erythematosus: a French multicenter study. J Pediatr 2005;146:648-53.

58. Hollander MC, Sage JM, Greenler AJ, Pendl J, Avcin T, Espada G, et al. International consensus for provisions of quality-driven care in childhood-onset systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2013;65:1416-23.

59. Richer O, Ulinski T, Lemelle I, Ranchin B, Loirat C, Piette JC, et al. Abdominal manifestations in childhood-onset systemic lupus erythematosus. Ann Rheum Dis 2007;66:174-8.

60. Bert J, Gertner E. Lupus gastrointestinal tract vasculopathy: lupus "enteritis" involving the entire gastrointestinal tract from esophagus to rectum. Case Rep Gastroenterol 2017;11:48-53.

61. Mina R, Brunner HI. Update on differences between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis Res Ther 2013;15:218.

62. Aberle T, Bourn RL, Chen H, Roberts VC, Guthridge JM, Bean K, et al. Use of SLICC criteria in a large, diverse lupus registry enables SLE classification of a subset of ACR-designated subjects with incomplete lupus. Lupus Sci Med 2017;4:e000176.

63. Fonseca AR, Gaspar-Elsas MI, Land MG, de Oliveira SK. Comparison between three systems of classification criteria in juvenile systemic lupus erythematous. Rheumatology (Oxford) 2015;54:241-7.

64. Egner W. The use of laboratory tests in the diagnosis of SLE. J Clin Pathol 2000;53:424-32.

65. Lang BA, Silverman ED. A clinical overview of systemic lupus erythematosus in childhood. Pediatr Rev 1993;14:194-201.

66. Wichainun R, Kasitanon N, Wangkaew S, Hongsongkiat S, Sukitawut W, Louthrenoo W. Sensitivity and specificity of ANA and anti-dsDNA in the diagnosis of systemic lupus erythematosus: a comparison using control sera obtained from healthy individuals and patients with multiple medical problems. Asian Pac J Allergy Immunol 2013;31:292-8.

67. Webb R, Kelly JA, Somers EC, Hughes T, Kaufman KM, Sanchez E, et al. Early disease onset is predicted by a higher genetic risk for lupus and is associated with a more severe phenotype in lupus patients. Ann Rheum Dis 2011;70:151-6.

68. Livingston B, Bonner A, Pope J. Differences in autoantibody profiles and disease activity and damage scores between childhood- and adult-onset systemic lupus erythematosus: a meta-analysis. Semin Arthritis Rheum 2012;42:271-80.

69. Wenderfer SE, Ruth NM, Brunner HI. Advances in the care of children with lupus nephritis. Pediatr Res 2017;81:406-14.

70. Gottlieb BS, Ilowite NT. Systemic lupus erythematosus in children and adolescents. Pediatr Rev 2006;27:323-30.

71. Kiani AN, Johnson K, Chen C, Diehl E, Hu H, Vasudevan G, et al. Urine osteoprotegerin and monocyte chemoattractant protein-1 in lupus nephritis. J Rheumatol 2009;36:2224-30.

72. Watson L, Midgley A, Pilkington C, Tullus K, Marks S, Holt R, et al. Urinary monocyte chemoattractant protein 1 and alpha 1 acid glycoprotein as biomarkers of renal disease activity in juvenile-onset systemic lupus erythematosus. Lupus 2012;21:496-501.

73. Hinze CH, Suzuki M, Klein-Gitelman M, Passo MH, Olson J, Singer NG, et al. Neutrophil gelatinase-associated lipocalin is a predictor of the course of global and renal childhood-onset systemic lupus erythematosus disease activity. Arthritis Rheum 2009;60:2772-81.

74. Goilav B, Putterman C, Rubinstein TB. Biomarkers for kidney involvement in pediatric lupus. Biomark Med 2015;9:529-43.

75. Al M, Ng L, Tyrrell P, Bargman J, Bradley T, Silverman E. Adipokines as novel biomarkers in paediatric systemic lupus erythematosus. Rheumatology (Oxford) 2009;48:497-501.

76. Brunner HI, Klein-Gitelman MS, Higgins GC, Lapidus SK, Levy DM, Eberhard A, et al. Toward the development of criteria for global flares in juvenile systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2010;62:811-20.

77. Tay SH, Fairhurst AM, Mak A. Clinical utility of circulating anti-N-methyl-d-aspartate receptor subunits NR2A/B antibody for the diagnosis of neuropsychiatric syndromes in systemic lupus erythematosus and Sjögren's syndrome: an updated meta-analysis. Autoimmun Rev 2017;16:114-22.

78. Weiss JE, Sison CP, Ilowite NT, Gottlieb BS, Eberhard BA. Flares in pediatric systemic lupus erythematosus. J Rheumatol 2007;34:1341-4.

79. Brunner HI, Silverman ED, To T, Bombardier C, Feldman BM. Risk factors for damage in childhood-onset systemic lupus erythematosus: cumulative disease activity and medication use predict disease damage. Arthritis Rheum 2002;46:436-44.

80. Jordan N, D'Cruz D. Current and emerging treatment options in the management of lupus. Immunotargets Ther 2016;5:9-20.

81. Tsang-A-Sjoe. Systemic lupus erythematosus: review of synthetic drugs. Expert Opin Pharmacother 2015;16:2793-806.

82. Kasturi S, Sammaritano LR. Corticosteroids in lupus. Rheum Dis Clin North Am 2016;42:47-62, viii.

83. Kan H, Nagar S, Patel J, Wallace DJ, Molta C, Chang DJ. Longitudinal treatment patterns and associated outcomes in patients with newly diagnosed systemic lupus erythematosus. Clin Ther 2016;38:610-24.

84. Brunner HI, Silva CA, Reiff A, Higgins GC, Imundo L, Williams CB, et al. Randomized, double-blind, dose-escalation trial of triptorelin for ovary protection in childhood-onset systemic lupus erythematosus. Arthritis Rheumatol 2015;67:1377-85.

85. Sagcal-Gironella AC, Fukuda T, Wiers K, Cox S, Nelson S, Dina B, et al. Pharmacokinetics and pharmacodynamics of mycophenolic acid and their relation to response to therapy of childhood-onset systemic lupus erythematosus. Semin Arthritis Rheum 2011;40:307-13.

86. Shum K, Askanase A. Belimumab and the clinical data. Curr Rheumatol Rep 2012;14:310-7.

87. Olfat M, Silverman ED, Levy DM. Rituximab therapy has a rapid and durable response for refractory cytopenia in childhood-onset systemic lupus erythematosus. Lupus 2015;24:966-72.

88. Kumar S, Benseler SM, Kirby-Allen M, Silverman ED. B-cell depletion for autoimmune thrombocytopenia and autoimmune hemolytic anemia in pediatric systemic lupus erythematosus. Pediatrics 2009;123:e159-63.

89. Moroni G, Raffiotta F, Trezzi B, Giglio E, Mezzina N, Del Papa N, et al. Rituximab vs mycophenolate and vs cyclophosphamide pulses for induction therapy of active lupus nephritis: a clinical observational study. Rheumatology (Oxford) 2014;53:1570-7.

90. Moroni G, Ponticelli C. The multifaceted aspects of refractory lupus nephritis. Expert Rev Clin Immunol 2015;11:281-8.

91. Mirabelli G, Cannarile F, Bruni C, Vagelli R, De Luca R, Carli L. One year in review 2015: systemic lupus erythematosus. Clin Exp Rheumatol 2015;33:414-25.

92. Mahmoud I, Jellouli M, Boukhris I, Charfi R, Ben Tekaya A, Saidane O, et al. Efficacy and safety of rituximab in the management of pediatric systemic lupus erythematosus: a systematic review. J Pediatr 2017;187:213-9, e2.

93. Dale RC, Brilot F, Duffy LV, Twilt M, Waldman AT, Narula S, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology 2014;83:142-50.

94. Harris JG, Maletta KI, Kuhn EM, Olson JC. Evaluation of quality indicators and disease damage in childhood-onset systemic lupus erythematosus patients. Clin Rheumatol 2017;36:351-9.

95. Compeyrot-Lacassagne S, Tyrrell PN, Atenafu E, Doria AS, Stephens D, Gilday D, et al. Prevalence and etiology of low bone mineral density in juvenile systemic lupus erythematosus. Arthritis Rheum 2007;56:1966-73.

96. Ruiz-Irastorza G, Egurbide MV, Olivares N, Martinez-Berriotxoa A, Aguirre C. Vitamin D deficiency in systemic lupus erythematosus: prevalence, predictors and clinical consequences. Rheumatology (Oxford) 2008;47:920-3.

97. Wright TB, Shults J, Leonard MB, Zemel BS, Burnham JM. Hypovitaminosis D is associated with greater body mass index and disease activity in pediatric systemic lupus erythematosus. J Pediatr 2009;155:260-5.

98. Alsufyani KA, Ortiz-Alvarez O, Cabral DA, Tucker LB, Petty RE, Nadel H, et al. Bone mineral density in children and adolescents with systemic lupus erythematosus, juvenile dermatomyositis, and systemic vasculitis: relationship to disease duration, cumulative corticosteroid dose, calcium intake, and exercise. J Rheumatol 2005;32:729-33.

99. Knight AM, Vickery ME, Muscal E, Davis AM, Harris JG, Soybilgic A, et al. Identifying targets for improving mental healthcare of adolescents with systemic lupus erythematosus: perspectives from pediatric rheumatology clinicians in the United States and Canada. J Rheumatol 2016;43:1136-45.

100. Knight A, Weiss P, Morales K, Gerdes M, Gutstein A, Vickery M, et al. Depression and anxiety and their association with healthcare utilization in pediatric lupus and mixed connective tissue disease patients: a cross-sectional study. Pediatr Rheumatol Online J 2014;12:42.

101. Jones JT, Cunningham N, Kashikar-Zuck S, Brunner HI. Pain, fatigue, and psychological impact on health-related quality of life in childhood-onset lupus. Arthritis Care Res (Hoboken) 2016;68:73-80.

102. Sandborg C, Ardoin SP, Schanberg L. Therapy insight: cardiovascular disease in pediatric systemic lupus erythematosus. Nat Clin Pract Rheumatol 2008;4:258-65.

103. Ardoin SP, Schanberg LE, Sandborg CI, Barnhart HX, Evans GW, Yow E, et al. Secondary analysis of APPLE study suggests atorvastatin may reduce atherosclerosis progression in pubertal lupus patients with higher C reactive protein. Ann Rheum Dis 2014;73:557-66.

104. Thakral A, Klein-Gitelman MS. An update on treatment and management of pediatric systemic lupus erythematosus. Rheumatol Ther 2016;3:209-19.

105. Schanberg LE, Sandborg C, Barnhart HX, Ardoin SP, Yow E, Evans GW, et al. Use of atorvastatin in systemic lupus erythematosus in children and adolescents. Arthritis Rheum 2012;64:285-96.

106. Hersh AO, Trupin L, Yazdany J, Panopalis P, Julian L, Katz P, et al. Childhood-onset disease as a predictor of mortality in an adult cohort of patients with systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2010;62:1152-9.

107. Björnådal L, Yin L, Granath F, Klareskog L, Ekbom A. Cardiovascular disease a hazard despite improved prognosis in patients with systemic lupus erythematosus: results from a Swedish population based study 1964-95. J Rheumatol 2004;31:713-9.

108. Fatemi A, Matinfar M, Smiley A. Childhood versus adult-onset systemic lupus erythematosus: long-term outcome and predictors of mortality. Clin Rheumatol 2017;36:343-50.

109. Bernatsky S, Clarke AE, Zahedi Niaki O, Labrecque J, Schanberg LE, Silverman ED, et al. Malignancy in pediatric-onset systemic lupus erythematosus. J Rheumatol 2017;44:1484-6.

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Figure 3. Active discoid lupus. (*Source*: Personal archive, Dr. Brunner.)

Table II. 1997 update of the 1982 ACR revised criteria for classification of systemic lupus erythematosus

Criterion	Definition
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 ≥2 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 d 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 ≥2 occasions *or* lymphopenia <1500/mm^3 on ≥2 occasions *or* thrombocytopenia <100 000/mm^3 in the absence of offending drugs.
10. Immunologic disorder	Positive lupus erythematosus cell preparation *or* anti-DNA antibody to native DNA in abnormal titer *or* anti-Smith antibody; presence of antibody to Smith nuclear antigen *or* false-positive serologic test for syphilis known to be positive for ≥6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test *or* positive lupus anticoagulant or anticardiolipin antibodies (IgM or IgG)
11. ANA	An abnormal titer of ANA 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.

Table III. Laboratory workup recommended for cSLE

Laboratory test	Clinical association
Basic laboratory tests	
CBC	Evaluate for cytopenia.
CMP	Transaminitis, hypoalbuminemia, elevated creatinine with lupus nephritis.
Inflammatory markers (ESR, CRP)	Nonspecific, but usually ESR is elevated with active disease owing to inflammation, useful in disease monitoring; may indicate a flare or increased disease activity if starting to increase in patients with controlled disease.
	Chronically high CRP levels are thought to reflect cardiovascular risk; however, acutely, a high CRP is more indicative of infection than disease flare.
Urinalysis	Screen for proteinuria, hematuria, leucocyturia, and granular or red cell cellular casts.
Complement levels, especially C3, C4	Low or undetected levels are expected in active disease and disease flares.
Autoantibodies against	
ANA	Positive in almost all patients with SLE, but not specific.
	Does not correlate with disease activity or flares.
	Not used for disease monitoring.
dsDNA	Very specific for cSLE.
	Present in up to 75% of patient with cSLE.
	Associated with lupus nephritis.
	May be useful for monitoring disease activity and predicting flares.
Histone	Positive in around 50%-80% of patients.
	Drug-induced lupus, not useful to differentiate between SLE and drug-induced lupus.
	Reflects disease activity.
SS-A(Ro)/SS-B (La)	Sjogren syndrome, congenital heart block in neonates, photosensitivity.
	Do not reflect disease activity.
Smith	Highly specific for SLE.
	Does not reflect or predict disease activity.
RNP	Positive in SLE but does not correlate with specific clinical feature, MCTD/overlap features.
Ribosomal P	Neuropsychiatric lupus.

CBC, Complete blood count; *CMP*, complete metabolic panel; *CRP*, C-reactive protein; *dsDNA*, double-stranded DNA; *ESR*, erythrocyte sedimentation rate; *MCTD*, mixed connective tissue disease; *RNP*, ribonuclear protein.