Pediatric systemic lupus erythematosus (pSLE) is a chronic multisystem autoimmune disease with complex clinical manifestations. Although the presentation, clinical manifestations, immunological findings and treatment issues of pSLE are similar to those of adult SLE patients, there are special issues which need to be considered when dealing with SLE in children. During the last decade survival has improved remarkably as a result of earlier diagnosis, recognition of milder disease and better approaches to therapy. However, pSLE remains a potentially serious condition. Although the pathogenesis of SLE remains poorly understood, susceptibility involves a combination of environmental, hormonal and genetic factors. Better understanding of SLE pathogenesis will hopefully lead to more specific and less toxic therapies for this disease.

Key words:

INTRODUCTION
Systemic lupus erythematosus (SLE) is a complex, multisystem autoimmune disease which results from the interplay of environmental, hormonal and genetic factors. In children, the presentation, clinical course and immunological findings differ slightly from adults with SLE.

In the last decade the outcome of SLE patients have improved remarkably, but even though many diagnostic and treatment options are similar for adults and children there are special issues that need to be considered in children and adolescents with SLE. For example, pSLE tends to be more severe and have higher impact on school adjustment and psychosocial aspects related, among others, to physical appearance and growth retardation.

EPIDEMIOLOGY
Pediatric SLE (pSLE) represents approximately 15-20% of all SLE patients. It is more common in females than in males, with a female to male ratio varying from 2.3:1 to 9:1, depending on the study.

The incidence of the disease varies according to different ethnic groups. In Caucasian females the incidence of SLE with onset before age of 19 years is between 6 and 18.9 cases per 100,000, while it is 20-30 per 100,000 in African American females and 16-36.7 per 100,000 in Puerto Rican females. The diagnosis of pSLE is rare before the age of 10, and the average age at presentation is 12.1 years.

Disease damage and mortality in pSLE have been linked to different risk factors which include young age at diagnosis, male sex and non-white ethnicity (African American, Asian, and Hispanic). African Americans tend to have a greater prevalence and a more severe renal and neuropsychiatric disease (NPSLE). However, the association between any of these risk factors and a poor prognosis remains controversial.

The survival rate for pSLE has improved dramatically over the past 50 years, with a 5-year survival rate increasing from 50% in 1955 to more than 90% in 2004.
**General clinical manifestations**

Clinical characteristics and organ involvement vary depending on age of onset, gender and race. In general children with SLE tend to have a more severe disease at onset with higher rates of organ involvement and a more aggressive clinical course than adult-onset SLE patients. At onset, 40-90% of children will present with constitutional symptoms (fever, fatigue or weight loss), 20-82% will have renal involvement, 20-74% musculoskeletal symptoms, 22-74% malar rash, 15-45% lymphadenopathy and 15-74% visceromegaly.

**Cutaneous manifestations**

The skin is commonly involved in pSLE. Different cutaneous manifestations have been reported in children during the course of their disease including: malar rash (22-74%) which is a hallmark of SLE, oral ulcers (26-48%), vasculitic rash (10-52%), photosensitivity (16-50%), alopecia (7-48%), discoid lesions (5-19%) and Raynaud’s phenomenon (10-20%).

**Musculoskeletal manifestations**

Arthritis occurs in more than 3/4 of pediatric patients with SLE. It can be variable, but usually presents as a symmetric non-erosive, very painful polyarthritis involving both, large and small joints and is rarely associated with radiographic changes.

In general, SLE arthritis responds well to conventional therapy. Indeed, arthritis can be the only presenting manifestation of SLE and some patients who initially meet the American College of Rheumatology (ACR) criteria for juvenile arthritis, subsequently fulfilled clinical and serological criteria for the classification of SLE.

Myalgia is seen in 20-30% of patients, however true myositis is less frequent. Musculoskeletal manifestations could be also seen as a side effect of the different drugs used. Treatment-induced musculoskeletal complications include avascular necrosis, osteoporosis and growth failure.

**Hematological disorders**

Thirty nine percent of children with SLE will develop hematological abnormalities, one of the ACR diagnostic criteria for SLE, during the course of the disease. Autoimmune thrombocytopenia is the initial manifestation in up to 15% of the pediatric cases although it can precede the onset of SLE by several years. It has been suggested that 20% to 30% of children with autoimmune idiopathic thrombocytopenic purpura who are ANA positive will evolve into SLE. Leukopenia is observed in 27-52% of pediatric cases primarily due to a decrease in lymphocyte number. Granulocytopenia is also common.

Coagulation abnormalities are frequently present in pSLE. The Coomb’s test is positive in approximately 30-40% of patients, however less than 10% will develop overt hemolysis. Antiphospholipid antibodies (aPL) are present in 75% of pSLE patients. Pediatric patients with SLE and aPL, specifically lupus anticoagulant (LAC), are at high risk of developing thromboembolic events and the incidence of TE in LAC positive patients is 54%. Therefore, lifelong anticoagulation must be considered after an initial thromboembolic event.

**Cardiac manifestations**

The spectrum of cardiac disease in pSLE mirrors that in adults with SLE. It encompasses 4 major types of manifestations: pericarditis (the most common form of cardiac involvement), myocarditis, valvular disease, and coronary artery disease due to either coronary arteritis or atherosclerosis. A few studies have reported silent cardiac abnormalities in children with SLE as a common finding. In fact, myocardial ischemia has been described in 16% of asymptomatic children.

Cardiac involvement in pSLE patients is now being recognized as a major cause of morbidity and mortality in this population. Children with SLE have markedly higher rates of coronary heart disease than controls, and these increased rates are partly explained by an increase in the conventional cardiovascular risk factors. Identified risk factors for premature atherosclerosis in pSLE include: dyslipidemia, high levels of homocystine, presence of aPL, LAC, hypertension, hyperinsulinemia, nephritic range proteinuria, upregulated CD40-CD40 ligand interactions and steroid-induced obesity. Currently, the multicenter Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) study group is assessing the role of statins for the prevention of atherosclerosis in the pediatric population with SLE.

**Neuropsychiatric manifestations**

Neuropsychiatric systemic lupus erythematosus (NPSLE), occurring in 20-45% of children and adolescents, is the third most common cause for mortality in pSLE. Unlike other manifestations of the disease, central nervous system (CNS) involvement occurs within the first year of disease in approximately 75% to 80% of patients. NPSLE involvement can range from global cerebral dysfunction with paralysis and seizures, to mild or focal symptoms such as headache or memory loss. The presence of aPL is often linked to thrombosis and CNS infarction.

The diagnosis of NPSLE continues to be difficult since there is a lack of specific serologic studies for its diagnosis and monitoring. Although neuroimaging is a clinically useful tool, CSF analysis, EEG, CT scan, and even MRI may be normal in these patients. On the other hand, functional imaging may be abnormal in otherwise asymptomatic lupus individuals which makes its interpretation difficult. Multiple imaging modalities have been studied to determine if there is a link between the clinical status...
and CNS imaging abnormalities, but to date there is no consensus.

**Pulmonary involvement**

The lung involved in 5-77% of pSLE patients and pulmonary manifestations vary from sub-clinical abnormalities to life-threatening disorders. The clinical spectrum includes pleuritis (the most common), pneumonia, pneumonitis, pleuropneumothorax, diffuse interstitial disease, pulmonary hypertension and pulmonary hemorrhage, a relatively uncommon and potentially lethal complication. In the majority of children, pulmonary symptoms are present at some point during their disease course. Asymptomatic or subclinical lung involvement in pSLE may be more prevalent than realized. Pulmonary function abnormalities were found in up to 40% of pSLE patients with no evidence of clinical symptoms or radiographic changes. The most frequent pattern observed was lung restrictive disease. Although pulmonary function tests do not correlate well with pulmonary symptoms, they provide objective quantification of the type and severity of the functional lesion observed.

**Renal involvement**

Not only does renal involvement represent the first clinical manifestation of the disease in 60-80% of children with SLE, but it also determines the course of the disease and the outcome of patients. About 80% of children and adolescents who develop renal abnormalities generally do so in the first year after diagnosis. Pathological findings can not be predicted from the clinical manifestations and therefore a renal biopsy is required for precise to establish diagnosis and subsequently planning effective therapy.

In 1982, the World Health Organization (WHO) classified lupus nephritis (LN) based on histologic features into 6 categories; WHO class IV is the most common form of pSLE nephritis and is most commonly associated with the development of end stage renal disease or death.

Renal flares are common throughout the disease course of LN and can frequently be detected by increasing proteinuria. The presence of hypertension and peripheral edema are usually associated with WHO class III or IV LN. The prognosis of children with LN depends primarily on the severity of the histopathological lesions according to the WHO classification. Although in most centers the treatment is determined by the WHO class on biopsy, long-term renal outcome is still unpredictable. Other biopsy indices have been developed to evaluate LN at diagnosis and to predict outcome, including the National Institutes of Health (NIH) classification and more recently an index focused on tubulointerstitial compartment changes in addition to features already included in the activity index and the chronicity indexes.

The prognosis of pediatric LN has improved dramatically in the past decade. The current 5-year survival rate for children with LN ranges between 78% and 92% and the 5-year kidney survival from time of diagnosis varying from 44 to 93%.

**DIAGNOSIS**

The heterogeneous nature of lupus can result in a diagnostic challenge for physicians. Since there is not a single symptom or finding that in itself is sufficient for making the diagnosis of SLE, the ACR has developed different criteria that can be useful as general clinical guidelines for the initial assessment of patients with suspected SLE. The guidelines, created in 1982 and updated in 1997 (table 1), combine 11 criteria (clinical and labora-
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It may be challenging to distinguish active inflammation from symptoms due to cumulative organ damage or medication side effects. A thorough history and physical examination, including all major systems, must be undertaken at each clinic visit (table 2). An assessment of disease activity is crucial for undertaking most treatment decisions. Several activity indices have been validated and are depicted in table 3.

### PATHOGENESIS

Although the pathogenesis of SLE remains poorly understood, susceptibility involves a combination of environmental, hormonal and genetic factors. One of the environmental factors that has been involved in lupus is ultraviolet light, which triggers a photosensitive skin rash that may be followed by a generalized disease flare. There is also growing evidence for infections, such as Epstein-Barr virus (EBV) as an initial trigger for lupus-specific autoimmune responses. A higher incidence of EBV infection, higher titers of anti-EBV proteins and an abnormally elevated EBV load have been reported in children and adults with SLE when compared to matched healthy individuals.

**Genetic factors**

The genetic component of the disease is strongly established through epidemiology data, strong familial aggregation of SLE, and the known disease concordance rate in twins. Siblings of SLE patients have an increased relative risk of developing the disease when compared to the general population and monozygotic twins have increased concordance (> 20%) compared with dizygotic twins and other full siblings (2-5%). Through association and genetic linkage studies, over 60 loci, including alleles from the HLA region, region Fc receptors and complement components have been implicated in the immunopathogenesis of SLE. Homozygous deficiency of any of the early components of the classical pathway (C1q, C1r, C1s, C4 and C2) have been linked with an increased predisposition to the development of SLE. Patients deficient in one of the C1-complex or C4 molecule exhibit the strongest prevalence (> 80%) and the most severe disease, while strength of association and disease severity decrease in C2-deficient patients.

**Immune alterations**

It is recognized that SLE can arise through many molecular routes and requires contributions by T cells, B cells, dendritic cells, and nonlymphoid cells at sites of tissue injury. The most commonly recognized immune abnormalities are: the ability to produce pathogenic autoantibodies; lack of T- and B-lymphocyte regulation; and defective clearance of autoantigens and immune complexes by the immune system.

**T cells**

Although numerous abnormalities in T cell functions have been described in SLE, none are common to all patients. There is evidence of T-cell lymphopenia. Many studies report reduction of CD8+ T cells while others report decrease in CD4+ T cells; functional defects, such as decreased cytotoxic activity of CD8+ cells, signaling de-

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**TABLE 2. Suggested routine laboratories and exams for monitoring pediatric systemic lupus erythematosus patients in the outpatient clinic**

<table>
<thead>
<tr>
<th>Each clinic visit</th>
<th>Every 6 months</th>
<th>Every 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>24 h urine test (protein/creat. clearance)</td>
<td>Chest X ray</td>
</tr>
<tr>
<td>ESR and CRP</td>
<td>Anticardiolipins</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Creatinine/Albumin/Electrolytes</td>
<td>Lupus anticoagulant</td>
<td>Chest CT</td>
</tr>
<tr>
<td>Uramyysis (protein/blood/casts)</td>
<td>Phosphatidyl serine</td>
<td>PFTs with diffusion coefficient</td>
</tr>
<tr>
<td>Aldolase/CPK</td>
<td>Apolipoproteins</td>
<td>MRI brain</td>
</tr>
<tr>
<td>Liver function</td>
<td>α2-glycoproteins</td>
<td>DEXA scan</td>
</tr>
<tr>
<td>CH50/C3/C4</td>
<td>PT/PTT</td>
<td>–</td>
</tr>
<tr>
<td>Anti-dsDNA antibody</td>
<td>Lipid profile</td>
<td>–</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Eye exam</td>
<td>–</td>
</tr>
</tbody>
</table>

CBC: complete blood count; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; CT: computerized tomography; MRI: magnetic resonance imaging; PFTs: pulmonary function tests; DEXA: dual-energy X-ray absorptiometry.

**TABLE 3. Instruments used for assessing children with systemic lupus erythematosus**

<table>
<thead>
<tr>
<th>Index</th>
<th>Assessment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECLAM</td>
<td>Global disease activity</td>
<td>10</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>Global disease activity</td>
<td>17</td>
</tr>
<tr>
<td>SLAM</td>
<td>Disease severity</td>
<td>17</td>
</tr>
<tr>
<td>BILAG</td>
<td>Organ-based disease activity</td>
<td>17</td>
</tr>
<tr>
<td>SLICC/ACR</td>
<td>Permanent organ damage</td>
<td>69</td>
</tr>
<tr>
<td>Short Form 36</td>
<td>Health status</td>
<td>70</td>
</tr>
<tr>
<td>CHAQ</td>
<td>Health status</td>
<td>71</td>
</tr>
</tbody>
</table>
flects and diminished ability to reduce autoantibody produc-
tion by B cells; sustained activation and abnormal cy-
tokine production. T cells of SLE patients exhibit ab-
errant responses to stimuli with increased calcium influx
and decreased production of interferon-α and IL-2. SLE
T cells display markers of activation such as increased
numbers of DR+ antigens and are able to facilitate the
production of immunoglobulins by B cells. SLE T cells
seem to use different mechanisms of survival upon co-sti-
mulation than normal T cells. Indeed, microarray profiling
studies have recently shown that activated T cells from
SLE patients resist anergy and apoptosis by upregulating
cyclooxygenase-2 (COX-2) expression, which in turn in-
creases c-FLIP (cellular homolog of viral FLICE inhibitory
protein) and attenuates FAS signaling. Only certain
components of the surface blebs that apoptotic material is normally taken up by immature
dendritic cells and cross-presented to induce T cell tole-
rance. There is evidence that unabated IFN-
production differentiates CD14+ blood monocytes from SLE
patients into mature dendritic cells able to capture dying
cells and present their antigens to autoreactive T and B
cells, leading to a break in tolerance.

Although only a fraction of patients with active disease
show circulating IFN-α, microarray analyses demonstrate
an IFN signature in blood mononuclear cells. These stu-
dies also demonstrated that high doses of glucocorticoids,
broad inhibitors of immune cell function extinguish the
IFN signature. Preliminary studies by Palucka et al show
that they induce the apoptosis of interferon-producing
cells or dendritic cells (Palucka et al unpublished). Glu-
cocorticoids may therefore, act by blocking IFN-α pro-
duction.

**Apoptosis**

A common feature of SLE autoantigens is that they are
components of the surface blebs and they come under
immune surveillance when they arise to the surface of
apoptotic cells. Furthermore, there is increasing evidence
that apoptotic material is normally taken up by immature
dendritic cells and cross-presented to induce T cell tol-
erance. Deficiency in apoptotic cell removal may provide
dendritic cells with an excessive load of nuclear antigens
and consequently develop overt SLE.

Several other factors that are linked to the pathogenesis
of SLE can influence apoptosis such as estrogens, UV
light, infections and autoantibodies themselves.

### TABLE 4. Current treatment for pediatric systemic lupus erythematosus

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Disease flare, major organ involvement</td>
<td>High</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Prevention of disease flares, skin and joint manifestations</td>
<td>Low</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Lupus nephritis, NP-SLE</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cyclophosphamide (CYC)</td>
<td>Life-threatening complications (nephritis, NP-SLE, pulmonary hemorrhage)</td>
<td>High</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Arthritis, lupus nephritis (in conjunction with CYC)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Positive anti-antiphospholipid antibodies</td>
<td>Low</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>Joint manifestations</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Lupus nephritis</td>
<td>High</td>
</tr>
<tr>
<td>Vitamin D and calcium</td>
<td>Prevention of osteoporosis</td>
<td>Low</td>
</tr>
<tr>
<td>Biphosphonates</td>
<td>Osteoporosis</td>
<td>Low</td>
</tr>
<tr>
<td>MMF</td>
<td>Lupus nephritis</td>
<td>High</td>
</tr>
</tbody>
</table>

TREATMENT

Treatment of SLE depends on the clinical manifestations and the presence/absence of major organ involvement (table 4). Corticosteroids are a major cause of morbidity and mortality in pSLE but they continue to be a mainstay of treatment due to their dramatic and rapid impact on lupus flares. Their effectiveness in treating SLE has been recognized since the 1950s. Intravenous (IV) pulse methylprednisolone (MEP) can be successfully used to translate into safer and more efficient treatments for children with SLE (table 5).

Although the prognosis for pSLE has improved over the last few years, pSLE remains a very challenging disease, especially in children with partial response to treatment or treatment resistant who are at a high risk for serious complications. With better understanding of SLE pathogenesis, novel therapies are emerging which will hopefully translate into safer and more efficient treatments for children with SLE (table 5).

BIBLIOGRAPHY


**TABLE 5. New treatments in development for systemic lupus erythematosus**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism of Action</th>
<th>Outcome of Treatments in Humans</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abetimus sodium (LJP 394)</td>
<td>B cell immunomodulator by binding to anti-dsDNA receptors</td>
<td>Serologic and quality of life improvement, minimum reduction of renal flares</td>
<td>72, 75</td>
</tr>
<tr>
<td>CD20 antagonist ( Rituximab)</td>
<td>B cell depletion</td>
<td>Improvement of disease activity, renal function and hemoglobin, ESR and C3</td>
<td>74, 75</td>
</tr>
<tr>
<td>Anti-CD40 ligand antibody (IDEC 131, BG9588)</td>
<td>B cell immunomodulator by affecting B cell autoantibody production</td>
<td>Reduction of anti-DNA antibody, proteinuria, hematuria and SLEDAI, increased thromboembolic events</td>
<td>76-78</td>
</tr>
<tr>
<td>mAb lymphocyte stimulator (Lymphostab B)</td>
<td>Immunomodulator of B cell development and differentiation</td>
<td>Reduction of anti-DNA antibody and immunoglobulins</td>
<td>79, 80</td>
</tr>
<tr>
<td>Recombinant IL-1 receptor antagonist (Anakinra)</td>
<td>Physiologic antagonist to IL-1 receptor</td>
<td>Reduction in joint manifestations, C3 and C4</td>
<td>81, 82</td>
</tr>
<tr>
<td>Anti-IL-10 mAb</td>
<td>IL-10 is a B cell differentiation factor</td>
<td>Reduction in joint and skin manifestations, and SLEDAI</td>
<td>83</td>
</tr>
<tr>
<td>Autologous hematopoietic SCT</td>
<td>Repopulation of bone marrow with healthy hematopoietic stem cells</td>
<td>Improvement of disease activity, organ function, anti-dsDNA titers, 12% mortality, &lt; 50% cure rate</td>
<td>84-86</td>
</tr>
<tr>
<td>Cytotoxic T-lymphocyte antigen 4 (CTLA 4, CD152)</td>
<td>Inhibitory effect on T cell activation</td>
<td>Upcoming trial with SLE patients (no disclosed results yet)</td>
<td>87, 88</td>
</tr>
</tbody>
</table>

mAb: monoclonal antibody. SCT: stem cell transplant.


