Pediatric SLE—towards a comprehensive management plan

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Abstract | Systemic lupus erythematosus (SLE) results from complex abnormalities of the innate and acquired immune systems. For reasons that are currently not well understood, the disease course and phenotype associated with SLE, although quite variable, are generally more severe when the diagnosis is made during childhood. Active disease, infections, lupus nephritis, and neuropsychiatric SLE manifestations are associated with higher morbidity and mortality. Unlike in adult-onset SLE, systemic glucocorticoid therapy and immunosuppressive medications are needed for the treatment of the majority of children and adolescents with SLE. The complex nature of childhood-onset SLE demands a comprehensive, multidisciplinary management approach that considers the patients' growth and development, their educational needs, and the unpredictable course of SLE and its complications.

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that manifests with widely disparate phenotypes. The exact basis and underlying mechanisms of SLE are not fully understood; genetic and environmental risk factors seem to contribute to the development of SLE, involving both the innate and the adaptive immune systems. The terms childhood-onset SLE, pediatric SLE (pSLE) and juvenile-onset SLE are used interchangeably in the medical literature to refer to SLE diagnosed in patients aged 16 years or younger. Disease onset during childhood is observed in 15–20% of all patients with SLE, with onset most frequently diagnosed between the ages of 12 and 14 years and rarely before the age of 5 years. Compared to adult-onset SLE (aSLE), the female preponderance is less pronounced in pSLE, where up to 20% of patients are male.[1] The American College of Rheumatology (ACR) Classification Criteria for SLE,[2] developed to help standardize research in aSLE, are equally accurate when used in pSLE;[3] however, despite the similarities of SLE features across age groups, the marked differences in disease severity between adult and pediatric patients, and concerns about growth, development and iatrogenic damage associated with the long-term use of medications that is necessary when SLE is diagnosed early in life, necessitates a comprehensive, multidisciplinary therapeutic approach to pSLE.

Clinical presentation

Although the principal signs and symptoms of aSLE and pSLE are identical, several studies that directly compared the two clinical presentations revealed a more fulminant disease onset and higher disease activity over time, as substantiated by a higher frequency of renal, neurologic, and hematologic manifestations, when SLE is diagnosed during childhood.[4,5] A comprehensive review of the phenotypic differences between aSLE and pSLE is available elsewhere.[6]

Prognosis

In the 1950s, only 30% of children with pSLE were still alive 5 years after their diagnosis, whereas some current studies suggest 5-year survival rates exceeding 90%.[7] Nonetheless, because of its more severe disease phenotype,[5,8] patients with pSLE continue to have twofold

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Key points

- Disease severity and issues of growth, development, educational and psychosocial needs are some of the features that distinguish pediatric SLE (pSLE) from adult-onset SLE (aSLE)
- Disease indices used to measure disease activity and damage in aSLE have been validated and are used in pSLE
- Patients with pSLE require monitoring for adherence and response to treatment, occurrence of disease flares and damage, as well as health-maintenance issues such as immunizations, bone density and premature atherosclerotic disease
- Patients with pSLE are at a high risk of tissue damage, and require prompt, often aggressive, management
- Research is ongoing to improve the available tests for assessing disease activity in pSLE, especially lupus nephritis
- Treatments for pSLE currently have similar limitations as those for aSLE; however, improvement in our understanding of the B-cell biology of SLE may result in more therapeutic options for pSLE

Box 1 | Disease indices, patient-reported outcomes and response criteria for pSLE

Disease damage
- Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index

Patient-reported outcomes

Physical function and disability
- Childhood Health Assessment Questionnaire (C-HAQ)

Health-related quality of life
- Child Health Questionnaire (CHQ)
- PedsQL Generic Core Module
- PedsQL Rheumatology Module
- Simple Measure of the Impact of Lupus Erythematosus in Youngsters (SMILEY)
- VAS of overall well-being

Fatigue
- Pediatrics Quality of Life Inventory Multidimensional Fatigue Scale

Pain
- VAS

Disease activity
- Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)
- British Isles Lupus Activity Group (BILAG) index
- Systemic Lupus Activity Measure (SLAM)
- European Consensus Lupus Assessment Measure (ECLAM)

Clinically relevant change in pSLE

Improvement criteria for pSLE[26]
- Improvement of 2 of any 5 core variables* by ≥50% without worsening of >1 variable by ≥30% and without increase in proteinuria

Criteria of Global Flares for pSLE[27]
- Flare score‡ ≥ 0.9

*Core variables: physician assessment of overall disease activity; parent assessment of patient overall well-being; global disease activity, as measured by a validated disease activity index; Child Health Questionnaire physical summary score; daily proteinuria. ‡Flare score: (0.45 × change in protein:creatinine ratio) + (0.5 × change in physician assessment of overall disease activity) + (0.02 × change in erythrocyte sedimentation rate) + (0.5 [0.4] × change in SLEDAI [BILAG index]). Abbreviations: PedsQL, Pediatrics Quality of Life Inventory; pSLE, pediatric systemic lupus erythematosus; VAS, Visual analog scale.

higher mortality rates than those with aSLE.[9] The primary risk factors for death or poor outcomes in pSLE are renal disease, severe disease flares, infections, and neuropsychiatric manifestations.[10–12]

Several studies showed that, despite a general lack of comorbid conditions, children with SLE are at a significantly higher risk of damage than adults with SLE.[13] An estimated 58% of children and adolescents will develop some disease damage within 5 years following the diagnosis of pSLE,[14] most frequently in the kidneys.

Avascular bone necrosis (AVN) is a known complication that affects predominantly the large, weight-bearing bones of patients with SLE.[15,16] A 2010 study that directly compared children and adults with SLE during the first year after the initiation of steroid therapy showed that pSLE patients aged 15–20 years are at the highest risk of developing AVN (49%) compared to adults with SLE (41%). Notably, AVN was found to be quite uncommon (6%) in younger pSLE patients.[17] The presence of antiphospholipid antibodies (aPL) or other thrombotic risk factors seems to increase the risk of AVN, and there is ongoing controversy surrounding whether steroid exposure or disease flares are associated with AVN in SLE.[17–21]

pSLE markedly impairs health-related quality of life, especially in patients with constitutional, musculoskeletal or neurological involvement or disease damage.[22] Compared to published norms of healthy children, patients with pSLE have significantly lower physical and psychosocial functioning levels.[22]

Disease indices

Disease activity in pSLE (that is, the degree of the theoretically reversible features of pSLE) cannot be captured by a single laboratory test or gauged by a certain clinical feature. This led to the development of disease activity indices in the 1990s and spurred the quest for biomarkers in recent years.

For both pSLE and aSLE, the most frequently used disease activity indices are the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the British Isles Lupus Assessment Group (BILAG) index. The Systemic Lupus International Collaborating Clinics/ACR (SLICC/ACR) damage index serves as the principal index with which to quantify irreversible disease damage in patients with pSLE or aSLE.[23,24]

Recently, consensus has been reached regarding standardized measures of response to therapy and criteria for global disease flare in pSLE,[25–27] which facilitates the conduct of clinical trials in pSLE (Box 1). The Childhood Health Assessment Questionnaire is a validated measure of physical function and disability in pSLE.[28] The Simple Measure of the Impact of Lupus Erythematosus in Youngsters and the Pediatric Quality of Life Inventory Rheumatology Module are disease-specific health-related quality of life questionnaires.[29] The main generic health-related quality of life measures validated for pSLE are the Pediatric Quality of Life Inventory Generic Core Scale and the Child Health Questionnaire.[22]

Laboratory measures

The current lack of laboratory measures to accurately forecast flares of SLE or predict early response to a given therapy is well documented. Despite initial promising reports of anti-double stranded DNA (dsDNA) antibodies and complement levels in smaller cohorts, more-recent studies indicated that the sensitivity of these tests

may not be much better than the flip of a coin. In 98 patients who experienced 146 flares, Ho *et al.*[30,31] showed that hypocomplementemia and anti-dsDNA antibodies accompanied SLE relapse in only 54% and 27% of patients, respectively. Other studies in lupus nephritis found decreased levels of C3 and/or C4 in 55–95% and anti-dsDNA antibodies in 61–100% of SLE patients concurrently at the time of a renal flare.[32] The sensitivity and specificity for predicting a lupus nephritis flare in these studies was 56% and 74% for a preceding fall in C3, 53% and 65% for a preceding fall in C4, and 53% and 69% for a preceding increase in anti-dsDNA antibodies.

Novel biomarkers of pSLE disease activity

Successes in biomarker discovery over the past 5 years will likely facilitate the management of pSLE in the upcoming years. The three lines of novel biomarkers that are closest to being available to clinicians, pending the results of ongoing biomarker qualification efforts, are cell-bound biomarkers, genomic biomarkers in the blood, and urinary biomarkers (Box 2).

The presence of complement split products bound to erythrocytes, thrombocytes and reticulocytes correlates with disease activity and can serve as a "time capsule" for the recent SLE course, especially with respect to extrarenal involvement.[33,34] Likewise, a Lupus Nephritis Renal Panel has been developed to help measure the degree of active inflammation in the kidneys, and initial studies suggest that these urinary proteins may be able to anticipate impending renal flares.[35–38] The Lupus Nephritis Renal Panel consists of CC-chemokine ligand 2 (also known as monocyte chemotactic protein 1 [MCP1]), neutrophil gelatinase-associated lipocalin (NGAL), hepcidin-20 and hepcidin-25, lipocalin-like prostaglandin D synthetase, alpha-1-acid-glycoprotein (orosomucoid), ceruloplasmin, and transferrin. Chaussabel *et al.*[39] developed a genetic disease activity score that holds great promise for quantifying current disease activity and predicting future flares of pSLE.

Box 2 | Novel biomarkers of pSLE activity

Urinary biomarkers

CC-chemokine ligand 2 (monocyte chemotactic protein-1)

CC-chemokine ligand 5

CX_3C-chemokine ligand 1 (fractalkine)

CXC-chemokine receptor 3

Neutrophil gelatinase-associated lipocalin

Hepcidin-20 and hepcidin-25

Lipocalin-type prostaglandin D synthase

Alpha-1-acid-glycoprotein (orosomucoid)

Ceruloplasmin

Transferrin

Adiponectin

Interferon-gamma-induced protein 10

TNF-like weak inducer of apoptosis

Vascular cell adhesion molecule 1

Tumor necrosis factor receptor p55

Cell-bound complement-activated products

Erythrocyte-bound: C4d, C3d, fragment Bb, complement receptor type 1

Reticulocyte-bound: C4d, C3d, fragment Bb

Platelet-bound: C4d

Genomic Activity Score

Interferon-inducible genes

Neutrophil genes

Interferon-inducible genes

Ribosomal proteins

T-cell proteins

Abbreviation: pSLE, pediatric systemic lupus erythematosus.

Treatment of active pSLE

No medication has been specifically approved for the treatment of pSLE in the USA. Currently, the off-label use of drugs prescribed in oncology and transplant medicine is standard practice, which likely negatively affects patient safety and medication effectiveness as optimal dosing for pSLE is not well established.

Therapeutic approaches to pSLE differ vastly between providers, but several principal approaches, mainly based on eminence, are widely accepted. Unlike aSLE, the majority of patients with pSLE will require glucocorticoids and often immunosuppressive drugs to control disease features.[5] Other key medications currently used for pSLE therapy are summarized in Table 1, while limitations of the contemporary approach to pSLE therapy are exemplified in the following sections.

Hydroxychloroquine

Similarly to aSLE, the current treatment paradigm is to treat all children and adolescents with hydroxychloroquine (HCQ) in an effort to minimize flare, treat skin disease, decrease the rate of autoantibody production, and limit the thrombotic and atherogenic risks associated with pSLE. Daily doses of 5–7 mg/kg are prescribed, and blood levels exceeding 900 ng/ml have been associated with improved symptom control in aSLE.[40] However, our data suggest that only a minority (38%) of adherent pSLE patients mount HCQ levels within the proposed therapeutic range (H. I. Brunner, unpublished data), emphasizing the need to study pediatric populations rather than deducing pediatric dosing from adult data.

Glucocorticoids

The mainstay of treatment in patients with pSLE and major organ involvement is glucocorticoids, mainly oral prednisone, prednisolone, or intravenous high-dose methylprednisolone. Prescription of glucocorticoids varies among providers, but, traditionally—and not based on data from large studies in pSLE—maximum daily doses are 2 mg/kg. Dosages of glucocorticoids are decreased over time and/or prescribed in alternate-day regimens to minimize drug adverse effects.[41] The optimal dosing regimens of glucocorticoids for pSLE remain to

Table 1 | Key medications for the treatment of pSLE

Drug	Suggested dose	Usual maximum dose	Clinical use	Comments
NSAIDs				
Naproxen	10–25 mg/kg per day	1,000 mg orally divided in 2 daily doses	Mild disease	Musculoskeletal disease; needs monitoring for effect on NPSLE and kidneys; avoid when renal damage is present
Ibuprofen	20–40 mg/kg per day	2,400 mg orally divided in 3 daily doses		
Glucocorticoids				
Prednisone	Up to 2 mg/kg per day	80 mg orally per day	Rapid control of moderate-to-severe acute disease symptoms	60 mg daily dose should rarely be exceeded; may be divided in four daily doses if necessary; some patients will require low-dose prednisone for maintenance therapy
Oral methylprednisolone	Up to 2 mg/kg per day	60 mg orally per day		Use in patients with liver involvement
Intravenous methylprednisolone	10–30 mg per dose	1,000 mg per dose		Acute manifestations of NPSLE, kidney, and hematological disease; may be given on 3 consecutive days or less frequently
Immunosuppressives				
Azathioprine	0.5–2.5 mg/kg per day	200 mg orally once daily	Moderate or severe disease	Vasculitis, NPSLE, glomerulonephritis; steroid sparing medications; use is associated with improved outcome of NPSLE, skin disease and kidney disease
Oral cyclophosphamide	0.5–2.0 mg/kg per day	150 mg once daily		Life-threatening organ involvement
Intravenous cyclophosphamide	500–1,000 mg/m^2	2,500 mg per dose		Life-threatening organ involvement
Mycophenolate mofetil	1,200 mg/m^2 per day	2,000 mg orally divided in 2 daily doses		Nephritis; steroid-sparing medication
Rituximab	375 mg/m^2 per dose	4 doses in 1 week intervals		Other dosing regimens have been used
Others				
Hydroxychloroquine	5–7 mg/kg per day	400 mg orally once daily	NS	Mucocutaneous disease, arthritis
Dapsone	2 mg/kg per day	100 mg orally once daily	NS	Skin disease and skin vasculitis
Immunoglobulins	1–2 mg/kg per dose	NA	NS	Hematological disease
Methotrexate	15–20 mg/m^2 per week	25 mg per week	NS	Arthritis (unless kidney disease is present)
Aspirin	81–162 mg per day	NA	NS	aPL-positive patients

Abbreviations: aPL, antiphospholipid antibodies; NA, not applicable; NPSLE, neuropsychiatric systemic lupus erythematosus; NS, not specified; pSLE, pediatric systemic lupus erythematosus.

be elucidated, but tapering to the lowest patient-tolerated dose is generally accepted. Whether discontinuation of prednisone is preferable to maintaining a child on a low dose of prednisone needs further study.[42] The expression of genes regulated by interferon alpha is markedly increased in children with active disease. If one accepts that elimination of this interferon alpha signature is a surrogate for well-controlled pSLE, then intravenous methylprednisolone pulse therapy, rather than oral glucocorticoids, may be the preferred approach to therapy, as suggested by the investigations of Guiducci *et al.* (Figure 1).[43] The findings of this small, single-center study will require confirmation in larger cohorts to establish the efficacy and safety of this treatment in comparison to standard oral prednisone regimens.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) has been intensely studied in aSLE, especially for the treatment of lupus nephritis.[44] MMF may also be useful for treating hematological and dermatological features of SLE, as well as having a steroid-sparing effect. Favorable responses to MMF in uncontrolled studies have led to its frequent use in pSLE[45,46] at a target daily dosage of 1,200 mg/m^2 in divided doses, which is reached after a careful dose increase to monitor for adverse effects. Current research, however, suggests that this strategy will only result in adequate MMF exposure for a minority of children with pSLE, one of the reasons being that there is a 57% inter-patient variability in MMF pharmacokinetics, making body-surface-based dosing a rather crude approach to achieving a suggested exposure to mycophenolic acid (the active metabolite of MMF) of around 45 mg*h/l[47,48]—levels that are associated with a favorable response of pSLE to MMF. There is mounting evidence that optimal MMF dosing warrants full pharmacokinetic profiling, or at least 2 h abbreviated pharmacokinetic studies that are repeated at regular intervals to account for intra-patient changes in MMF metabolism over time.

Cyclophosphamide

Cyclophosphamide is still frequently used for the treatment of lupus nephritis, neuropsychiatric manifestations and life-threatening organ involvement in patients with pSLE. In North America, intravenous cyclophosphamide is preferred, initially using monthly infusion during

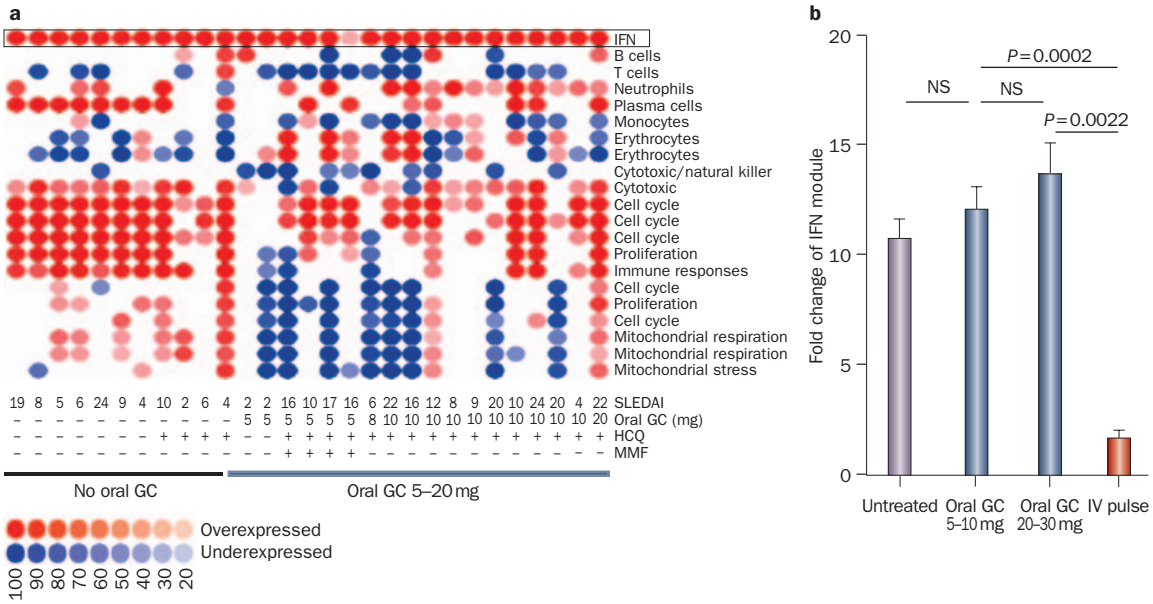

Figure 1 | Effects of glucocorticoid therapy on gene expression profiles in patients with SLE. **a** | Module-level analysis of whole blood from 29 SLE patients either receiving ($n=18$) or not receiving ($n=11$) oral glucocorticoid treatment. SLEDAI scores and other therapies used are indicated at the bottom. **b** | Comparison of IFN module expression levels in pediatric SLE patients receiving no treatment ($n=30$), oral prednisone 5–10 mg daily ($n=29$), oral prednisone 20–30 mg daily ($n=6$) or intravenous pulsed methylprednisolone (3 consecutive doses, $n=6$). Abbreviations: GC, glucocorticoids; HCQ, hydroxychloroquine; IFN, interferon; MMF, mycophenolate mofetil; NS, not significant; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index. Adapted from Guiducci, C. *et al.* TLR recognition of self nucleic acids hampers glucocorticoid activity in lupus. *Nature* **465**, 937–941 (2010).

induction therapy and less-frequent infusions during maintenance therapy. The so-called Euro Lupus regimen (biweekly intravenous cyclophosphamide at a fixed dose of 500 mg for six doses),[49] shown to be effective for the treatment of lupus nephritis in adults, has not been adapted or studied for use in pSLE.

Ovarian damage due to cyclophosphamide therapy is well recognized in adult females with SLE, and gonadotropin releasing hormone (GnRH) agonists seem to be useful for avoiding this treatment complication in adults with SLE.[50] However, the safety, optimal dosing and timing of GnRH agonist injections in relationship to cyclophosphamide infusions for adolescents with pSLE have not been established. This raises the question of whether ovarian protection should be offered at all, as the risk of clinically overt ovarian damage in girls and adolescents with pSLE is much lower than for women with aSLE.[51]

B-cell-targeted therapies

The multiple roles of B lymphocytes in the pathogenesis of SLE have led to the production of several B-cell-targeted therapies that are currently under investigation for the treatment of SLE.[52] A large proportion of B cells can be targeted by the anti-CD20 monoclonal antibody rituximab, as CD20 is expressed on B cells from the pre-B-cell stage through to the development of a subset of antibody-producing plasmablasts. Despite favorable performances of rituximab in preliminary studies, for both adults and children with SLE,[53] clinical trials in aSLE failed to meet their superiority endpoint,[54] suggesting that the benefits of rituximab might be limited to a subgroup of SLE patients with specific clinical and immunological features. To date, no randomized controlled trials of rituximab therapy have been performed in patients with pSLE. Perhaps a combination of B-cell-directed therapies that target B cells at different developmental stages may be preferable for the treatment of SLE. Understanding the similarities and differences of B-cell biology between pSLE and aSLE would aid in the extrapolation of clinical trial results from aSLE to pSLE.[55]

Health surveillance in pSLE

When caring for a child with pSLE, clinicians must remain vigilant to unexpected complications of pSLE and its treatment. These may be life-threatening if timely interventions are not provided. Flares of pSLE are common, and close surveillance of patients at intervals no longer than 2–3 months seems to be warranted. Current standard laboratory tests include CBC with differential, renal and liver panels, erythrocyte sedimentation rate, urinalysis and sediment, and urine protein:creatinine ratio as measured in a random sample, preferably in the first-morning void to exclude orthostatic proteinuria (Box 3). Quantification of urine microalbumin level, as opposed to total protein, may be more specific for glomerular inflammation associated with lupus nephritis.[56] Despite their shortcomings, serial measurement of complement C3 and C4 and anti-dsDNA antibody levels is still advisable. Additional health maintenance and surveillance strategies, including recommended vaccinations shown to be safe and effective in pSLE, are summarized in Box 4.

Box 3 | Laboratory disease surveillance measures

Laboratory testing to monitor pSLE activity

At every visit (at least every 3 months)*
- CBC with differential
- Urinalysis and sediment; urine protein and creatinine (random or morning void)
- Complement components C3, C4
- Anti-dsDNA antibodies
- Erythrocyte sedimentation rate
- Renal and liver panels

Every 12 months
- Autoantibody screening: aPL, anti-ENA antibodies (anti-Ro, anti-La, anti-Sm, anti-RNP)‡
- Vitamin D (25-hydroxyvitamin D)§
- Serum lipid profile§
- Thyroid stimulating hormone and free thyroxin§

Laboratory testing to monitor medication safety

Hydroxychloroquine
- CBC, liver panel and creatine kinase measurement at baseline, 1 month after the start of treatment and then every 3 months; educate about skin hyperpigmentation

Intravenous/oral cyclophosphamide
- Renal panel and complete blood count with differential on the day of infusion; repeat white blood cell count 7–10 days after dose for nadir >3.0×10^3 cells/dl; track cumulative dose; pneumocystitis pneumonia prophylaxis recommended

Rituximab
- B-cell panel prior to therapy and 6–8 weeks after completion of treatment course; if possible, update immunization against encapsulated organisms before treatment; monitor IgG levels and treat hypogammaglobulinemia as necessary

MMF
- CBC with differential and liver function tests at baseline, 1 month and then every 3 months; consider pharmacokinetic profiling to adjust MMF dose

Azathioprine/6-mercaptopurine
- CBC with differential and liver function testing at baseline, 1 months and then every 3 months; consider thiopurine methyltransferase testing

*Additional testing may be warranted according to disease symptoms or manifestations.
‡Repeat tests at regular intervals are not necessary if initial antibody testing is positive.
§More-frequent testing is warranted if findings are abnormal and/or treatment is given.
Abbreviations: aPL, antiphospholipid antibodies; dsDNA, double-stranded DNA; ENA, extractable nuclear antigens; MMF, mycophenolate mofetil; pSLE, pediatric systemic lupus erythematosus; RNP, ribonucleoprotein.

Bone health

The majority of patients with pSLE require long-term exposure to glucocorticoids and are advised to avoid sun exposure—a combination that results in an increased risk of poor bone health. Besides counseling about weight-bearing exercises, and ensuring sufficient calcium and vitamin D intake,[57] attention must be paid to serum levels of 25-hydroxyvitamin D (25[OH]D), which serve as a reflection of total vitamin D exposure—from food, supplements and synthesis. Although 75 nmol/l (30 ng/ml) is often stated as the lower limit of the normal range for 25(OH)D recent recommendations from the Institute of Medicine (IOM) are based on target 25(OH)D levels of 50 nmol/l (20 ng/ml); for children and adolescents aged 1–18 years, the IOM recommends a daily vitamin D intake of 600 IU per day, with an upper limit set at 4,000 IU.[57] Obesity, dark skin pigmentation and use of sun screen, among other factors, are associated with hypovitaminosis D. With respect to calcium, the IOM-recommends an intake for children 9 years and older of 1,300 mg per day, and the upper limit of the daily allowance is set at 3,000 mg.

The use of dual-energy X-ray absorptiometry (DEXA) for supporting the diagnosis and treatment of osteoporosis in pediatric patients is still in evolution. However, in children and adolescents with diseases that may affect the skeleton, DEXA of the lumbar spine and the total body (except the head) is recommended at the time of diagnosis and at 1–2-year intervals for surveillance thereafter, but at least 6 months apart for the monitoring of interventions that affect bone health.[58]

Cardiovascular disease

Although overt cardiovascular damage is rare in patients with pSLE, the disease and its treatment promote the development and progression of artherosclerosis.[13,42] Counseling about the known traditional risk factors for atherosclerosis seems warranted, including weight management, avoidance of smoking, and hyperlipidemia. The results of a clinical trial that assessed the benefits of atorvastatin in reducing the progression of atherosclerosis in patients with pSLE are eagerly awaited.[59] Recent guidelines published by the American Society of Hematology recommend primary prophylaxis with aspirin and HCQ to reduce the frequency of thrombotic events, even in asymptomatic, aPL-positive patients with SLE.[60] Given the favorable safety profile of these medications, this proposed prophylaxis strategy should be strongly considered in pSLE.

Infection

Patients with pSLE are frequently immunosuppressed, leaving them vulnerable to infection. Preventive vaccinations are warranted, but are frequently withheld owing to the possibility of them inducing or exacerbating pSLE. Available data suggest that, with the exception of attenuated live-virus vaccines, immunizations are safe in pSLE, and, although their effectiveness is lower than in healthy children, protection still seems to be sufficient.[61] The annual influenza vaccination with inactivated virus is effective, and is recommended for all children and adolescents with pSLE.[62]

Puberty

Onset and progression of puberty may be delayed in patients with pSLE, but a true absence of puberty is exceedingly rare.[51] Growth failure occurs in about 15% of children with pSLE. Uncontrolled disease activity, exposure to high doses of steroids, and, infrequently, neuropsychiatric SLE manifestations and thyroid disease can result in delayed puberty, poor linear growth and short stature upon entering adulthood.[8,17–20] The safety and effectiveness of growth hormone in pSLE has not been well studied, but may be associated with an increased risk of disease flares.[63,64] Education regarding contraception and reproductive health must be an integral part of clinical care, as many commonly used medications in pSLE, including MMF, methotrexate, cyclophosphamide, angiotensin inhibitors, angiotensinogen receptor blockers and warfarin, are contraindicated during pregnancy.

Self management and standardization of care

Achieving optimum outcomes in chronic diseases requires synergetic interactions between families and patients, society, and medical professionals. Provision of high-quality medical care can be promoted by means of multidisciplinary clinics and standardized treatment plans, which are deduced from the best-available scientific evidence. The consistent implementation of scientific knowledge in daily clinical practice can likely be improved by the measurement and systematic appraisal of quality indicators.[65] As with other chronic diseases, adherence to medications and clinic visits, as well as self-management training, seem to be critical in pSLE.[66,67] Physical therapy, psychological support and dietary services are exceedingly useful for mitigating the untoward effects of pSLE and its treatment. For almost all patients, the burden of pSLE can be decreased by social worker support to assist with school and work adaptation, access to medications and medical providers, with the ultimate goal of transition to adult health care providers.

Conclusions

Although the prognosis of pSLE has markedly improved in recent years, disease control and damage are still worse in children than among adults with SLE. The complexity of the disease, and its profound negative effects on children and adolescents, demands a multidisciplinary approach to treatment. We are in dire need of pSLE therapies for which high quality medical evidence is available, stressing the importance for ongoing clinical research in pSLE. Undoubtedly, the consequent translation of the available scientific evidence and new research findings into the clinical care of children and adolescents with pSLE will improve disease outcomes in years to come.

Review criteria

The references included in this Review were obtained from the authors' collection of articles pertaining to biomarkers, treatment, and health surveillance of systemic lupus erythematosus. A search of the Web of Science database was performed to identify further articles published since 2007.

Box 4 | Clinical disease surveillance, health maintenance and education

At every visit

Disease activity

Physician global assessment of disease

Patient assessment of well-being and pain

Every 12 months

Eye screening
- Especially in patients treated with antimalarial drugs and/or corticosteroids; more frequent if pSLE-associated eye disease and/or keratoconjunctivitis sicca is present

Health-related quality of life
- Use a validated measure; implementation may not be possible in certain clinical settings

Bone health assessment
- Dual-energy X-ray absorptiometry at diagnosis and then every 1–2 years; treat abnormal bone density as per current recommendations

Influenza vaccinations
- Avoid attenuated live-virus vaccine

Review need for other immunizations
- Patients with SLE are at an increased risk for infection by encapsulated organisms: immunizations against pneumococcus, meningococcus and *Haemophilus influenzae* type b are suggested
- Discuss risks and benefits of potential cancer prevention with vaccination against human papilloma virus and hepatitis B; discuss potential risks and benefits of varicella zoster virus vaccination

At least once every 12 months

Review of risk factors for coronary artery disease
- Tobacco use, obesity, hypertension, hypercholesterolemia and family history

Review importance of weight management
- Dietary counseling may be warranted

Assist with exercise regimen
- Physical therapy assessment may be warranted

Review reproductive health issues
- The following are recommended in postpubertal patients: cervical Papanicolaou smear test; contraception assessment; education about teratogenic medications, including mycophenolate mofetil, angiotensin inhibitors, methotrexate and warfarin; pregnancy risks and fertility in relation to clinical features and antibody status

Education about photoprotection
- Rationale and options: use of sun screen, sun avoidance and sun-protective clothing

Abbreviation: pSLE, pediatric systemic lupus erythematosus.

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