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Pediatric Lupus – Are There Differences in Presentation, Genetics, Response to Therapy, Damage Accrual Compared to Adult Lupus?

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Summary

Some complement deficiencies predispose to SLE early in life. Currently, there are no known unique physiological or genetic pathways that can explain the variability in disease phenotypes, as is suggested by studies directly and indirectly comparing cohorts of children and adults with SLE. Children present with more acute illness and have more frequent renal, hematologic and central nervous system involvement at the time of diagnosis compared to adults with SLE. Almost all children require corticosteroids during the course of their disease, and many are treated with immunosuppressive drugs. Despite of a general lack of co-morbid conditions, mortality rates remain higher with pediatric SLE compared to aSLE. Children and adolescents accrue more damage as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, especially in the renal, ocular and musculoskeletal organ systems. Conversely, cardiovascular mortality is more prevalent in adults with SLE.

Keywords

Pediatric SLE; children; lupus; adults; lupus nephritis; complement

Introduction

An estimated 10 to 20% of patients experience the onset of SLE prior to adulthood. More precise estimates are difficult due to a lack of a clear age limit for the diagnosis of pediatric SLE. The maximum age at diagnosis most commonly used to define pediatric SLE is 16 years but ages range from 14 to 20 years in various studies^{1–8}. This review article explores the differences and similarities of pediatric SLE and aSLE, preferably using studies that provide a direct comparison between groups. Issues pertaining to neonatal SLE are not addressed.

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Gender Ratio & Disease Onset

Albeit uncommon, onset of pediatric SLE is described even in children younger than 2 years of age⁹. The female to male ratio with pediatric SLE changes from 4:3 with disease onset during the first decade of life to 4:1 during the second decade to 9:1 in aSLE, and decreases to 5:1 in SLE commencing after the age of 50 years^{10–13}.

Pediatric SLE often presents with more acute and severe disease features than aSLE based on studies providing direct comparisons^{2, 8, 14}. Almost all published research suggests a higher frequency of renal, neurological, and hematological involvement with pediatric SLE than with aSLE at the time of diagnosis^{2, 5–8, 15}. In a Canadian inception cohort of 67 pediatric SLE patients the average disease activity score, as measured by the SLE Disease Activity Index (SLEDAI), was 16.8 at diagnosis but only 9.3 in the comparison group of 131 patients with aSLE ($p = 0.0001$)¹. The most pronounced differences in disease activity between aSLE and pediatric SLE pertain to the renal or neurological organ systems¹⁶.

Despite widely variable estimates, fever and lymphadenopathy are more frequently described with pediatric SLE than aSLE in studies directly comparing both groups (*see* Table 1). Conversely, adults with SLE more commonly present with arthritis than children with SLE^{2, 4, 17}. When comparing pre-pubertal to post-pubertal onset of pediatric SLE, the former group presents more often with hemolytic anemia and renal involvement whereas in the latter group cutaneous and musculoskeletal features are more common at disease onset^{9, 18}. As with aSLE, about one third of the children and adolescents with SLE present with anemia, thrombocytopenia, or lymphopenia at the time of SLE onset^{19–21}. On the contrary, leukopenia is more common in pediatric SLE than aSLE at onset (31 to 35% vs. 18%)^{19–20, 22}, and 49% of children with SLE as compared to 18 to 65% of aSLE patients will test Coombs' positive at the time of diagnosis^{19, 21, 23}. Equally frequent in pediatric SLE and aSLE at the time of initial presentation (5 to 20%) are anti-Smith, anti-ribonucleoprotein, anti-Ro, and anti-La antibodies as is suggested by one study².

Disease Course

Besides significantly more active disease at the time of disease onset, there is also more active disease over time with pediatric SLE when compared to aSLE^{1, 8}. In the Canadian study previously mentioned, the average time-adjusted mean SLEDAI score was 5.7 with pediatric SLE but only 4.6 with aSLE ($p = 0.012$)¹. Similarly, there was a trend towards more active disease during the course of the disease in adolescent-onset SLE patients (SLE onset between age 13 and 18 years) recruited to the Lupus in Minorities (LUMINA) study than in those with aSLE⁸.

At least five contemporary cohorts provide a direct comparison of disease features and laboratory abnormalities with pediatric SLE and aSLE over time. Specific details are presented in Table 2 and Table 3^{2, 4–5, 17, 24}. The variability in the estimates between studies may be a reflection of sample sizes or recruitment criteria but true divergence of SLE features due to race, ethnicity, specific environmental or health milieus are likely important as well. For this review we excluded some earlier studies that compared pediatric SLE to historic aSLE cohorts or research not designed to allow for the delineation of statistically significant differences between the groups^{7, 25}.

Mucocutaneous and Musculoskeletal Manifestations

When directly comparing pediatric SLE to aSLE inflammatory rashes, including the typical malar erythema, are significantly more frequent in children than adults^{2, 5, 24}. Exceptions are photosensitivity and discoid skin lesions which are more prominently found with aSLE. Indeed,

isolated discoid lupus erythematosus (DLE) is uncommon in childhood, with less than 5% of all DLE cases reported in patients under the age of 15 years^{2, 26}. Lesions of DLE in children are indistinguishable from those in adults but children with DLE suffer less often from photosensitivity, and there is a less pronounced female predominance. Conversely, children with DLE more often have a positive family history of DLE or SLE and, more importantly, 25 to 30% of the children with DLE will progress to SLE as opposed to only 5 to 10% of adults^{26–27}.

Painful non-erosive arthritis and arthralgias are common in both aSLE and pediatric SLE. There may be a trend towards more overt arthritis with pediatric SLE, while arthralgias and myalgias appear to be more frequently encountered in aSLE^{2, 4–5, 24}. Whether differences in the frequencies of subjective musculoskeletal features between groups are related to the underlying disease or are a reflection of more common joint symptoms in adulthood remains to be determined. Jaccoud's arthropathy²⁸ and drug-induced myopathy, however, are more often described with aSLE^{29–30}.

With a reported prevalence of about 40%, osteopenia (z-scores less than -1 or -1.5) is quite common in pediatric SLE, and osteoporotic fractures occur in 6% to 10% of the children^{31–32}. This compares to reports of osteopenia at 40% and osteoporosis at 5% in premenopausal women with aSLE; much higher estimates are provided for aSLE cohorts that include postmenopausal patients^{33–34}.

Traditional risk factors for osteoporosis that contribute to impaired bone health in aSLE are unlikely important in pediatric SLE³⁵. Possibly due to inflammation, corticosteroid use, reduced physical activity, inadequate sun exposure, and low calcium and vitamin D intake, children and adolescents with SLE are often unable to reach their peak bone mass^{103,130,199}. For reasons not fully understood, there is a higher prevalence of vitamin D deficiency in children and adults with SLE as compared to the general population³⁶.

Lupus Nephritis

Lupus nephritis (LN) is often a presenting feature of pediatric SLE². In comparative studies of pediatric SLE and aSLE, the prevalence of LN in adults with SLE is at 34 to 48%^{19, 24, 37}. Despite large variations between racial groups, most studies report LN to be present in 50 to 67% of the children, at a higher frequency than with aSLE^{17, 19, 24, 37}. Consequently, proteinuria and urinary cell casts during the disease course are more common with pediatric SLE than aSLE⁴. A study by Brunner et al. supports a similar distribution of LN histological classes in pediatric SLE as compared to aSLE¹, with diffuse proliferative LN (Class IV) occurring in 40 to 60%, focal proliferative LN (Class III) in 10 to 20%, and membranous LN (Class V) in 3 to 28% of pediatric SLE patients with renal disease³⁸. Overlap between proliferative and membranous changes are reported in 12% of the cases on initial kidney biopsy³⁸. Hypertension occurs in 40% of pediatric SLE patients with LN^{3, 8, 39–40}, and African-American children, particularly boys, may have a significantly higher risk of hypertension than Caucasians.

Neuropsychiatric SLE

Lack of specific laboratory tests and imaging modalities make the diagnostic process of neuropsychiatric involvement with SLE (NPSLE) difficult in children and adults with SLE. The types of NPSLE syndromes are similar in pediatric SLE and aSLE^{41–42}.

NPSLE is at least as common in children as it is in adults^{43–46}. Within the first year post diagnosis, 70% of the children, as compared to only 28% of adults, develop features compatible with NPSLE^{47–48}. Depression is the most common mood disorder in children and adults

without apparent differences in prevalence between groups^{4, 41–42}. The Grupo Latino Americano de Estudio del Lupus (GLADEL) cohort reported a significantly higher prevalence of pseudotumor cerebri, transient ischemic attack, and seizures in their pediatric SLE cohort when directly compared with aSLE⁸. Despite a general lack of comorbid conditions, cerebrovascular disease is reported in up to 25% of children with NPSLE, and may be more common than in aSLE^{4, 24}. Approximately 20% of children with NPSLE will develop psychosis which usually presents with visual hallucinations^{45, 49}. Psychosis, chorea, or any type of encephalopathy occurs preferentially with pediatric SLE^{2, 8, 44, 50}. Cerebral vein thrombosis is reported in 15 to 25% of the children with SLE, often presenting with severe headache in lupus anticoagulant (LAC) positive patients⁵¹. Conversely, cranial nerve abnormalities are more frequently encountered in aSLE than pediatric SLE⁸.

Neurocognitive dysfunction is reported in as many as 30 to 60% of all children with SLE^{43–45, 52}. This wide range of numeric estimates reported in the literature is likely due to differences in design and case ascertainment between studies. Nonetheless, neurocognitive dysfunction appears to be similarly widespread among children and adults with SLE¹⁶. The 1999 ACR case definitions of NPSLE have not been validated for use in children and adolescents, and the proposed 1-hour ACR battery of standardized tests to assess neuropsychiatric function is not suited for use in pediatrics⁵³. More recently an alternative battery for children has been developed⁵⁴.

Cardiopulmonary & Gastrointestinal Involvement

Pericarditis is the most commonly diagnosed cardiac manifestation of SLE and presents in about 17 to 33 % of SLE patients, irrespective of age⁵⁵. Symptomatic coronary artery disease and myocardial infarction are both exceedingly rare in children and adolescents with SLE⁵⁶. Conversely, clinically recognizable coronary artery disease is reported in 6 to 9% of adults with SLE, and ischemic heart disease remains a major factor for morbidity and mortality in aSLE^{57–58}. Symptomatic and asymptomatic pulmonary manifestations are described in up to 60% of the children and adolescents with SLE⁵⁹, which compares to estimates of 20 to 90% in aSLE^{60–61}. In studies directly comparing children and adults with SLE, there is a trend towards more common occurrence of pleuritis with aSLE^{2, 4–5, 24}. Among the most common pathological features reported in both pediatric SLE and aSLE are restrictive lung defects and impaired diffusion capacity⁶². Shrinking lung syndrome, e.g. restrictive lung disease combined with diaphragmatic paralysis, is a rare complication of SLE with less than 150 cases in adults and fewer than 10 cases reported in pediatrics^{63–64}. Pulmonary hemorrhage is still linked to high mortality rates in children and adults with SLE⁶⁵.

The frequency of ascites in pediatric SLE is comparable to that in aSLE. Adults with SLE are commonly diagnosed with conventional age or medication related abdominal pathology^{66–67}, while in children symptoms are more often due to SLE itself⁶⁸. In a review of 175 adults hospitalized for aSLE, 22% presented with acute abdominal pain, which was due to aSLE in 44% of the cases⁶⁷. Conversely, some abdominal pain was reported in 19% of 201 French children with SLE⁶⁸. In this review in 87% of the cases the gastrointestinal pathology was attributed to pediatric SLE⁶⁸.

Distinguishing surgical from non-surgical cases of acute abdomen is challenging, especially in children with SLE. Acute onset of even mild abdominal pain and low-grade fever in an otherwise well-controlled patient on immunosuppressive medications may be due to bacterial peritonitis. Abnormalities on ultrasound are present in about half of the children with SLE with abdominal pathology, while abnormalities on computer tomography are seen in 80% of the cases⁶⁸.

Hematologic Manifestations

Chronic disease is the most common cause of anemia in both pediatric SLE and aSLE. There is a higher incidence of anemia in the very young, affecting 77% of patients with infantile SLE, i.e. SLE with onset prior to age one year, as compared to only 35% of children older than one year at onset of pediatric SLE⁹. Anemia in pediatric SLE is usually of a mild to moderate degree and normochromic normocytic but becomes microcytic and hypochromic over time⁴³.

Hemolytic anemia is more prevalent in pediatric SLE than aSLE as is suggested by several studies comparing pediatric SLE to aSLE^{2, 4, 24}.

With a reported prevalence between 42 and 74% during the course of the disease, leukopenia occurs with similar frequency in pediatric SLE and aSLE^{4, 24}. Leukopenia may be less frequent in young children with SLE as compared to pediatric SLE with onset at or after puberty⁹.

Lymphopenia is as common with aSLE as it is with pediatric SLE over time. It changes with disease activity, is correlated with anti-double stranded DNA antibodies levels, and is associated with NPSLE and mucocutaneous involvement in pediatric SLE and aSLE⁶⁹.

Neutropenia is similarly frequent in aSLE and pediatric SLE, occurring in about 12 to 15% of children and 4 to 20% of adults. Neutropenia has been associated with thrombocytopenia and NPSLE in both pediatric SLE and aSLE^{19, 70}. Overall the prevalence of thrombocytopenia appears to be somewhat higher in pediatric SLE than aSLE^{4, 24}. Thrombocytopenia occurs in about two thirds of children with infantile SLE and in 25 to 30% of pediatric SLE patients with disease onset later in life⁹. Low platelet counts are associated with the presence of antiphospholipid (aPL) and anti-platelet autoantibodies.

Prior to developing pediatric SLE, children and adults with thrombocytopenia may have carried a diagnosis of idiopathic thrombocytopenic purpura (ITP)⁷¹. In a study by Pamuk et al., six of 321 adults (2%) with ITP developed aSLE during a 4-year follow-up time⁷². In this cohort, 27% of the adult patients with ITP tested positive for antinuclear antibodies (ANA). In contrast, in a single retrospective study of 365 Turkish children with ITP, ANA titers of 1:80 or higher were present in 9% of the children but none developed pediatric SLE during the mean follow-up of 3.6 years⁷³. However, given the low frequency of ANA positivity in the cohort, any potentially increased risk of ANA positive individuals to develop pediatric SLE might have been missed, and the observations from Turkey may not be typical for other parts of the world. In our experience, careful follow-up is warranted for any child with ITP who is found to have ANA at high titers.

Hemolytic uremic syndrome or thrombotic thrombocytopenic purpura (TTP) are rarely features of the initial presentation of pediatric SLE^{74–75}. ANA positivity and high grade proteinuria at the time of presentation are both risk factors for children with TTP to subsequently develop pediatric SLE⁷⁴. Based on a systematic review of the literature, at least 35% of children with TTP will subsequently develop pediatric SLE which compares to only 2 to 3 % among adults with TTP^{74, 76}.

Although it has been described in all age groups, macrophage activation syndrome may be more common, or at least more recognized, in pediatric SLE than aSLE^{77–78}. The morphologic features in the bone marrow of pediatric SLE and aSLE with macrophage activation syndrome are indistinguishable from those with other causes. Bone marrow dysplasia has been described in both pediatric SLE and aSLE⁷⁹.

Antiphospholipid Antibody & Sjogren's Syndromes

The prevalence of anti-cardiolipin (aCL) antibodies and LAC appears similar in groups of adults and children with SLE⁹. Thrombosis in patients who test positive for aPL antibodies is,

however, more common in aSLE than pediatric SLE, likely reflective of underlying co-morbidities and longer disease duration in adults⁸⁰. In a cross-sectional Canadian cohort study, children with SLE who tested persistently positive for LAC had a 28-fold increased risk of experiencing a thrombotic event compared to those without LAC⁸¹. About one third of pediatric SLE patients with aPL syndrome will experience recurrent thromboses within 13 months of the initial event, especially if anticoagulation is discontinued or when there are other predisposing thrombophilic factors⁸¹.

While 6.5% of all aSLE patients have Sjogren's syndrome, it is less common in children with SLE (Table 2). Although a case series (n=34) from Japan reports that 41% of the children with SLE have secondary Sjogren's syndrome, the prevalence of Sicca syndrome at 3.9% in pediatric SLE vs. 9.3% in aSLE was considerably lower in the much larger GLADEL cohort^{24, 82}. Primary, as opposed to secondary Sjogren's syndrome, is very rare prior to adulthood. In a cohort study of 180 children with primary pediatric Sjogren's syndrome, the mean age at diagnosis was 9.8 years⁸³. Common clinical manifestations of pediatric Sjogren's syndrome are bilateral parotid swelling, which is present in 70% of the cases. Extraglandular manifestations were reported in 5% of the children in one series of patients with pediatric Sjogren's syndrome. ANA positivity is less frequently observed in children than in adults with Sjogren's syndrome⁸⁴.

Endocrine Abnormalities

Types of endocrine aberrations are comparable in adults and children with SLE⁸⁵. An estimated 50 to 85% of pediatric SLE and aSLE have dyslipidemia^{86–87}. Pro-atherogenic lipid profiles in children and adults with SLE exist even prior to commencing steroid therapy^{86–88}. Low density lipoprotein (LDL) particles are smaller with active compared to inactive disease in pediatric SLE and aSLE, contributing to their atherogenicity^{89–90}. Compared to healthy controls, both adults and children with SLE have higher insulin levels which, if persistent, are associated with metabolic syndrome^{91–92}. There may be higher rates of diabetes in aSLE compared to pediatric SLE^{1, 7}.

Autoimmune thyroid disorders are associated with SLE and present in about 15 to 20% of the patients without apparent differences in prevalence between adults and children^{93–94}.

There is a trend towards higher levels of follicle stimulating hormone, luteinizing hormone, and prolactin in cSLE patients compared to healthy children^{95–96}. Elevated prolactin levels occur in subsets of pediatric SLE and aSLE patients with active disease, especially those with NPSLE^{96, 97}.

Menarche in females with pediatric SLE is, on average, delayed by one year. The delay in puberty progression increases with longer disease durations and the higher cumulative doses of corticosteroids used for treatment ($R^2 > 0.3$; $p < 0.009$)⁹⁸. Transient or permanent amenorrhea has been reported in 12% of 298 adolescents with pediatric SLE and is positively correlated with both the presence of disease activity and damage. Ovarian failure is a well-known complication of intravenous cyclophosphamide therapy in aSLE. The risk of ovarian failure after cyclophosphamide is considerably lower in pediatric SLE than in aSLE^{99–100}. Based on limited information from case series, the average risk of premature ovarian failure is 11% in females with pediatric SLE who are younger than 21 years of age^{98, 101–102}. In a cohort of 77 patients with pediatric SLE, of whom 47% were treated with cyclophosphamide, a reduced ovarian reserve, but not overt ovarian failure, was observed in 31% of the females who were treated with cyclophosphamide¹⁰². Different from aSLE, ovarian protection has not been studied in pediatric SLE but a randomized trial of a gonadotropin-releasing hormone agonist is ongoing to assess the benefits and risks of transient ovarian suppression¹⁰².

As with aSLE, semen abnormalities, low testicular volumes, and high gonadotropin levels all appear to be more frequent in males with pediatric SLE than their healthy peers, especially following cyclophosphamide therapy with initiation after the onset of puberty^{103–104}. Sertoli cell dysfunction is more common in pediatric SLE males than in healthy adolescents. Semen abnormalities are more common with immunosuppressive use, especially with cyclophosphamide¹⁰⁴.

Immunological Features

As with aSLE, circulating ANA are the hallmark of pediatric SLE, and present in virtually all children¹⁰⁵. An estimated 30 to 50% of children referred to pediatric rheumatologists who test ANA positive have a musculoskeletal pain syndrome and not pediatric SLE¹⁰⁶. In a retrospective study of 110 children who tested positive for ANA, 10 children eventually developed pediatric SLE after follow-up of up to four years. The median ANA titer of the children who developed pediatric SLE was 1:1,080¹⁰⁷, while ANA titers of 1:320 or lower appeared not to confer a sizeable risk for the subsequent development of pediatric SLE¹⁰⁷.

Most studies that directly compare pediatric SLE to aSLE suggest that elevated levels of anti-double stranded DNA (anti-dsDNA) antibodies to be more common in pediatric SLE than in aSLE (61 to 93% vs. 25 to 78%)^{2, 4–5, 17, 24}. An estimated 92% of children with infantile SLE test positive for anti-dsDNA antibodies⁹. As with aSLE, changes in the levels of anti-dsDNA antibodies are used to monitor disease activity in pediatric SLE¹⁰⁸. There are conflicting reports as to whether anti-dsDNA antibodies and complement levels are predictive of future pediatric SLE or aSLE flares¹⁰⁹. Although traditionally viewed to be specific to SLE, anti-dsDNA antibodies can be present with autoimmune hepatitis, Epstein Barr virus infections, rheumatoid arthritis, and very rarely, in healthy people¹¹⁰.

Besides anti-dsDNA antibodies, anti-histone and anti-ribosomal P antibodies are all more frequently encountered in pediatric SLE than aSLE⁴. Anti-ribosomal P antibodies are elevated in 25 to 42% of the patients with pediatric SLE⁴ compared to only 6 to 11% of the patients with aSLE^{4, 47, 111}. One study directly comparing pediatric SLE and aSLE for the presence of anti-histone antibodies suggest a significantly higher prevalence in the former than the latter, 39% and 26% respectively⁴.

The prevalence of anti-Smith (Sm), anti-ribonucleoprotein (RNP), anti-Ro/SSA and anti-La/SSB antibodies appears not to differ between pediatric SLE and aSLE⁴. Anti-Sm antibodies are present in up to 51%, anti-RNP antibodies in about 37%, anti-Ro antibodies in 33%, and anti-La antibodies in 15% of pediatric SLE patients during the course of their disease, respectively^{2, 4–5, 16–17, 24}. The disease association of the antibody clustering in pediatric SLE may be different from that observed in aSLE¹¹². Similar to what has been reported in aSLE, there are ethnic variations in the frequency of auto-antibodies with pediatric SLE; anti-U1RNP and anti-Sm antibodies occur more frequently in non-Caucasian patients with pediatric SLE^{112–113}. Despite a lack of comparative studies, the frequency of anti-nucleosome antibodies appears comparable in aSLE and pediatric SLE^{114–115}. The Rheumatoid Factor (RF) is positive in 5% of the pediatric SLE patients at diagnosis and in 10 to 54% of them over time, exceeding the frequency at which RF is reported in Juvenile Idiopathic Arthritis^{2, 5, 7, 17}. A comparative study of aSLE and pediatric SLE suggests a trend towards more common RF positivity among adults at both diagnosis and during the course of the disease².

Genetics

There is limited knowledge about the relative risk of children of different races to develop SLE. However, as with aSLE, non-Caucasian children appear to be at a higher risk of being diagnosed with SLE. Genetic studies in pediatric SLE provide, for the most part, confirmation of genetic

variants reported in aSLE and presently do not explain differences in disease presentation, activity, and outcomes between pediatric SLE and aSLE^{21, 116}.

Congenital complement deficiencies are present in about 1% of patients with SLE¹¹⁷. The closest association between SLE and complement deficiencies is seen with C1q deficiency, where there is a risk of over 90% to develop a lupus-like illness early in life^{117–118}. Deficiency of C1q is a rare condition with only about 50 cases reported in the literature. Other complement deficiencies include homozygous C4 deficiency with a 75% association rate with SLE¹¹⁹ and C1s or C1r deficiency which has a 50% association rate with SLE, again with onset early in life. Homozygous C2 deficiency is present in 1/10,000 to 1/30,000 Caucasians, and 10 to 30% of them may develop SLE¹¹⁷.

The Major Histocompatibility Complex (MHC) Class II and III alleles have long been implicated in conveying risk for developing SLE. HLA DRB1*15:03, DRB5*01:01, DQA1*01:02, DQB1*06:02 are more common in American Blacks with SLE, independent of age at disease onset¹²⁰. HLA DRB1*03:01, DQA1*05:01, and DQB1*02:01 are more common in Caucasians with SLE, again independent of age at disease onset¹²¹. Non-MHC loci that have been associated with pediatric SLE and aSLE are the 1858T single nucleotide polymorphism (SNP) of PTPN22, a gene which encodes for the enzyme lymphocyte phosphatase (Lyp) and inhibits T-cell activation^{116, 122–123}. A polymorphism (–28C/G polymorphism) of the RANTES (also CCL5) gene also has been associated with aSLE, and its importance was confirmed in a study of Chinese children with SLE¹²⁴. A genome-wide scan in children and adults proposed that susceptibility to SLE is conveyed by the N673S polymorphism of the P-selectin gene (SELP), a cell adhesion molecule expressed on activated endothelial cells, and of the C203S polymorphism of the interleukin-1 receptor-associated kinase 1 gene (IRAK1), which is involved in the signaling cascade of the toll/interleukin-1 receptor family¹²⁵. Another SNP, PD1.3G/A, located within the regulatory area of the programmed cell death 1 (PDCD1) gene, is also a proposed susceptibility locus of aSLE and pediatric SLE from Mexico¹²⁶.

Therapy

Treatment approaches to pediatric SLE and aSLE vary across centers and are largely determined by organ involvement, disease activity and damage, access to medications, and institutional preferences^{18, 127}. Comparative studies of adults and children support that pediatric SLE is more often treated with high doses of corticosteroids and immunosuppressive medications than aSLE (*see* Table 4). When comparing therapies of patients treated at two Canadian tertiary hospitals, children with SLE were more often prescribed oral corticosteroids than adults (97% of 67 pediatric SLE patients vs. 70% of 131 aSLE patients)¹. In the same study, children with SLE were treated with intravenous methylprednisolone almost three times more often than adults¹. This is similar to what has been reported from a cohorts of 90 pediatric SLE and 795 aSLE patients managed in the United States (U.S.)³, but no important differences in steroid use between aSLE and pediatric SLE were noted by others^{2, 8}.

More frequent utilization of any immunosuppressive medication with pediatric SLE compared to aSLE is reported by several investigators^{1–3, 16}, although the types of immunosuppressive drugs prescribed appear not to differ between children and adults, except for a more common use of methotrexate in aSLE than pediatric SLE (31% vs. 9%)¹.

There is a trend towards a more frequent administration of intravenous cyclophosphamide in the adolescent-onset group compared to aSLE in the LUMINA cohort⁸. How the increasing use of rituximab in recent years has affected overall medication profiles in pediatric SLE and aSLE is unknown at this point.

Patients with SLE of all ages older than 6 years are equally likely to be prescribed antimalarials^{1, 3}. Adults and children with SLE are comparable in their use of non-steroidal anti-inflammatory medications^{2–3}, except for cyclooxygenase 2 inhibitors which appear to be less commonly prescribed to children and adolescents³.

Corticosteroids, intravenous immunoglobulins, dapsone, vincristine, and various immunosuppressive medications have all been used to treat SLE-associated thrombocytopenia in both children and adults. Successful therapy of chronic treatment-resistant hemolytic anemia and thrombocytopenia in pediatric SLE with rituximab is reported from a single center; no serious infections were observed, despite prolonged B-cell depletion¹²⁸.

Children and adolescents with NPSLE appear to have an excellent response to treatment, and the majority of them will experience a resolution of symptoms. As with NPSLE in adults, high dose glucocorticoids, often combined with immunosuppressive medications including cyclophosphamide, are the mainstays of NPSLE treatment of children^{44, 129}. For NPSLE-associated cerebral vein thrombosis or arterial strokes anti-coagulation is added to the anti-inflammatory drug regimen¹³⁰. There are no longitudinal randomized studies addressing target parameters for anticoagulant therapy or anti-thrombotic prophylaxis in pediatric NPSLE. Academic delays of children and adolescents with NPSLE have not been quantified but are likely considerable. Educational interventions and psychological support appear important for children with NPSLE, based on studies in aSLE¹³¹.

Treatment of LN in pediatric SLE is adapted from protocols used in adults. As with aSLE the best induction and maintenance therapy for pediatric SLE-associated LN remains to be determined^{132–133}. In children with severe LN cyclophosphamide use is associated with better renal survival compared to corticosteroids therapy alone¹³⁴. Lehman et al. treated 16 patients with Class III or IV LN with monthly intravenous pulse cyclophosphamide for six months, followed by three monthly infusions for a total of 36 months. A significant reduction of proteinuria, disease activity, and prednisone dosage at one year post initial diagnosis was observed as well as improvement of LN on re-biopsy. No significant treatment complications were reported by this group during the 3-year study¹³⁵. The combination therapy of cyclophosphamide and methotrexate for refractory Class IV therapy in children with SLE has been suggested but is rarely used in pediatric or adults clinical practice, given its potentially severe side effects¹³⁶.

Different from aSLE, there are no randomized trials of mycophenolate mofetil for specifically pediatric SLE treatment. The efficacy and safety of mycophenolate mofetil in controlling LN in children has been reported: in a case series mycophenolate mofetil was effective in five of thirteen patients (38%), partially effective in four (31%), and ineffective in four (31%). No severe side-effects were observed¹³⁷.

Some studies suggest that proliferative LN in children progresses in 9 to 15% of the cases to end-stage renal disease within 5 years^{38, 138}, which is comparable to what has been reported from some aSLE cohorts¹³⁹. LN accounts for 3% of end-stage renal disease leading to kidney transplantations among children in North America¹⁴⁰, while adults with SLE account for 1.9% of the adult kidney transplant population, based on the U.S. Renal Data System.

A review of the North American Renal Transplant Cooperative Study database supports 1-year graft survival rates with pediatric SLE at 91% after living donor, and 78% after cadaveric transplants. This compares to estimates of graft survival in aSLE at 88% at one year, and 67% at five years. In both aSLE and pediatric SLE kidney graft survival is similar to that with other adult or pediatric diseases^{139, 141–142}.

Prognosis and Survival

Delay in aSLE diagnosis is associated with higher mortality and a reduced likelihood of achieving remission¹⁴³. In adults with SLE remission for 1-year is reported in as many as 6.5% of the patients¹⁴⁴. Conversely, despite a lack of firm estimates, remission is exceedingly rare in pediatric SLE in North America³.

Historically, children and adolescents have higher mortality rates and are perceived to encounter more disease damage than adults with SLE^{1, 8}. The 5-year survival rates have improved in pediatric SLE from 30–40% in 1950's, to over 90% in the 1980's^{145–147}. Similarly survival has much improved with aSLE¹⁴⁸. In both aSLE and pediatric SLE recent 5-year survival rates well over 90% are reported from developed countries^{149–152}. Nevertheless, in the LUMINA cohort, there is an almost 2-fold higher mortality with adolescent-onset SLE than with aSLE (19.4% vs. 10.4%, $p=0.37$)²⁴.

Major causes of death in pediatric SLE and aSLE include renal disease, severe disease flares, and infections^{146–147, 153–154}. While NPSLE is a risk factor of poor outcome in pediatric SLE, cardiovascular disease remains an important cause of death in aSLE. There is an ongoing controversy as to whether age at SLE onset constitutes a risk factor for poor disease outcome (*see* Table 5)^{18, 39, 155}. Male sex, Black race, low socioeconomic status, thrombocytopenia, disease damage, and non-adherence to treatment, have all been linked with worse survival^{149, 156–157}. Non-adherence to visits and medications is a universal challenge for SLE patients of all ages. In a single center study, 39% of 55 adolescents and adults with SLE were non-adherent (adherence rates less than 80%) to prednisone and 51% to hydroxychloroquine, based on pharmacy refill data¹⁵⁸. Significant risk factors of insufficient adherence included being single, low educational level, and presence of other comorbidities but not age at disease onset. Initial study suggests text messaging to be a promising venue to enhance adherence to pediatric SLE therapies¹⁵⁹.

Despite improved survival rates in SLE patients of all ages, there remains substantial morbidity due to disease damage^{160–161}. In aSLE, increasing age and longer duration of disease are correlated with disease damage. About 50 to 70% of adults with SLE will have accrued some disease damage at 10 years post diagnosis^{149, 162}. In a study of 1,015 pediatric SLE patients from 39 countries, 40% of the children acquired some disease damage during mean disease durations of four years. This percentage increased to 58% in those with disease durations of over five years¹⁶³, with similar results reported by others^{16, 18}.

Statistically significant differences in the development of damage between aSLE and pediatric SLE were noted in the past. Comparison of Canadian inception cohorts found children with SLE to have mean SLICC/ACR damage index scores of 1.7 and adults of 0.76, respectively¹. Ocular and musculoskeletal damage were statistically more common in children but there was a trend towards higher rates of malignancy with aSLE (Table 5)¹. In the LUMINA cohort there was a trend towards higher rates of any disease damage in the adolescent-onset group as compared to the aSLE group (mean SLICC/ACR damage index score at last available visit, 2.3 vs. 1.6)⁸, and renal damage was significantly less frequent in those with disease onset in adulthood ($p = 0.023$). In the LUMINA cohort, patients with diagnosis during adolescence also had a trend towards more neuropsychiatric, ocular, and musculoskeletal damage but there were more diabetes and peripheral vascular damage in those with disease onset during adulthood⁸.

Cost of Care

Cost of care is considerably higher in children than adults with SLE^{164–165}. The estimated economic burden of pediatric SLE ranges from \$146 to \$650 million annually in the U.S.¹⁶⁴.

In a study utilizing administrative databases from two tertiary pediatric rheumatology centers in the U.S., the annual cost of care of pediatric SLE was \$14,944 (cost basis: 2000), excluding outpatient medication expenses. Cost was accrued mostly by hospitalizations (28%), laboratory testing (21%), and outpatient clinic visits (20%), while emergency department visits contributed to only 1% to the total cost of care. Renal replacement therapy, although required for only three of the 119 children, constituted 11% of the total cost. Previous studies examining the cost of health services in aSLE used a slightly different valuation system than that used for the above mentioned study in children. Nonetheless, using a conservative estimate, the direct cost of care for a child with SLE appears to be roughly three times higher than for an adult. Whether this difference in cost between adults and children is due to differences in health care delivery systems, adherence to therapies, or differences in disease severity remains to be determined¹⁶⁶.

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Table 1
Clinical and Laboratory Features in Pediatric SLE (pedSLE) and Adult SLE (aSLE) at Disease Onset ^a

Study	Carreno 1999 ^a				Font 1998 ^b			
	pedSLE n=49	aSLE n=130	p-value	pedSLE n=34	aSLE n=396	p-value		
Fever	20	15	NS	41	21	0.006		
Lymphadenopathy	-- [†]	--	--	6	0.5	0.03		
Malar rash	22	16	NS	44	35	NS		
Discoid lupus	--	--	--	0	3	NS		
Subcutaneous cutaneous lupus	--	--	--	0	3	NS		
Livedo reticularis	--	--	--	3	0.5	NS		
Oral ulcers	--	--	--	9	13	NS		
Photosensitivity	--	--	--	23	20	NS		
Arthritis	22	39	<0.05	65	62	NS		
Arthralgias	26	23	NS	--	--	--		
Myositis	--	--	--	3	4	NS		
Nephropathy	--	--	--	20	9	0.04		
Neurological involvement	--	--	--	0	6	NS		
Chorea	--	--	--	3	0	NS		
Serositis	--	--	--	12	13	NS		
Pleuritis	6	6	NS	--	--	--		
Lung involvement	--	--	--	0	1	NS		
Hemolytic anemia	--	--	--	9	3	NS		
Thrombocytopenia	--	--	--	12	9	NS		
Vasculitis	8	2	NS	--	--	--		
Cutaneous vasculitis	--	--	--	--	--	--		
Raynaud's phenomenon	8	8	NS	12	16	NS		
Thrombosis	--	--	--	0	1	NS		
Sicca Syndrome	--	--	--	0	0.5	NS		

^aCarreno L, Lopez-Longo FJ, Monteagudo I, et al. Immunological and clinical differences between juvenile and adult onset of systemic lupus erythematosus. *Lupus*. 1999;8(4):287-92.

^b Font J, Cervera R, Espinosa G, et al. Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. *Ann Rheum Dis*. 1998 Aug;57(8):456–9.

[¶] Values expressed as percentages (%)

[‡] NS statistically not significant

^{*} -- no data in original article

Table 2

Clinical Features in Pediatric SLE (pedSLE) and Adult SLE (aSLE) Over Time[†]

Study	Hoffman 2009 ^a				Ramirez-Gomez 2008 ^b				Rood 1999 ^c				Carreno 1999 ^d				Font 1998 ^e			
Organ systems	pedSLE n=56	aSLE n=194	p-value	pedSLE n=230	aSLE n=984	p-value	pedSLE n=31	aSLE n=135	p-value	pedSLE n=49	aSLE n=130	p-value	pedSLE n=34	aSLE n=396	p-value					
<u>Constitutional</u>																				
Fever	67.3	51	<0.05	63.5	55.2	0.02	-- [‡]	--	--	--	--	--	62	43	NS [†]					
Fatigue	78.6	83.5	NS	--	--	--	87	--	--	--	--	--	--	--	--					
Weight loss	--	--	--	--	--	--	71	--	--	--	--	--	--	--	--					
Lymphadenopathy	--	--	--	--	--	--	36	--	--	--	--	--	6	1	NS					
<u>Mucocutaneous</u>																				
Malar rash	69.6	58.6	NS	70.4	59.1	0.002	71	40	<0.05	59.1	59.2	NS	79	51	0.002					
Discoid lupus	18.9	28.4 [‡]	NS	12.6	11.6	NS	10	27	<0.05	26.5	13.8	<0.05	15	4	NS					
Subcutaneous cutaneous lupus	9.6	2.2	<0.05	--	--	--	--	--	--	--	--	--	3	6	NS					
Alopecia	41.1	45.1	NS	--	--	--	48	--	--	--	--	--	--	--	--					
Generalized erythema	20	9.5	<0.05	--	--	--	--	--	--	--	--	--	--	--	--					
Livedo reticularis	--	--	--	--	--	--	--	--	--	--	--	--	6	1	NS					
Oral ulcers	28.6	23.5	NS	49.1	39.9	0.01	48	42	NS	40.8	37.6	NS	38	25	NS					
Genital ulcers	3.6	4.3	NS	--	--	--	--	--	--	--	--	--	--	--	--					
Photosensitivity	44.6	53.2	NS	53	56.8	NS	39	43	NS	40.8	50.7	NS	44	35	NS					
<u>Musculoskeletal</u>																				
Articular manifestations	--	--	--	--	--	--	--	--	--	85.7	96.1	<0.05	--	--	--					
Arthritis	59.3	66.8	NS	83	82	NS	100	94	NS	--	--	--	88	81	NS					
Arthralgia	75	98.7	<0.005	--	--	--	--	--	--	--	--	--	--	--	--					
Myalgias	42.4	35.2	NS	11.7	18.9	0.01	--	--	--	--	--	--	--	--	--					
Myositis	--	--	--	--	--	--	--	--	--	--	--	--	3	7	NS					
<u>Renal</u>																				
Proteinuria	63.6	4.2	<0.01	49.1	45.3	NS	61	43	NS	--	--	--	--	--	--					
Urinary cell casts	57.1	32	<0.001	--	--	--	65	53	NS	--	--	--	--	--	--					
Nephropathy	62.5	36	<0.001	--	--	--	--	--	--	67.3	48.4	<0.05	50	34	NS					
<u>Neuropsychiatric</u>																				
Chorea	--	--	--	2.2	0	0.000	--	--	--	--	--	--	9	0	<0.001					

Study	Hoffman 2009 ^a			Ramirez-Gomez 2008 ^b			Rood 1999 ^c			Carreno 1999 ^d			Font 1998 ^e		
Organ systems	pedSLE n=56	aSLE n=194	p-value	pedSLE n=230	aSLE n=984	p-value	pedSLE n=31	aSLE n=135	p-value	pedSLE n=49	aSLE n=130	p-value	pedSLE n=34	aSLE n=396	p-value
Seizures	14.5	6.9	NS	11.3	7.4	0.05	26	14	NS	--	--	--	--	--	--
Cerebrovascular accident	5.6	6.9	NS	5.2	2.2	0.01	--	--	--	--	--	--	--	--	--
Transient ischemic attack	--	--	--	0.9	0	0.03	--	--	--	--	--	--	--	--	--
Cranial nerve abnormalities	--	--	--	1.3	42	0.03	--	--	--	--	--	--	--	--	--
Pseudotumor cerebri	--	--	--	0.9	0	0	--	--	--	--	--	--	--	--	--
Headache	25.5	30.9	NS	--	--	--	61	--	--	--	--	--	--	--	--
Concentration disorder	20.4	17.8	NS	--	--	--	--	--	--	--	--	--	--	--	--
Psychosis	9.3	5.9	NS	4.8	3.9	NS	13	6	NS	--	--	--	--	--	--
Depression	12.7	15.8	NS	--	--	--	--	--	--	--	--	--	--	--	--
Encephalopathy	20.4	5.3	<0.005	--	--	--	--	--	--	--	--	--	--	--	--
Neurologic disorder	--	--	--	--	--	--	--	--	--	36.7	20	<0.05	--	--	--
<u>Cardiopulmonary</u>															
Pericarditis	16.7	18.2	NS	17.0	17.3	NS	26	33	NS	16.3	13	NS	--	--	--
Serositis	--	--	--	--	--	--	--	--	--	--	--	--	32	27	NS
Pleuritis	18.5	32.1	NS	17.4	23.2	NS	48	58	NS	28.5	33	NS	--	--	--
Pneumonitis	--	--	--	--	--	--	10	--	--	--	--	--	--	--	--
Lung involvement	--	--	--	--	--	--	--	--	--	--	--	--	6	4	NS
<u>Miscellaneous</u>															
Thrombosis	--	--	--	--	--	--	--	--	--	--	--	--	0	8	NS
Raynaud's phenomenon	39.3	41.1	NS	--	--	--	26	--	--	36.7	34.6	NS	20	25	NS
Chillblains	9.4	1.1	<0.01	--	--	--	--	--	--	--	--	--	--	--	--
Cutaneous vasculitis	--	--	--	--	--	--	--	--	--	44.8	27.6	<0.05	--	--	--
Sicca Syndrome	--	--	--	3.9	9.3	0.007	--	--	--	--	--	--	9	15	NS
Xerophthalmia	3.8	18.7	<0.01	1.7	6.6	0.004	--	--	--	--	--	--	--	--	--
Xerostomia	7.5	21.4	<0.05	--	--	--	--	--	--	--	--	--	--	--	--

^aHoffman IE, Lauwerys BR, De Keyser F, et al. Juvenile-onset systemic lupus erythematosus: different clinical and serological pattern than adult-onset systemic lupus erythematosus. Ann Rheum Dis. 2009 Mar;68(3):412-5.

^bRamirez Gomez LA, Uribe O, Osio Uribe O, et al. Childhood systemic lupus erythematosus in Latin America. The GLADEL experience in 230 children. Lupus. 2008;17(6):596-604.

^cRood MJ, ten Cate R, van Suijlekom-Smit LW, et al. Childhood-onset Systemic Lupus Erythematosus: clinical presentation and prognosis in 31 patients. Scand J Rheumatol. 1999;28(4):222-6.

^dCarreno L, Lopez-Longo FJ, Monteagudo I, et al. Immunological and clinical differences between juvenile and adult onset of systemic lupus erythematosus. *Lupus*. 1999;8(4):287–92.

^eFont J, Cervera R, Espinosa G, et al. Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. *Ann Rheum Dis*. 1998 Aug;57(8):456–9.

^fLocalized and disseminated discoid lesions

For legend please see legend Table 1

Table 3

Laboratory Findings in Pediatric SLE (pedSLE) and Adult SLE (aSLE) Over Time[¶]

Study	Hoffman 2009 ^a			Ramirez-Gomez 2008 ^b			Rood 1999 ^c			Carreno 1999 ^d			Font 1998 ^e		
Laboratory test	pedSLE n=56	aSLE n=194	p-value	pedSLE n=230	aSLE n=984	p-value	pedSLE n=31	aSLE n=135	p-value	pedSLE n=49	aSLE n=130	p-value	pedSLE n=34	aSLE n=396	p-value
<i>Antibodies</i>															
Antinuclear AB [*]	-- [‡]	--	--	96.9	98.2	NS [†]	100	99	NS	100	99.2	NS	--	--	--
Anti-ds DNA AB	60.7	24.9	<0.001	67	71.3	NS	93	66	<0.05	89.7	78.4	NS	--	--	--
Anti-Smith AB	17.9	12.4	NS	51.3	47.6	NS	30	32	NS	20.4	14.6	NS	--	--	--
Anti-Ro AB	23.2	33.5	NS	--	--	--	--	--	--	36.7	38.4	NS	--	--	--
Anti-La AB	7.1	17.0	NS	--	--	--	--	--	--	12.2	13	NS	--	--	--
Anti-ribonucleoprotein AB	14.3	17.5	NS	--	--	--	--	--	--	38.7	41.5	NS	--	--	--
Anti-ribosomal P AB	25	11.3	<0.001	--	--	--	--	--	--	--	--	--	--	--	--
Anti-histone AB	39.3	25.8	<0.05	--	--	--	--	--	--	--	--	--	--	--	--
Rheumatoid factor	--	--	--	--	--	--	54	--	--	24.4	31.5	NS	--	--	--
Antiphospholipid AB	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
IgM aCL ^{**} AB	--	--	--	47.5	36.8	0.05	--	--	--	--	--	--	--	--	--
IgG aCL AB	--	--	--	51.8	50.2	NS	--	--	--	--	--	--	--	--	--
Lupus anticoagulant	--	--	--	34.4	29.6	NS	23	--	--	--	--	--	--	--	--
<i>Hematology</i>															
Anemia	--	--	--	--	--	--	84	56	<0.05	--	--	--	--	--	--
Hemolytic anemia	38.5	13	<0.001	16.1	10.8	0.02	--	--	--	20.4	10	NS	15	6	NS
Leukocytopenia	63.6	56.8	NS	46.1	41.5	NS	74	50	<0.05	55.1	56.9	NS	--	--	--
Lymphopenia	67.9	64.1	NS	60.4	59	NS	30	26	NS	30.6	21.4	NS	--	--	--
Thrombocytopenia	31.5	25	NS	25.2	17.8	0.01	48	36	NS	30.6	38.4	NS	26	23	NS

^aHoffman IE, Lauwerys BR, De Keyser F, et al. Juvenile-onset systemic lupus erythematosus: different clinical and serological pattern than adult-onset systemic lupus erythematosus. *Ann Rheum Dis*. 2009 Mar;68(3):412–5.

^bRamirez Gomez LA, Uribe Uribe O, Osio Uribe O, et al. Childhood systemic lupus erythematosus in Latin America. The GLADEL experience in 230 children. *Lupus*. 2008;17(6):596–604.

^cRood MJ, ten Cate R, van Suijlekom-Smit LW, et al. Childhood-onset Systemic Lupus Erythematosus: clinical presentation and prognosis in 31 patients. *Scand J Rheumatol*. 1999;28(4):222–6.

^dCarreno L, Lopez-Longo FI, Montegudo I, et al. Immunological and clinical differences between juvenile and adult onset of systemic lupus erythematosus. *Lupus*. 1999;8(4):287–92.

^eFont J, Cervera R, Espinosa G, et al. Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. *Ann Rheum Dis*. 1998 Aug;57(8):456–9.

* AB Antibodies
** aCL anti-cardiolipin

For legend please see legend Table 1

Table 4

Medication Prescribed During Follow-up in Pediatric SLE (pedSLE) and Adult SLE (aSLE) [†]

Study	Hersh 2009 ^a			Brunner 2008 ^b			Tucker 2008 ^c			Font 1998 ^d		
Medication	pedSLE n=90	aSLE n=795	p-value	pedSLE n=67	aSLE n=131	p-value	adoSLE ^{¶¶} n=31	aSLE n=48	p-value	pedSLE n=34	adoSLE n=34	p-value
Traditional non-steroidal anti-inflammatory drugs	81.8	88.1	NS [†]	-- [‡]	--	--	--	--	--	88	81	NS
COX-2 inhibitors	23	49.9	<0.001	--	--	--	--	--	--	--	--	--
Antimalarials	87.6	83.8	NS	81	73	NS	--	--	--	85	82	NS
Oral corticosteroids	100	89.3	0.001	97	70	<0.0001	96.8	85.4	NS	94	84	NS
Pulse methylprednisolone	48.8	38.4	0.064	30	11	0.001	--	--	--	3	1	NS
Immunosuppressive medications	--	--	--	66	37	0.0001	--	--	--	--	--	--
Azathioprine	33.7	28.4	NS	64	75	NS	--	--	--	15	2	0.00004
Methotrexate [†]	26.9	30.9	NS	9	31	NS	--	--	--	--	--	--
Mycophenolate mofetil	28.1	13	<0.001	0	2	NS	--	--	--	--	--	--
Cyclosporine	18.6	9.9	0.014	2	0	NS	--	--	--	--	--	--
Intravenous cyclophosphamide	30.7	14.1	<0.001	25	21	0.009	16.1	4.2	NS	--	--	--
Oral cyclophosphamide	3.5	7.5	NS	--	--	--	--	--	--	9	4	NS

^aHersh AO, von Scheven E, Yazdany J, et al. Differences in long-term disease activity and treatment of adult patients with childhood- and adult-onset systemic lupus erythematosus. *Arthritis Rheum.* 2009 Jan 15;61(1):13-20.

^bBrunner HI, Gladman DD, Ibanez D, et al. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. *Arthritis Rheum.* 2008 Feb;58(2):556-62.

^cTucker LB, Uribe AG, Fernandez M, et al. Adolescent onset of lupus results in more aggressive disease and worse outcomes: results of a nested matched case-control study within LUMINA, a multiethnic US cohort (LUMINA LVII). *Lupus.* 2008;17(4):314-22.

^dFont J, Cervera R, Espinosa G, et al. Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. *Ann Rheum Dis.* 1998 Aug;57(8):456-9.

[†]Values expressed as percentages (%)

^{¶¶}adoSLE: The cohort pediatric SLE patients had disease onset between the ages 13 and 18 years

For legend please see legend Table 1

Table 5

Damage Accrual in Pediatric SLE (pedSLE) and Adult SLE (aSLE) as measured by the SLICC/ACR Damage Index [†]

Study	Brunner 2008 ^a			Tucker 2008 ^b		
Damage Domain	pedSLE n=66	aSLE n=131	p-value	adoSLE [‡] n=31	aSLE n=48	p-value
SDI [‡] Domains						
Ocular	42.2	13	<0.0001	9.7	4.3	NS
Neuropsychiatric	12.1	9.9	NS	29	19.6	NS
Renal	9.1	6.1	NS	45.2	17.4	0.023
Pulmonary	3.0	2.3	NS	3.2	6.5	NS
Cardiovascular	1.5	4.6	NS	6.5	4.3	NS
Peripheral vascular	3.0	1.5	NS	0	8.7	NS
Gastrointestinal	3.0	2.3	NS	3.2	10.9	NS
Musculoskeletal	24.2	9.9	0.007	19.4	15.2	NS
Integument	7.6	6.9	NS	9.7	15.2	NS
Gonadal	0	1.5	NS	12.9	10.9	NS
Diabetes	3.0	4.6	NS	3.2	8.7	NS
Malignancy	0	3.8	NS	3.2	0	NS
Mean (SD) [‡] of SDI score at study entry						
	--	--	--	0.7 (1.1)	0.5 (1.0)	NS
Mean (SD) in months of disease duration at study entry						
	1.13 (5.01)	2.83 (3.43)	0.014	1.7 (1.5)	1.6 (1.4)	NS
Mean (SD) of SDI score at the end of follow-up						
	1.76 (2.67)	0.76 (1.16)	0.008	2.3 (2.5)	1.6 (2.0)	NS
Mean (SD) in years of disease duration at the end of the study						
	3.2 (2)	3.5 (2.6)	NS	5.1 (3.0)	4.0 (2.8)	NS
Proportion [‡] of patients with ANY damage as measured by the SDI						
	56.1	43.5	NS	64.5	66.7	NS

^aBrunner HI, Gladman DD, Ibanez D, et al. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. *Arthritis Rheum.* 2008 Feb;58(2):556–62.

^bTucker LB, Uribe AG, Fernandez M, et al. Adolescent onset of lupus results in more aggressive disease and worse outcomes: results of a nested matched case-control study within LUMINA, a multiethnic US cohort (LUMINA LVII). *Lupus.* 2008;17(4):314–22.

[‡]SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index

Values are percentages (%) of patients of the total group unless otherwise noted

adoSLE: The cohort pediatric SLE patients had disease onset between the ages 13 and 18 years

Standard deviation

For legend please see legend Table 1