

REVIEW

Update on differences between childhood-onset and adult-onset systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a complex autoimmune disease and occurs worldwide in both children and adults. The estimated annual incidence among children is 2.22/100,000 and among adults is 23.2/100,000 in the United States. There is increasing understanding about differences in disease manifestations, medication use, and disease severity between those with childhood-onset SLE as compared with adult-onset SLE. Children have a more fulminant disease onset and course than adults with SLE, resulting in two to three times higher mortality. In future years, we anticipate more insight into the genetics between childhood-onset SLE and adult-onset SLE to help delineate the best therapies for both subsets of patients.

Keywords: childhood-onset systemic lupus erythematosus, systemic lupus erythematosus, children, lupus, adults, adolescents

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease that can affect all organ systems due to alterations of both the innate and adaptive immune systems. Although onset during infancy is rare, the incidence of SLE rises steadily during childhood until mid-adulthood, especially among females. This review appraises recent updates concerning the differences and similarities of SLE with onset in childhood (cSLE) as opposed to onset in adulthood (aSLE). Focus is placed on updates addressing nomenclature, epidemiology, lupus nephritis treatment, clinical and immunological manifestations, and pathogenesis as they have been published in the peer-reviewed medical literature since 2008.

Updates on classification and nomenclature

Diagnostic criteria are used to establish the presence of disease clinically, while classification criteria are needed for research to define more homogeneous patient subgroups for diseases with heterogeneous phenotypes. Various classification criteria have been developed and validated in aSLE. Currently, the classification criteria set most widely used in children and adults with SLE is that of the American College of Rheumatology (ACR) updated in 1997 [1]. Concerns about lack of sensitivity in adequately capturing the diverse SLE phenotypes prompted the development of revised classification criteria for aSLE by the Systemic Lupus International Collaborating Clinics (Table 1) [2]. Initial validation studies suggest the Systemic Lupus International Collaborating Clinics classification criteria to be more sensitive than the 1997 ACR classification criteria (97% vs. 83%, $P < 0.0001$) but less specific (84% vs. 96%, $P < 0.0001$) [2].

Unfortunately, previous studies have failed to address the accuracy of the Systemic Lupus International Collaborating Clinics or the 1997 ACR classification criteria that have been developed for aSLE when used in pediatrics. Indeed, Ferraz and colleagues published the only peer-reviewed study that validated SLE classification criteria for cSLE, reporting 96% sensitivity and 100% specificity of the 1982 American Rheumatism Association classification criteria, based on data from 103 children with cSLE and 101 children with other rheumatic diseases from Brazil [3].

In contrast to juvenile idiopathic arthritis and various other forms of autoimmune-mediated arthritis, including rheumatoid arthritis, there is no universally accepted maximum age up to which cSLE rather than aSLE is diagnosed. A recent systematic review by Silva and colleagues reports that previously published research used various age thresholds when referring to cSLE, ranging from 14 to 20 years. This variation probably impacted on past epidemiological estimates and diminished the comparability of earlier cSLE studies [4]. The authors suggest an upper age limit for the diagnosis of cSLE at 18 years based on the published literature and issues pertaining to the provision of medical care. The

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Table 1. Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus

Clinical criteria	Immunological criteria
1. Acute cutaneous lupus: including lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash in the absence of dermatomyositis, or subacute cutaneous lupus	1. Antinuclear antibody above laboratory reference range
2. Chronic cutaneous lupus: including classical discoid rash, localized or generalized, hypertrophic lupus, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblain lupus, discoid lupus/lichen planus overlap	2. Anti-dsDNA antibody above laboratory reference range, except ELISA: twice above laboratory reference range
3. Oral ulcers: palate, buccal, tongue, or nasal ulcers, in the absence of other causes	3. Anti-Smith antibody
4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs) in the absence of other causes	4. Anti-phospholipid antibody: any of the following lupus anticoagulant, false-positive RPR, medium or high titer anticardiolipin (IgA, IgG or IgM), anti-β ₂ -glycoprotein I (IgA, IgG or IgM)
5. Synovitis involving two or more joints, characterized by swelling or effusion or tenderness in two or more joints and 30 minutes or more of morning stiffness	5. Low complement, low C3, low C4, low CH50
6. Serositis: typical pleurisy for more than 1 day, or pleural effusions, or pleural rub, typical pericardial pain for more than 1 day, or pericardial effusion or pericardial rub, or pericarditis by ECG, in the absence of other causes	6. Direct Coombs test in the absence of hemolytic anemia
7. Renal: urine protein/creatinine (or 24-hour urine protein) representing 500 mg protein/24 hours, red blood cell casts	SLICC criteria for SLE classification require:
8. Neurologic: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state, in the absence of other causes	1. Fulfillment of at least four criteria, with at least one clinical criterion <i>and</i> one immunologic criterion
9. Hemolytic anemia	<i>or</i>
10. Leukopenia (<4,000/mm ³ at least once) in the absence of other known causes or lymphopenia (<1,000/mm ³ at least once) in the absence of other known causes	2. Lupus nephritis as the sole clinical criterion in the presence of antinuclear antibody or anti-dsDNA antibodies
11. Thrombocytopenia (<100,000/mm ³) at least once in the absence of other known causes	

ECG, electrocardiogram; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics. Adapted from [2].

same review attempts to achieve more uniformity in terminology when referring to children and adolescents with onset of SLE prior to adulthood [4].

Recent epidemiologic estimates of adult-onset SLE and childhood-onset SLE

The female to male ratio increases from 4:3 for cSLE to 9:1 during the reproductive years. SLE is also more common among non-White populations. Changes in the ethnic and racial composition of some countries, such as the United States, Canada, and several European countries, may partly explain the rising incidence and prevalence of SLE in some geographic regions. The importance of sociodemographic factors and changed environmental factors for the development of SLE is supported by the highest SLE prevalence in the South of the United States and in high-poverty areas [5,6].

MEDICAID is the US health program for individuals and families with limited monetary incomes and resources [7]. Recent analyses of the US administrative MEDICAID database suggest that aSLE is about 10 times more common than cSLE; 84% of cSLE patients are female, 40% of them are African American and 25% are

Hispanic [6]. Among the 23.9 million MEDICAID enrollees aged 18 to 65 years, the annual incidence and prevalence of aSLE is 23.2 and 143.7 cases per 100,000 enrollees, respectively, with a female to male ratio of 6:1. Likewise, the annual incidence of cSLE is 2.22 (95% confidence interval (CI) = 2.05 to 2.40) per 100,000 children and its prevalence is 9.73 (95% CI = 9.38 to 10.08) per 100,000 children between the ages of 3 and 18 years enrolled in MEDICAID. With respect to lupus nephritis, the annual incidence and prevalence rates of lupus nephritis are 0.72 (95% CI = 0.63 to 0.83) and 3.64 (95% CI = 3.43 to 3.86) per 100,000 children for the over 30 million children covered by MEDICAID [8]. This compares with annual incidence and prevalence rates of lupus nephritis at 6.9 and 30.9 per 100,000 adults [5]. MEDICAID data confirmed non-White race and female gender to be risk factors for developing lupus nephritis in both cSLE and aSLE [5,8].

One must note that especially the adult MEDICAID population does not provide a good representation of the overall US population, and that patients with end-stage renal disease are generally covered by other state programs than MEDICAID.

Updates on pathogenesis

The pathogenesis of SLE remains a vibrant area of research [8]. Early onset of SLE features is associated with an increased number of known SLE-susceptibility risk alleles, which may partly explain the increased severity of cSLE compared with aSLE [9]. Type 1 interferons are thought to be associated with the increased incidence of SLE in early adulthood. Indeed, about one-half of genetic variants associated with SLE to date can be linked to type 1 interferon production or signaling. Serum IFN α activity was found to be higher among younger and affected individuals in SLE family cohorts [10]. Interestingly, known genetic risk factors contribute to the risk of developing SLE by an average of 48% in Gullah and 25% in African-Americans, but not importantly among Hispanic and European-American individuals [9].

There is increasing evidence that miRNAs are involved in the differential expression of SLE-associated genes [11,12]. These noncoding RNAs may be useful organ-specific SLE biomarkers [13]. Several miRNAs – such as miR-146a, a negative regulator of the type I interferon pathway, miR-21, miR-148a, and miR-125a – are differentially expressed in SLE, and the concentrations of some miRNAs are associated with SLE activity.

Targeted assessment of ~1,000 genes (~10,000 SNPs) that are part of candidate pathways of SLE was performed in 253 trios of parents and children with cSLE (753 subjects). This assessment led to the identification of two novel SLE-associated genes, namely SELP (P-selectin gene) and IRAK1 (interleukin-1 receptor-associated kinase 1 gene) [14]. Another large multi-ethnic cohort study of 5,317 controls, 5,337 aSLE cases and 769 cSLE cases yielded confirmation of two SLE risk genes: PTPN22 (protein tyrosine phosphatase nonreceptor 22 gene) and IRF5 (interferon regulatory factor 5 gene) [15]. Furthermore, five novel SLE risk loci were described: KLRG1 (killer cell lectin-like receptor G1), IL-16, PTPRT (tyrosine-protein phosphatase T), TLR8 (toll-like receptor 8) and caspase 10 [15].

Further research is needed to delineate the biological effects caused by such genetic variations and establish their importance for the noted phenotypic differences between cSLE and aSLE.

Updates on differences in the clinical presentation and course

Remission is uncommon with aSLE and exceedingly rare with cSLE in North America [16]. There are reports from Canada suggesting a higher frequency of neurological and renal involvement at the time of diagnosis among children as compared with adults with SLE [17,18]. The histological classes of lupus nephritis are similarly distributed in cSLE and aSLE [19]. A study evaluating patient data from 28 cSLE cases, 107 aSLE cases and

14 late-onset SLE cases (that is, onset at age <16 years, 16 to 50 years and \geq 50 years, respectively) found age to be unrelated to kidney damage after adjustment for baseline renal parameters, duration of lupus nephritis, use of cyclophosphamide, and initial treatment response [20]. A study comparing the histopathology and course of lupus nephritis in patients age \leq 18 years ($n = 23$) and those of age \geq 50 years ($n = 13$) reports crescents on biopsy to be more common in the cSLE group than in the late-onset group (74% vs. 30%, $P = 0.02$), but there are no statistically significant differences in the activity or interstitial fibrosis on biopsy, or in clinical kidney parameters including hypertension and estimated glomerular filtration rate at presentation. However, there appear to be differences in response to therapy because, after 12 months of treatment, three of the cSLE patients but none of the late-onset patients progressed to dialysis [21].

Despite the suggested relevance of hormonal factors for the pathoetiology of SLE, a matched cohort study comparing prepubertal with pubertal cSLE demonstrated no important differences in disease features between groups; irrespective of pubertal status, the most commonly encountered cSLE features at the time of diagnosis were malar rash, arthritis, hematologic abnormalities, and lupus nephritis [22]. Further investigations are needed to study the effects of the hormonal changes that occur during puberty in relations to the mechanisms leading to overt cSLE.

Several studies from Europe and Latin America directly compared disease features and laboratory abnormalities with cSLE and aSLE [23-25]. The relationship between the age at onset and phenotypes of SLE was explored in a multi-racial cohort study of 1,317 cSLE and aSLE patients. Compared with aSLE, disease onset during childhood carried a higher risk of developing lupus nephritis, malar rash, anti-dsDNA antibody positivity, and hemolytic anemia (odds ratio (OR) = 3.03, 2.13, 2.08, and 2.50, respectively; all Bonferroni corrected $P < 0.004$) [9]. Additionally, patients with aSLE have less active disease over time than those with cSLE – that is, lower time-adjusted mean SLE Disease Activity Index scores (4.6 vs. 5.7, $P = 0.012$) [18] – with differences largely accounted for due to renal and central nervous system involvement [17]. The abovementioned observations are in line with those of a recent meta-analysis of a total of 905 cSLE patients and 5,993 aSLE patients [26], which confirmed higher average disease activity at diagnosis in cSLE than aSLE (mean (95% CI) difference in SLE Disease Activity Index scores = 4.73 (2.13 to 7.32)). As per this meta-analysis fever, thrombocytopenia, mucocutaneous involvement, urinary casts, seizures, and hemolytic anemia are all more commonly encountered in cSLE than aSLE, with ORs ranging from 1.3 to 2.4. Conversely,

Sicca syndrome and pleuritis are both about twice more common in aSLE than in cSLE (Table 2) [26].

While virtually all patients with SLE test positive for circulating antinuclear antibodies, cSLE and aSLE cohorts also feature similar frequencies for anti-Smith, anti-RNP, anti-Ro/SSA, and anti-La/SSB antibodies [24,25]. However, based on meta-analysis, the frequency of some other immunological abnormalities is associated with the age at diagnosis. Anticardiolipin IgG/IgM antibody positivity appears to be significantly more common among cSLE patients than aSLE patients (OR = 1.66; 95% CI = 1.20 to 2.28). Because of their high frequency of infectious processes, transient and nonpathogenic anticardiolipin antibody positivity may occur more commonly in children. In general, antiphospholipid antibody-related thrombosis is rare in children, and prothrombotic or vasculopathic factors that are frequent in adults are uncommon in children. Rheumatoid factor positivity is more frequently encountered when SLE starts in adulthood as opposed to earlier in life (OR = 0.53; 95% CI = 0.32 to 0.87) (Table 2) [27]. Both of the above-mentioned meta-analyses are limited by discrepancies in the threshold age used to define cSLE and the heterogeneity of the data considered [26,27].

Neuropsychiatric involvement with SLE is at least as common in children as it is in adults, with the former experiencing symptoms especially within 1 year post diagnosis with SLE (70% vs. 28%) [28,29]. The Grupo Latino Americano de Estudio del Lupus cohort reports a significantly higher prevalence of pseudotumor cerebri, transient ischemic attack, and seizures in cSLE when directly compared with aSLE [25]. Psychosis, chorea, and any type of encephalopathy occur with cSLE preferentially, while cranial nerve abnormalities are more frequent in aSLE. Depression is the most common mood disorder in SLE patients of all ages, without apparent differences in prevalence across age strata. Neurocognitive impairment seems similarly common among children and adults with SLE [17] but reported frequencies vary depending on the chosen categorization scheme [30,31]. A recent review further outlined differences and similarities in cSLE and aSLE with respect to neuropsychiatric involvement [32].

The prevalence of osteopenia and osteoporosis is similar among cSLE and premenopausal aSLE patients. Poor bone health is much more common among postmenopausal aSLE patients, probably reflecting the effects of traditional osteoporosis risk factors [33,34]. In children, the prescribed dose of steroids is negatively associated with bone formation as measured by serum osteocalcin (Spearman rank correlation coefficient $r = -0.34$, $P < 0.0001$) [35]. Compared with the general population, hypovitaminosis D is more prevalent among children and adults with SLE. There remains conflicting

evidence as to whether high SLE disease activity and/or proteinuria increases the risk of vitamin D deficiency and *vice versa* [35-38].

Longer-term morbidity

A 2011 meta-analysis found no significant differences in the average SLE damage index scores between cSLE and aSLE [26]. It is noteworthy that the SLE damage index includes several items that are more common among older populations in general but no items of health concerns that are specific to children, including but not limited to growth and physical maturation. Future studies directly comparing cSLE and aSLE for risk factors of early versus late disease damage are needed.

While rare during childhood, clinically recognizable coronary artery disease is reported in 6 to 9% of adults with SLE. Ischemic heart disease remains an important cause of morbidity and mortality in aSLE. A 3-year randomized, double-blind, placebo-controlled clinical trial of atorvastatin in cSLE suggests male gender ($P < 0.001$), higher body mass index ($P < 0.001$), decreased creatinine clearance ($P = 0.031$), older age ($P < 0.001$), and azathioprine use ($P = 0.005$ to 0.0102) all to be positively associated with an increased burden of subclinical coronary artery disease as measured by carotid intima-media thickening [39]. Notably, moderate prednisone doses (0.15 to 0.4 mg/kg/day) were associated with fewer abnormal carotid intima-media thickening measurements ($P = 0.024$), and there was a trend towards slowed progression of subclinical atherosclerosis over time [40].

Five-year renal survival rates in cSLE patients with proliferative lupus nephritis are at 85 to 91%, comparable with those reported from some aSLE cohorts [41]. Lupus nephritis accounts for 1.9% of kidney transplants among adults and 3% among children, according to the US Renal Data System [42]. The poor prognosis of children with cSLE and end-stage renal disease is troublesome. There is a 22% mortality rate during the 5-year period since the initiation of renal replacement therapy, with cardiopulmonary compromise and infections accounting for 47% of all causes of death [43]. Long-term outcomes beyond 5 to 10 years are lacking, emphasizing the need for further research in long-term renal outcomes of children with cSLE. Based on the North American Renal Transplant Cooperative Study Database, cSLE and aSLE kidney graft survival is similar to that for patients with other adult or pediatric diseases, for both living and cadaveric kidney donors [41].

Mortality

There are encouraging reports from developed countries of 5-year survival rates that exceed 90% among both children and adults with SLE, 86% at 10 years, and 79% at

Table 2. Comparison of clinical manifestations in childhood-onset SLE and adult-onset SLE

Clinical manifestations	Odds ratio	95% confidence interval	<i>P</i> ^a (%) ^a
More common in childhood-onset SLE			
Fever	1.48	1.24 to 1.76	0
Thrombocytopenia	1.30	1.10 to 1.55	0
Ulcers/mucocutaneous	1.35	1.13 to 1.61	0
Urinary cellular casts	2.35	1.68 to 3.29	0
Seizures	2.32	1.65 to 3.25	16
Hemolytic anemia	1.90	1.44 to 2.52	17
Combined IgG and IgM aCL	1.66	1.20 to 2.28	41
More common in adult-onset SLE			
Sicca	0.42	0.27 to 0.64	0
Pleuritis	0.69	0.54 to 0.88	0
Rheumatoid factor	0.53	0.32 to 0.87	0

aCL, anti-cardiolipin antibody; SLE, systemic lupus erythematosus. ^a*P* statistic was used to examine the between-study heterogeneity. Only disease features with *P* <50% were included in the table.

15 years [44,45]. However, the prognosis of SLE reported from developing countries remains less favorable. A cohort study from Thailand suggests survival rates of only 76% at 5 years and 64% at 10 years after diagnosis with cSLE [46].

Higher disease activity is associated with higher disease damage and mortality in both cSLE and aSLE [47,48]. cSLE continues to carry a higher mortality risk than aSLE [27]. Compared with aSLE, patients with cSLE enrolled in the LUMINA cohort had a twofold higher mortality risk [49] and those in the University of California Lupus Outcomes Study had a more than three times higher risk of dying (hazard ratio = 3.1, 95% CI = 1.3 to 7.3) [50]. Corrected for age, disease duration, and other patient characteristics [50], low socioeconomic status (hazard ratio = 1.9, 95% CI = 1.1 to 3.2) and the presence of end-stage renal disease (hazard ratio = 2.1, 95% CI = 1.1 to 4.0) were found to be important risk factors of SLE-associated mortality.

Updates on surrogate and biological measures

The SLE Responder Index has been developed to capture improvement of aSLE in the clinical trials of belimumab. When used in children and adolescents, the SLE Responder Index has high specificity but only modest sensitivity in capturing cSLE improvement as rated by the treating physician or patient (parent) [51]. International consensus formation efforts resulted in several key criteria for clinical remission and inactive disease in cSLE [52] (Table 3). Similarly, criteria for global flares have been developed for cSLE and aSLE [53,54]. The recently published consensus treatment plans for lupus nephritis in cSLE utilized renal response definitions adapted from those proposed by the ACR for proliferative and membranous renal disease in aSLE [55,56].

There is active research in improved SLE biomarkers. Several novel lupus nephritis biomarkers appear useful for the early diagnosis of lupus nephritis and suited for anticipating renal flares [57-59]. Among these urinary biomarkers, neutrophil gelatinase-associated lipocalin and monocyte chemoattractant protein 1 will most probably be first available to clinicians over the upcoming years. Select cell-bound complement activation products have been associated with extra-renal flares in cSLE and aSLE, with confirmation from longitudinal studies being awaited [60]. The interested reader is directed towards a recent review of lupus nephritis biomarkers [61].

Updates on differences in management strategies

There has been an increased focus on the development of quality indicators; that is, measures of the quality of medical care delivered to individuals with SLE [2]. Two sets of quality indicators for aSLE are available, and international consensus yielded cSLE quality indicators recently [62-64]. Quality indicators can be used to help define minimum treatment standards of medical care for cSLE and aSLE. About one-third of the quality indicators for cSLE are identical to those for aSLE, while the remaining quality indicators for children are somewhat more conservative in terms of recommending closer monitoring than that deemed necessary for aSLE.

Steroids are more commonly used for the treatment of cSLE than aSLE [16,18], probably to address differences in disease phenotypes. Furthermore, a retrospective cohort study of cSLE patients treated between 1988 and 2008 reports that the early-onset group (age <12 years) requires significantly higher daily steroid doses than children diagnosed with cSLE during adolescence (0.6 mg/kg prednisone-equivalent vs. 0.2 mg/kg prednisone-equivalent, *P* <0.05) [22].

Table 3. Definitions of inactive disease and clinical remission in childhood-onset systemic lupus erythematosus

Construct	Minimal time interval	Medication usage			
		Corticosteroids	Immunosuppressives	Preventive medications ^a	Medications to treat damage
Inactive disease ^b	Yes	Permissible	Permissible	Permissible	Permissible
Clinical remission on medication	6 months	Permissible	Permissible	Permissible	Permissible
Clinical remission on preventive medication	6 months	No	No	Permissible	Permissible
Clinical remission off medication	12 months	No	No	No	Permissible

^aPreventive medications include systemic medications that can be used to prevent disease damage, such as statins, aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, bisphosphonates, vitamin D, and omega-3 fatty acids. ^bMedication exposure is not considered.

The same armamentarium of immunosuppressive drugs is used for cSLE and aSLE. Overall, nonbiologic disease-modifying medications are prescribed more frequently to children than adults with SLE [16-18], but methotrexate is more commonly used for aSLE (31% vs. 9%) [18] and intravenous cyclophosphamide for cSLE therapy [49]. In 2012 belimumab (anti-BLyS/BAFF) was approved by health-regulatory agencies for the treatment of active, autoantibody-positive aSLE despite use of standard therapy [65,66]. Added to background therapy, clinical trials showed that significantly more patients improve with belimumab compared with placebo, especially with respect to mucocutaneous and musculo-skeletal SLE involvement and immunological abnormalities. A clinical trial aimed at assessing the safety and pharmacokinetics of belimumab in cSLE is ongoing (NCT01649765), with results expected in 2016.

Based on case reports and anecdotal experience, anti-CD20 blockade leads to improvement of hematologic abnormalities, neuropsychiatric SLE, anti-phospholipid-mediated pathology, and lupus nephritis of SLE patients of all ages [67,68]. However, a randomized, double-blind, placebo-controlled trial failed to document a benefit of rituximab over placebo for the control of aSLE activity [69]. There is an ongoing clinical trial of rituximab in cSLE (results expected in 2015) and several clinical trials of rituximab in aSLE, mainly assessing rituximab benefits for the treatment of select disease features or as part of combination therapy.

To promote evidence-based treatments in SLE, standardized therapy regimens have been developed for children and adults with lupus nephritis [55,70,71]. The delineation of uniform steroid regimens for children with proliferative lupus nephritis must be considered a major achievement [55]. Notably, lower steroid doses are recommended for adults as compared with children with lupus nephritis [16-18].

Mycophenolate mofetil and cyclophosphamide are deemed cornerstones of lupus nephritis therapy. A subanalysis of a total of only 25 children with lupus

nephritis who were enrolled in a large randomized clinical trial of mycophenolate mofetil (target dose 3.0 g/day) versus cyclophosphamide (0.5 to 1.0 g/m²/month) [72] showed a trend towards better renal response to 24-week induction therapy with mycophenolate mofetil than with cyclophosphamide (7/10 (70%) vs. 8/15 (53%)) [73]. Although this subanalysis is vastly underpowered, the trend is in line with the results of larger trial published in 2005 [72]. Likewise, both the cSLE subanalysis and the main trial report more effective maintenance of renal remission with mycophenolate mofetil as compared with azathioprine, although this difference was not statistically significant in the cSLE subanalysis (7/8 (87.5%) vs. 3/8 (37.5%), *P* = not significant) [73,74]. The EuroLupus trial enrolled patients as young as 14 years old; however, there are no published subanalyses regarding the efficacy of the EuroLupus regimen specific for cSLE or the number of patients with cSLE enrolled in this study. The interested reader is referred to a 2012 Cochrane review of the treatment of lupus nephritis, which, unfortunately, does not consider information from children with lupus nephritis [75].

Cost of care

Based on a systematic review, the annual direct medical cost of aSLE in the United States ranges from \$13,735 to \$20,926, with medications, hospitalization, and outpatient care accounting for 19 to 30%, 16 to 50%, and 24 to 56% of the overall cost, respectively [76].

Higher direct costs were accrued by patients with lupus nephritis compared with those without kidney disease (range: \$29,034 to 62,651 vs. \$12,273 to 16,575). These estimates, which were derived from medical claim data and self-reported resource utilization, are in line with a recent analysis of the US Healthcare Cost and Utilization Project KIDs Inpatient Database. The presence of lupus nephritis was identified to be a key determinant for higher hospitalization charges; these, on average, for children with lupus nephritis were \$43,100 as compared

with only \$28,500 for cSLE patients without kidney disease ($P < 0.0001$) [77]. To date, there is only one study that directly compares the cost of medical care of cSLE with that of aSLE [16]. Herein, the care of a child is roughly 300% that of an adult with SLE.

Estimates of the mean annual indirect costs with aSLE in the United States are \$1,093 to 14,614, while employment rates range from 35.8 to 55%, and average durations of annual short-term sick leave are between 7.0 and 64.8 days [78]. Indirect costs incurred with cSLE have not been studied in detail, but one must consider anticipated loss of productivity upon entry into the workforce and reduction of productivity of family members currently involved in the care of the child with cSLE. Whether there are differences in indirect costs and disability rates between cSLE and aSLE remains to be seen.

Conclusions

aSLE is about 10 times more common than cSLE in the United States but children with cSLE have a more severe disease than their adult counterparts. Lupus nephritis has a profound negative impact on survival and results in high healthcare expenditure of both children and adults. During the preceding 5 years, there has been a move towards defining differences between cSLE and aSLE on a biological level but clear explanations are still lacking. Standardization of lupus nephritis treatments of children and adults with SLE has occurred, and measures of quality of medical care have been defined. One hopes that this will result in improved health outcomes with cSLE and aSLE. Nonetheless, there remains a dire need for more efficacious and less toxic therapies. In this millennium only belimumab has been newly approved for the treatment of aSLE, while not a single drug has ever obtained an indication for cSLE. Benefitting from the findings of basic and translational research as well as improved measures of drug effectiveness, several medications are now in the drug development pipeline and are expected to help improve the prognosis of children and adults with SLE.

This article is part of the series on *Childhood rheumatic diseases*, edited by Patricia Woo. Other articles in this series can be found at <http://arthritis-research.com/series/childhood>

Abbreviations

ACR, American College of Rheumatology; aSLE, adult-onset systemic lupus erythematosus; CI, confidence interval; cSLE, childhood-onset systemic lupus erythematosus; dsDNA, double-stranded DNA; ELISA, enzyme-linked immunosorbent assay; IFN, interferon; IL, interleukin; miRNA, microRNA; OR, odds ratio; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism.

Competing interests

The authors declare that they have no competing interests.

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