Pediatric systemic lupus erythematosus

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Systemic lupus erythematosus is an autoimmune disease characterized by multiorgan system involvement and the presence of autoantibodies. The disease is significantly more prevalent in women than men, with peak incidence in women of child-bearing age. Approximately 20% of all cases of systemic lupus erythematosus occur in the pediatric age group and this is the focus of this review.

The prevalence of pediatric systemic lupus erythematosus (pSLE) varies in different ethnic populations, with estimates of 0.4–0.9 per 100,000 in Finland, 0.47 per 100,000 in Canada and a significantly higher rate of 6.3 per 100,000 in Taiwan [1–3]. The estimate for girls under the age of 18 in Taiwan is 11.2 per 100,000 and boys 1.8 per 100,000. It is more common in post- than prepubertal adolescents, and the female:male ratio is lower than that seen in adults, with SLE at approximately 4.5:1. In our experience, the female:male ratio does not significantly differ between pre- and post-pubertal patients. The American College of Rheumatology (ACR) 1982 Classification Criteria (**Box 1**) is used in pSLE although it was validated only for adults [4]. Most pediatric rheumatologists accept these classification criteria and require the presence of four criteria for a patient to be classified as having SLE. It has been estimated that pSLE leads to a 50-fold increase in standardized mortality [5]. As mucocutaneous features, serositis and arthritis do not differ between patients with pSLE and adult SLE and this article will not review these features. The only comment regarding mucocutaneous features is that a true discoid rash is much less common in pSLE than adult SLE. Similarly, hematological involvement and autoantibodies, with the exception of anticardiolipin (aCL) antibodies and the lupus anticoagulant, are similar in pSLE and adult SLE and, therefore, will not be reviewed. This article will focus on the most clinically significant features, which are CNS involvement, renal disease and the role of antiphospholipid (aPL) antibodies. However, the frequency of major organ involvement in pSLE reported in the literature since 1977 is shown in **Table 1**.

Keywords: autoantibodies, CNS, cyclophosphamide, lupus nephritis, pediatric, systemic lupus erythematosus

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Clinical features of CNS disease

CNS involvement includes the criteria outlined in the 1982 classification criteria plus other features (**Box 1 & Table 2**). **Box 2** shows the sensitivity and specificity of the 1982 criteria for neurological disorder (adult data only available). Many features were not well defined until 1999, when a consensus conference was held and the ACR nomenclature and case definitions for neuropsychiatric lupus syndromes were produced (**Table 3**) [6]. CNS involvement in pSLE (CNS-SLE) is common and has been reported to occur in as few as 25% to as many as 95% of patients (**Table 4**) [7–15]. The lowest incidences of CNS disease were seen in a nationwide Japanese survey of 373 patients, while the highest incidence used the 1999 revised ACR case definition for CNS involvement [9,13]. Interestingly, this latter study had a female:male ratio similar to the one seen in adult studies, rather than the lower female:male ratio seen in most pediatric studies [13]. Studies prior to 1999 used the revised 1982 ACR criteria, which had a narrower definition of CNS involvement, and this is particularly true for the definition of headache [6]. The difference in definitions used in different studies makes comparisons very difficult. This was part of the reason for the development of the 1999 ACR classification criteria. However, to date, these criteria have only been validated in adult but not pediatric populations. The relative frequencies of CNS disease, including individual disease manifestations in pSLE, are shown in **Table 4**. In 25–58% of the patients, the CNS manifestation is a presenting symptom and in approximately 75% of patients who develop CNS disease it occurs within the first year of diagnosis of SLE. In the remaining 25% it took up to 7 years for the CNS disease to become evident [8,11]. In approximately a third of patients, there is more than one CNS manifestation [8]. Furthermore, CNS involvement may be the first manifestation of pSLE with very few other clinical features [12,15].

Using the 1999 ACR case definition for neuropsychiatric systemic lupus erythmatosus (NPSLE), headache is the most common

Box 1. Revised American College of Rheumatology Classification criteria for systemic lupus erythematosus.

- Malar Rash
- Oral/nasal ulcer
- Photosensitivity
- Discoid lesions
- Arthritis
- Pleuritis/pericarditis
- Hematological disorder:
  - Coombs' positive hemolytic anemia
  - Thrombocytopenia
  - Lymphopenia
- Neurological disease:
  - Seizures
  - Psychosis
- Renal disorder
- Positive antinuclear antibody
- Immunological disorder:
  - Anti-DNA antibodies
  - Anti-SM antibodies
  - Antiphospholipid antibodies

Adapted from [4].

symptom, occurring in up to 75% of all patients with pSLE [8,11,13,16]. By contrast, 6–22% of pSLE patients meet the criteria for lupus headache and this has been frequently associated with cerebral vein thrombosis (as discussed later) [8,16]. An association of the presence of aPL antibodies and headache has been reported in one study [16]. Following headache, the most common manifestation is NPSLE, which includes depression, concentration or memory problems and frank psychosis. It is difficult to compare relative frequency of individual neuropsychiatric (NP) features, as different authors use different wording to describe similar features. This is the reason for the many blank columns in **Table 3**. The 1999 case definitions for neuropsychiatric lupus syndromes was devised in an attempt to overcome some of the difficulties in comparing different studies by having more uniform categories. One other major change is the use of the term 'acute confusional state', which should replace 'organic brain syndrome'. Acute confusional state is defined as a disturbance in the level of consciousness, with reduced ability to maintain focus and associated change in cognitive function or effect. It spans the spectrum from mild changes of consciousness to coma [6]. Seizures and cerebral vascular accidents (CVA), which frequently occur together, are seen in 20–60% and 12–15% of patients, respectively. Chorea is present in 5–20% of patients with pSLE and is more common than in adult patients [8,11,13,15,17,18]. Most patients have only one episode of chorea during the course of their illness and unilateral is more commonly seen than bilateral chorea [15,19,20]. Less common CNS symptoms are diabetes insipidus, Parkinson's syndrome, cranial nerve involvement and leukoencephalopathy [7,18,21]. In both pSLE and adult SLE there is a frequent association of lupus cystitis with CNS involvement [22,23]. The reason for this association is not clear. Ocular involvement is common and has been reported to occur in up to 25% of cases with pseudotumor cerebri, papilledema and visual disturbances the most common findings [7,15,24]. Retinal vascular disease, consisting of arterial or venous occlusion, cotton-wool spots, optic disc edema, retinal hemorrhages or ischemic optic neuropathy can be found in up to 10% of patients. The majority of these patients have detectable aPL [25].

Peripheral nerve system (PNS) involvement occurs in 5–15% of all patients with pSLE [8,13,26]. It may occur with or without concomitant CNS disease. Nerve conduction studies can show sensory and motor polyneuropathy with or without an associated mononeuritis [26]. Peripheral neuropathy and transverse myelitis are the most common PNS manifestations, each occurring in approximately 5–10% of patients [11,13]. Less commonly, PNS involvement includes aseptic meningitis, polyneuropathy, mononeuritis, myasthenia gravis, cranial neuropathy, demyelinating disease and Guillain–Barre syndrome [7,18,27]. Unlike studies in adults with SLE, autonomic dysfunction has been only rarely reported in pediatric patients.

Outcome

The overall patient survival has been reported to be 90–95% at both 5- and 10-year follow-up, although few studies have reported on patient survival [7,8]. Most patients in our experience have good recovery from CNS-SLE, although patients with CVA may have residual sequelae [8]. One study demonstrated learning difficulties as a consequence of CNS involvement in a third of patients, while a second study described residual sequelae in 40% of patients [11,12]. In addition, early deaths secondary to uncontrollable disease, in particular cerebral hemorrhage, have been

Table 1. Frequency of major organ involvement in pediatric systemic lupus erythematosus.

Study	Area affected						Ref.
	Musculoskeletal	*Cutaneous*	*Renal*	*CNS*	*Pleuritis*	*Pericarditis*	
Cassidy (1977) n = 58 (%)	76	76	86	31	36	47	[222]
Koster King (1977) n = 108 (%)	79	70	61	18			[223]
Pande (1993) n = 83 (%)	90	83	79	46			[224]
Tucker (1995) n = 37 (%)	89	82	32	21			[225]
Takei* (1997) n = 373 (%)	37	80	70	17	17¶	17¶	[9]
Font (1998) n = 34 (%)	88	79	50	26	32¶	32¶	[226]
Iqbal‡ (1999) n = 39 (%)	74	72	28	28	5	5	[227]
Bader-Meunier‡ (2005) n = 155 (%)	64	73	50	17			[228]
Hiraki (2005)§ n = 256 (%)	67	66	56	42	15	15	

**Nationwide survey from Japan.*

‡At presentation only.

§Presented in abstract form only.

¶These studies did not differentiate pleuritis and pericarditis.

reported in up to 5% of patients [7,8,11,12] One adult study suggested that initially high disease activity was associated with subsequent development of psychosis and cognitive impairment [28]. CNS involvement is associated with renal involvement in between 55 and 89% of patients with CNS disease, and has been associated with increased development of end-stage renal disease and mortality compared with renal patients without CNS disease [11,13,29]. One study of adults with SLE suggested that the presence of seizures increased the risk of death but, to date, this association has not been reported in pSLE [30].

Autoantibodies & CNS involvement

The two most important autoantibodies associated with CNS disease are aPL and antiribosomal P antibodies.

Antiphospholipid antibodies

aPLs consist of multiple different autoantibodies, of which aCL and the lupus anticoagulant (LAC) are the most commonly measured. A more detailed description of the role of aPL antibodies in pSLE is given later. Multiple studies in adults and pediatric patients have demonstrated an association of aCL with both CNS and PNS disease [8,16,18,25,31]. The specific features associated with aPL are headache, CVAs, chorea and transverse myelitis [8,16,18,32,33]. Almost all reported cases of both chorea and transverse myelitis have been shown to be associated with aPL [8,15,16]. In addition, there is a strong association of CNS thrombotic events, including CVA and sinus venous thrombosis, with aPL and, in particular, with the LAC [28,34]. It is often difficult to determine the individual roles of CNS vasculitis and thrombosis in patients presenting with CVA secondary to arterial disease, as both CNS vasculitis and thrombosis may contribute to the CVA and aPL are associated with both. In addition to arterial events, patients with the LAC are at risk of cerebral vein thrombosis (CVT). One study demonstrated that CVT was frequently seen in pSLE patients who meet the criteria for lupus headache [8]. In this study, all of the patients with CVT had the LAC. The presence of a CVT should be ascertained in all pediatric patients who develop a severe headache, and in particular in patients with aPL and LAC. The most commonly affected veins in CVT were the superior sagittal sinus and the lateral sinuses [35]. Studies in adults have demonstrated an association of aPLs, both LAC and aCL, with seizures but, to date, this association has not been found in pediatric studies [18,36]. However, one pediatric study has suggested that patients with aPL were more likely to accrue damage, as measured by the

Table 2. CNS involvement using 1982 criteria.

Pathology	Sensitivity (%)	Specificity (%)
Neurological disorder	20	98
Psychosis	13	99
Seizures	12	99
Focal neurologic	12	96
Dementia	6	99
Coma	5	100

Adapted from [4].

Box 2. CNS involvement using 1999 American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes.

Central

- Headache
- Psychosis
- Cognitive dysfunction
- Mood disorder
- Acute confusional state
- Anxiety disorder
- Seizure disorder
- Movement disorder
- Cerebral disease
- Aseptic meningitis
- Myelopathy
- Demyelinating syndrome

Peripheral

- Mononeuropathy
- Cranial neuropathy
- Myasthenia gravis
- Guillain–Barre syndrome
- Autonomic neuropathy
- Plexopathy

Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR-DI), compared with aPL-negative patients [16]. Although polyneuropathy, mononeuritis, myasthenia gravis, cranial neuropathy, demyelinating disease and Guillain–Barre syndrome are infrequent manifestations of CNS involvement, these features are also commonly associated with aPL.

Antiribosomal P antibodies

The most important association of antiribosomal P antibodies is with psychosis and depression, but not with other CNS manifestations or cognitive impairment [35,36–38]. To date, there have been two studies of patients with pSLE examining antiribosomal P antibodies and clinical associations. Elevated levels were found in 17–42% of all patients with pSLE [39,40]. Changes in antiribosomal P antibody levels tended to reflect clinical changes in the psychosis [39,40]. The presence of antiribosomal P antibodies may be helpful in determining SLE-associated psychosis from other forms of psychosis, as the latter group of patients do not have these autoantibodies [39]. This is true in both adult and pediatric studies. However, they are not helpful in the diagnosis of CNS involvement, as antiribosomal P antibodies are present in many patients without CNS involvement. As with the pediatric studies, in studies of adults with SLE, the frequency of antiribosomal P autoantibodies has been reported to be as high as 80% in patients with active psychosis, and changes in anti-P antibody levels are associated with changes in psychosis [41]. Unlike other antibodies associated with CNS involvement, cerebrospinal fluid (CSF) antiribosomal P antibodies are not elevated in patients with psychosis or depression, even when serum levels are elevated [41,42]. One of the studies in pSLE found that more than 90% of patients with both anti-P and anti-DNA had nephritis and that the levels of these two autoantibodies usually varied together [40]. As with the above mentioned study, many studies in adult SLE populations have shown that there is a strong association of the simultaneous presence of anti-double-stranded DNA and anti-P antibodies, and that of renal disease [43].

Cross-sectional studies in patients with adult SLE demonstrated the presence of antiribosomal P antibodies in 12–19% patients with SLE [38,44]. Antibody titers have been demonstrated to change with disease activity and have been reported to be present in 20–40% of patients with active SLE, with a prevalence of up to 75% in patients with active nephritis, and disappearance of the antibody in over 90% of patients during remission. The presence of antiribosomal P antibodies appears to differ in different ethnic populations with rates of approximately 40% in Japanese and Malaysian Chinese patients compared with the usually reported 12–15% prevalence rate [45,46].

In addition to their association with anti-DNA antibodies, antiribosomal P antibodies have been reported to be associated with aCL antibodies, anti-β2 glycoprotein I antibody and/or lupus anticoagulant, as well as with an increased risk of thrombosis [38]. To date, the only association of antiribosomal P antibodies and other autoantibodies in patients with pSLE is the demonstration that patients with antiribosomal P antibodies had a higher prevalence of anti-U1 ribonucleoprotein and anti-Sm than antiribosomal P-negative patients with pSLE [40]. This association with anti-Sm antibodies was also demonstrated in one study of adults with SLE [47]. Other clinical features reported to be associated

Table 3. Clinical presentations of CNS involvement in pediatric systemic lupus erythematosus using 1999 revised case definitions.

Study	Any (%)	Headache (%)	Seizures (%)	Peripheral nervous system (%)	Psychosis (%)	Cerebral vascular accident (%)	Chorea (%)	Mood disorder (%)	Acute confusional state (%)	Ref.
Yancey (1981) n = 37	43	44	31	6	19				37	[7]
Steilin (1995) n = 91	44	30	15	5	27	15	3	15	20	[8]
Parikh (1995) n = 108	23	60	20		5	20	28	36	32	[19]
Takei (1997)* n = 373	17	30	42		33	15	6			[9]
Schmutzler (1997) n = 17	71	35	24	12			8			[230]
Haji Muhammad Ismail Hussain n = 24	75	28	61	6		17	17		22	[11]
Rood (1999) n = 31‡		36	23		10	16				[229]
Quintero-Del-Rio (2000) n = 86	29	24	56		16	12	4		25	[231]
Loh (2000) n = 21	71		43		33	20	5		47	[12]
Sibbitt (2002) n = 75	95	72	51	15	12	12	7	57	35	[13]
Olfat (2004) n = 90	22	55	50		50	30	20		25	[15]
Bader-Meunier (2005) n = 155	17	59	22			11	4	30		[228]

**Nationwide survey.*

‡No overall incidence given.

with antiribosomal P antibodies include hemolytic anemia, leukopenia or lymphopenia and alopecia [48].

In 1993, it was first suggested that there was an association of antiribosomal P antibodies and liver disease in SLE [49]. These autoantibodies have been reported to occur in up to 69% of patients with SLE-associated liver disease, but not in patients with autoimmune hepatitis [50]. One study suggested that the appearance of antiribosomal P antibodies and liver dysfunction may predict onset of CNS lupus [50]. To date, no study has examined the association of antiribosomal P antibodies and liver disease in patients with pSLE.

Antineuronal antibodies

In 1979, Bluestein reported the presence of antibodies reactive with neuronal or glial cell lines in 15 out of 18 sera from patients with SLE and CNS involvement. Bluestein concluded that each sera had a different antibody specificity profile [51]. Since that first report, multiple studies have examined the significance of antineuronal antibodies in patients with CNS involvement. Multiple reports have demonstrated the presence of antibodies directed against human and mouse neuroblastoma cell lines, bovine brain, brain-lymphocyte cross-reactive antibodies and antiganglioside antibodies in the sera or CSF of adult and pediatric patients with NPSLE [42,52,53]. The problem with these studies has been the lack of standardization of reference cell line or antigen source and a lack of specificity, as well as the requirement of multiple testing in research laboratories. One pediatric report suggested that antineuronal antibodies were positive in most patients with CNS involvement and that the titer decreased with clinical improvement, but other studies have not reproduced these findings [54]. The presence of these antibodies has been associated with cognitive impairment but not other features of CNS involvement. However, measuring the presence of these antibodies was

Table 4. Comparison of WHO 1982 modified classification of lupus nephritis and ISN/RPS 2003 classification.

WHO classification of lupus nephritis (modified 1982)	ISN/RPS 2003 classification of lupus nephritis [86]
Class I normal	***Class I minimal mesangial lupus nephritis***
A. Nil (by all techniques)	
B. Normal by light microscopy, deposits by electron microscopy	
Class II pure mesangiopathy	***Class II mesangial proliferative lupus nephritis***
A. Mesangial widening and/or mild hypercellularity (+)	
B. Moderate hypercellularity (++)	
Class III focal segmental glomerulonephritis	***Class III focal lupus nephritis***
A. Active necrotizing lesions	Active lesions (A)
B. Active and sclerosing lesions	Active and chronic lesions (A/C)
C. Sclerosing lesions	Chronic inactive lesions with glomerular scars (C)
Class IV diffuse glomerulonephritis	***Class IV diffuse segmental (IV-S) or global (IV-G)***
A. Without segmental lesions	IV-S (A) Active with diffuse segmental proliferation
B. With active necrotizing lesions	IV-G (A) Active with diffuse global proliferation
C. With active and sclerotic lesions	IV-S (A/C) Active and chronic with diffuse segmental proliferation and sclerosis
D. With sclerosing lesions	IV-G (A/C) Active and chronic with diffuse global proliferation and sclerosis
	IV-S (C) Chronic inactive with scars with diffuse segmental sclerosis
	IV-G(C) Chronic inactive with scars with diffuse global sclerosis
Class V diffuse membranous glomerulonephritis	***Class V membranous***
A. Pure membranous glomerulonephritis	
B. Associated with lesions of category II (A or B)	May occur in combination with class III or IV and both are diagnosed
Class VI advanced sclerosing glomerulonephritis	***Class VI advance sclerotic lupus nephritis***
	>90% of glomeruli are globally sclerosed without residual activity

ISN: International Society of Nephrology; RPS: Renal pathology section.

not of clinical benefit over neurocognitive testing [55]. In addition, a large study in adult SLE suggested that antineuronal antibodies were not helpful in determining CNS involvement beyond what information could be obtained by a combination of physical examination and magnetic resonance imaging (MRI) scans [56]. As the presence of antineuronal antibodies lacks specificity for CNS involvement and the measurement of these antibodies requires multiple testing in a research setting, the determination of antineuronal antibodies remains a research tool with limited, if any, clinical value [57].

Investigations

Electroencephalography

Many studies of CNS involvement in pSLE suggest that electroencephalography (EEG) findings are rarely helpful in diffuse NP disease and are usually abnormal only when seizures are present [8,11,15]. The reported incidence of EEG abnormalities is 0–60%, depending on the incidence of seizures reported in the study [8,11,15]. By contrast, EEG abnormalities have been reported to occur in up to 65% of adult patients with bilateral temporal slow activity, the most common abnormality seen. One study reported that an abnormal EEG was observed in 71% of patients with aPL [58]. This association has not been reported in pSLE. The only study in pSLE comparing EEG findings in patients with and without CNS involvement showed the presence of the fast bands in frontal regions of patients with CNS disease compared wth those without CNS disease. We suggest that conventional EEG has little to no value in assessing cerebral SLE, except for identifying epileptic activity and focal pathology.

Computed tomography & magnetic resonance imaging scans

Computed tomography (CT) scans have a limited role as a result of the use of MRI as the latter are better able to detect early lesions and lesions secondary to small vessel vasculitis. However, a true CNS vasculitis that is demonstrable on cerebral angiogram is rarely seen. The most common CT abnormality is cerebral atrophy with or without infarcts, which was reported in more than 50% of patients with pSLE and CNS involvement [11,12]. In addition to detecting cerebral atrophy, CT scans are helpful to detect infarcts, CNS hemorrhage and cerebral vein thrombosis if MRI is not readily available [59].

As early as 1989, studies in adults demonstrated that MRI was a more useful investigation than CT scan in patients with NPSLE [59]. Pediatric studies have reported that MRI studies are common in patients with seizures and CVA [8,15]. These findings are similar to those in adults, which found that MRI abnormalities were more frequent in patients with LAC and CVA and in patients with hypertension. Lesions may be focal but, more commonly, high-signal intensity multifocal white matter lesions (best seen on T2-weighted and diffusion-weighted images [DWI]) are found [15,60]. Multiple abnormalities in these sequences, and in particular in DWI images, likely represent the presence of small vessel vasculitis [60]. Abnormal MRI scans have been reported in patients without CNS disease with a frequency of up to 50% of patients [61]. It is not clear if these abnormalities represent subclinical CNS involvement or are nonspecific. Similarly to CT scans, the most common abnormality is cerebral atrophy. Adult studies have suggested that seizures are the most frequent NP feature associated with cerebral atrophy, while the use of steroids is associated with atrophy in patients with or without CNS disease [62]. Although steroid use is associated with cerebral atrophy in all studies, a direct correlation of atrophy with corticosteroid dose and duration of therapy is controversial [2].

The only pediatric study examining MR spectroscopy (hydrogen MR spectroscopy [H-MRS]) demonstrated abnormal *N*-acetylaspartate/creatine (NAA/Cr) ratios in SLE patients compared with controls. However, there was no correlation between H-MRS and CNS disease [61].

A study in adult SLE showed that SLE patients, with or without CNS involvement, had lower NAA and increased metabolites compared with controls, although abnormal NAA/Cr ratios were more commonly seen in patients with a current or prior history of NPSLE [62]. The most common areas of abnormal metabolites were in the frontal lobes. However, abnormalities in these areas were seen not only in patients with CNS-SLE, but also in patients with both mild symptoms or no CNS disease [63]. MRS remains a research tool only.

Single photon emission CT

It is clear from pathological studies that CNS disease in SLE is associated with a microvascular injury, although true vasculitis is less commonly seen [64]. Therefore, testing of cerebral perfusion should be a good test of active diffuse CNS disease. This was the principle used to examine the role of cerebral single-photon emission CT using hexamethylpropylamineoxine labeled with technetium-99 (single photon emission CT [SPECT]) to determine active CNS-SLE. In the

early 1990s, publications in adults began to appear suggesting a role for SPECT scans in CNS-SLE [65]. Large studies in adults have shown that, although SPECT scans are abnormal in the vast majority of patients with NPSLE, they are also abnormal in up to 85% of patients with only minor CNS involvement, such as headache and dizziness, and in up to 65% without any CNS signs or symptoms [65–67]. The most common finding is multiple areas of hypoperfusion, although one study found a predominance of lesions in the territory of the middle cerebral artery [66].

Smaller studies have been performed in pSLE [8,54,68–72]. These studies have shown perfusion defects in the majority of patients with active CNS disease, although, in some patients, CNS disease was manifested only by headache or isolated seizures, and abnormal SPECT scans were seen in up to 40% of patients without overt CNS involvement [8,54,68–72]. We found that, although a diffusely abnormal SPECT scan was highly sensitive for diffuse CNS involvement, the specificity was lower, as only 69% of patients with an abnormal scan had detectable CNS disease [72]. The most common abnormal SPECT scan pattern in patients with CNS-SLE was one of widespread multiple small areas of decreased uptake at multiple sites, suggestive of generalized patchy hypoperfusion [72]. Lastly, SPECT scans have little or no value in monitoring CNS disease activity as studies in both pediatric and adult SLE populations have shown that SPECT abnormalities persist following resolution of clinical disease [54,72]. However, one small pediatric study (involving four patients only) of weekly SPECT showed that the perfusion abnormality was reversed with treatment [70]. Multiple studies demonstrated that there was no correlation between SPECT findings and CNS manifestations, CT scans or MRI scans [65,73].

It has been suggested that an abnormal SPECT scan may reflect either overall SLE disease activity or damage [67]. This latter suggestion may explain the finding that SPECT scans remain abnormal with resolution of clinical CNS disease. However, it appears that SPECT adds little, if any, information to that obtained by clinical examination in patients with SLE. Nevertheless, there may be a role for SPECT scans in patients without obvious SLE who present with chorea, as one study has shown that patients with Sydenham's chorea may have areas with hyperperfusion in the basal ganglia compared with the hypoperfusion seen in patients with SLE [72]. One adult study suggested that abnormalities in both MRI and SPECT scans in patients without CNS disease may indicate the subsequent development of CNS manifestations after starting steroid therapy [73]. These findings need further investigation.

Although not routinely available, some authors have suggested that positron emission tomography (PET) scans are sensitive to detect CNS-SLE, particularly in patients with normal MRI scans [74,75]. However, one adult study suggested that PET was not helpful beyond clinical examination, neuropsychological testing and MR scans [56]. The characteristic finding on PET scan is hypometabolism in at least one brain region [74,75]. Decreased regional cerebral metabolic rates for glucose are most commonly seen in the parietal and temporal lobes [74,75]. It has been suggested that changes in serial PET scans correlate well with clinical changes [75]. Occasionally, relative increased metabolism has been reported [74]. Similarly to what has been reported with SPECT scan, PET scans may be able to differentiate chorea secondary to SLE from other causes of chorea.

Neurocognitive testing

Although there are multiple studies examining neurocognitive testing in adults with SLE in the literature, there have been few studies in pSLE. One study of 21 pediatric patients with SLE reported that 43% had abnormalities on neurocognitive testing and that the longer the disease duration, the lower the cognitive function [76]. In studies of adults with SLE, neurocognitive dysfunction has been reported to be present in approximately 50% of patients without clinically detectable evidence of CNS-SLE [55,77,78]. However, prospective longitudinal studies by Hanly and colleagues demonstrated a lower baseline cognitive impairment of approximately 20% of all patients with SLE, while, upon repeat testing 1 year later, less than 15% of patients remained impaired, suggesting that cognitive impairment may improve over time [79]. This is the only group to report statistically significant differences in the prevalence of cognitive dysfunction between patients with and without CNS-SLE [79]. In patients with a history of CNS involvement, it has been suggested that cognitive dysfunction remains relatively stable over time [80]. Although initially high overall disease activity at presentation of SLE has been associated with neurocognitive dysfunction activity, active SLE at the time of testing has not [77]. Various studies have

shown that short- and long-term memory, visual, spatial and verbal information processing and executive function are abnormal, but do not differ between patients with and without a history of CNS-SLE [78,81].

Therapy

Most investigators advocate treatment of CNS involvement with monthly intravenous pulse cyclophosphamide and corticosteroids with or without the addition of pulse methylprednisolone. However, there has not been any large controlled study of therapy in CNS-SLE either in pSLE or in adult SLE, but generally only case series. The first large series of patients with pSLE was in 1981 by Yancey and colleagues. They reported that all five patients who received either azathioprine or cyclophosphamide in addition to prednisone had a good recovery, while two out of 11 patients treated with prednisone alone died and three other patients had residual neurological defects [7]. Baca and colleagues reported on ten patients treated with high-dose daily prednisone and monthly pulses of both cyclophosphamide and methylprednisolone. This treatment regimen was associated with improvement in all patients, with complete recovery in six [82]. Olfat and colleagues found no significant difference in the outcome between ten patients treated with cyclophosphamide compared with seven patients treated with azathioprine. However, the cyclophosphamide-treated patients tended to have more extensive disease [15]. One large study reserved cyclophosphamide for patients who relapsed on steroids alone and found that only 44% of patients had full recovery [11]. Taken together, these studies in pSLE suggest that patients with significant CNS involvement should be treated with a combination of high-dose steroids and an immunosuppressive agent. Although rarely seen in pSLE, transverse myelitis generally requires early, aggressive treatment with a combination of intravenous pulse methylprednisolone and cyclophosphamide [38].

One study of patients with adult SLE and CNS involvement compared the use of low-dose intravenous cyclophosphamide and prednisone with prednisone alone. These investigators found that a higher percentage of patients treated with the combination of cyclophosphamide and prednisone had significant improvement compared with patients treated with prednisone alone [83]. Barile-Fabris and colleagues compared the effect of monthly intravenous cyclophosphamide with that of bimonthly intravenous methylprednisolone in 32 adult patients with CNS disease. They found a statistically significant difference in the response rate of cyclophosphamide- compared with methylprednisolone-treated patients [84]. Ramos and colleagues described a good early response in 25 adult patients with SLE disease to weekly low-dose intravenous cyclophosphamide pulses [85]. Case reports have suggested that plasmaphoresis may be of some benefit in treating resistant CNS-SLE, although the benefit of this therapy remains controversial.

We would suggest that all patients with major CNS involvement receive high-dose prednisone and an immunosuppressive agent. We have generally treated patients with azathioprine, except when patients are unable to function as a result of organic brain syndrome or psychosis or when patients have a significantly altered level of consciousness. In these patients, we use pulse intravenous cyclophosphamide. Many of these patients also require pulse methylprednisolone during the acute presentation.

Renal disease

The most common major organ involved in pSLE is the kidney, which is affected in approximately 50–60% of patients. In 85–90% of patients who develop renal lupus, the nephritis will be manifested within the first year of diagnosis of SLE. The WHO defined the histological classification of kidney biopsies in SLE. This classification has recently been redefined and ranges from mild mesangial (Class I) to advanced sclerotic lesions (Class VI) (**Table 5**) [86]. Although conceived for patients with adult SLE, similar to what was seen in the original classification, it is likely that the new classification will have prognostic and therapeutic significance in pSLE [87]. The most severe lesions are Class III and IV lupus nephritis (LN). These two classes of LN should be considered as a spectrum of proliferative nephritis. Proliferative LN is the most common form of nephritis in pediatric patients, occurring in 54–82% of all cases of nephritis, depending on the series. Most patients who go on to develop end-stage renal disease (ESRD) have one of these two lesions. The presence of a true vasculitis occurs in less than 10% of patients with renal lupus. A thrombotic microangiopathy may also be present with or without true vasculitis. The frequency of renal involvement, and of individual histological classes, in large published series of patients with pSLE and renal involvement is shown in **Table 6**.

Table 5. Renal involvement in pediatric systemic lupus erythmatosus: summary of large published series reported since 1977. The International Society of Nephrology/Renal Pathology Society 2003 classification is shown.

Study	Any renal involvement (%)	Class Ib/II (%)	Class III (%)	Class IV (%)	Class V (%)	Ref.
King (1977) n = 108*	61	27	18	52	3	[223]
Celermajer (1984) n = 56‡		41	18	36	5	[232]
McCurdy (1992) n = 44‡		27	16	49	8	[233]
Yang (1994) n = 167‡		33	18	41	8	[234]
Takei (1997) n = 373§	70	38	14	36	12	[9]
Emre (2001) n = 43		16	14	68	2	[133]
Miettunen (2004) n = 51*	49	12	16	56	16	[235]
Bogdanovic (2004) n = 53‡		28	2	64	6	[134]
Bader-Meunier (2005) n = 155*	50	22	60*	60*	11	[228]
Hiraki (2005)¶ n = 256*	55	18	29	46	21	

**n refers to total cohort of patients sampled.*

‡In these series only patients with renal disease were reported.

§Nationwide survey from Japan.

¶Published in abstract form only.

Although it may be easy to predict that patients who present with renal failure, nephrotic syndrome and hypertension have a form of proliferative LN, it is often difficult to predict the histological lesion in patients who present with less severe renal disease. Patients with a normal serum creatinine, normal blood pressure and minimally active urine sediment can have Class I, II, III, IV or even V nephritis. As treatment options vary for differing forms of SLE nephritis, we strongly recommend that an early renal biopsy is warranted in the presence of proteinuria, hematuria or elevated creatinine, even if the findings are minimal. The results of the biopsy should direct subsequent therapy.

Classes I and II LN are relatively mild lesions and the choice of therapy should reflect this. These patients generally require at most low-dose steroids, since these lesions are associated with excellent renal and patient long-term survival. Class I or II LN account for 15–30% of pSLE with LN (Table 4). However, transformation from Classes I and II LN to a proliferative lesion (Class III or IV) may occur after months to years in 20–30% of patients, and the long-term patient and renal survival is then similar to that of patients initially presenting with proliferative LN.

Table 6. 5-year renal and patient survival rate in pediatric systemic lupus erythematosus patients with proliferative lupus nephritis.

Study	ESRD* (%)	Patient survival (%)	Ref.
Platt (1982) n = 42	6	85	[236]
Yang (1994) n = 69	12	82	[234]
Emre (2001) n = 43	16	91	[133]
Bogdanovic (2004) n = 53	18	Not reported	[134]
Vachvanichsanong (2004) n = 19	31	84	[132]
Miettunen (2004) n = 25	12	100	[235]

**Percentage of patients developing end-stage renal disease.*

ESRD: End-stage renal disease.

Isolated membranous nephritis occurs in approximately 5–10% of pediatric patients with renal disease. The clinical presentation ranges from mild proteinuria to nephrotic range proteinuria with or without hematuria or casts. The possibility of lupus nephritis should always be considered in adolescents with what appears to be idiopathic nephrotic syndrome, nephrotic syndrome with hematuria or in patients with resistant nephrotic syndrome. Class V nephritis may be seen in conjunction with another renal lesion and, when present, the prognosis is related to the other lesion. Patients with a combination of Class V and II lesions have an excellent prognosis, while the prognosis of patients with Class III, IV or V is similar to that seen in patients with proliferative LN without features of membranous nephritis.

Hypertension is seen in up to 50% of patients with Class III or IV LN and is rarely seen in patients with Class I or II LN. The hypertension may be exacerbated following steroid treatment. Hypertension is an important comorbidity and should be aggressively treated. The presence of

undertreated hypertension in previous reports, when multiple effective antihypertensive agents were not available, may partially explain the higher morbidity and mortality previously described.

Treatment & prognosis of LN

Therapy of children with LN should be based on the renal histology, as the long-term prognosis is dependent on the renal lesion, emphasizing the importance of an early kidney biopsy.

Class I or II lupus nephritis

Patients with mesangial (Class I or II) LN require a relatively short course of treatment with low-dose steroids (prednisone 0.1–0.5 mg/kg/day) with a relatively rapid taper. As the long-term outcome of these patients is excellent, steroid side effects should be kept to a minimum. Proteinuria may be controlled with the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blocking (ARB) medications.

Proliferative nephritis: Class III &IV

As stated above, Class III and IV LN should be considered as a spectrum of disease and therefore the management should be the same. The mainstay of proliferative nephritis therapy is high-dose steroids (initially 2 mg/kg/day, maximum 60 mg/day) with a slow taper and an immunosuppressive agent. We generally treat patients with this dose for a total of 6 weeks. For the first 4 weeks, the dose is delivered three times a day and then as a single daily dose for the last weeks. This dose of prednisone is equivalent to the recommendation in adults of moderate-dose prednisone of 1 mg/kg/day. We then taper by approximately 10% every 2–4 weeks. The very early introduction of an immunosuppressive agent at the time of initiation of steroid therapy is crucial to the long-term outcome of proliferative LN.

In most centers, both pediatric and adult, the immunosuppressive agent of choice is intravenous monthly cyclophosphamide. This recommendation followed the publication by Austin and colleagues in 1986, which demonstrated superiority of prednisone and an immunosuppressive agent compared with prednisone alone [88]. This study pooled the results of multiple studies comparing the effect of prednisone alone with prednisone plus an immunosuppressive agent. The different immunosuppressive agents used were: azathioprine, oral cyclophosphamide, azathioprine plus oral cyclophosphamide and intravenous pulse cyclophosphamide. These arms spanned different eras and did not directly compare one immunosuppressive with another. The pooled results showed that prednisone plus an immunosuppressive agent was superior to prednisone alone. The greatest success appeared to be in the group treated with intravenous cyclophosphamide, but the difference between the outcome of patients treated with intravenous cyclophosphamide plus prednisone compared with patients treated with azathioprine plus prednisone was not statistically significant. It is interesting to note that 25% of patients treated with intravenous cyclophosphamide had Class V LN and not proliferative LN. These results confirmed the 1984 meta-analysis by Felson and colleagues, which demonstrated the superiority of the combination of prednisone and immunosuppressive agents as compared with prednisone alone in the treatment of proliferative LN [89].

Since the publication of the NIH article in 1986, there has not been a published trial comparing the efficacy of intravenous monthly cyclophosphamide with azathioprine in proliferative LN. What has been reported are large case series beginning in 1988, mainly in adult patients, of patients treated with intravenous monthly cyclophosphamide for 6 months followed by a further six courses of therapy over a 2-year period [90]. This treatment is currently accepted as the standard of care in most centers in most countries. However, a closer look at the studies since the NIH trials is warranted.

An American study in 1997 reported that renal survival declined annually from 89% (year one), to 86, 81, 75 and, finally, to 71% at year five, respectively [91]. In this study, African–American patients had a poorer outcome despite similar therapy [91]. Similarly, a study from the West Indies of 34 patients of African descent with Class IV LN treated with intravenous cyclophosphamide showed that only 29% of patients went into complete remission, while 18% developed ESRD. A study from the UK demonstrated that 60% of patients with Class III and 19% with Class IV LN developed ESRD, despite adequate treatment with intravenous cyclophosphamide [92]. A report from Taiwan University Hospital demonstrated a 5-year renal survival rate of 88% with a 10-year survival rate of 81%, while a study from Spain showed that 13% of patients developed ESRD and 39% of patients relapsed [93,94].

In addition to response rate, the rate of relapse is important in the long-term outcome. A study of 85 patients with proliferative LN and treated

with intravenous cyclophosphamide reported a 78% remission (median time to remission: 10 months) with a relapse rate of 35% (median time to relapse: 79 months) [95]. The long-term follow-up of 145 patients treated with pulse cyclophosphamide in the NIH cohort showed that 50% (73 patients) had a complete response and a further 13% (19 patients) had a partial response. Of these 92 patients, 44% had a renal flare. The mean time to renal flare was 36 months in the patients who were designated as complete responders. The mean time to flare was 18 months in the patients with a partial response. Of the 92 patients, 12 (13%) with complete/partial remission developed ESRD and 31 of the 48 patients (65%) who failed to respond developed ESRD or died (five patients were lost to follow-up). The overall rate of development of ESRD or death was 31% [96]. As can be seen from these multiple studies from multiple countries, treatment with intravenous cyclophosphamide is associated with an initial response rate of up to 80–85%, with a relapse rate of 40–50% and a 5-year renal survival rate of approximately 80%. However, a major problem when comparing studies is that different studies have used different definitions of response, partial response and relapse. In the future, studies should (must) use uniform outcome measures, such as those recently recommended by the ACR [97].

In addition to efficacy, the safety of the drug should be considered when deciding on the appropriate immunosuppressive agent. All studies demonstrate that treatment with intravenous cyclophosphamide and prednisone is associated with a higher rate of infection and gonadal toxicity than treatment with either azathioprine or mycophenolate mofetil (MMF) [98]. Infections are more commonly seen in patients with cyclophosphamide, many of which require hospitalization. Although some investigators have stated that lower rates of infections are seen in patients treated with lower doses of steroids, it has been reported that the risk of infection is unrelated to prednisone dose [99]. Most studies would suggest that sustained amenorrhea is common in women aged 32 years or older, even with short courses of intravenous cyclophosphamide with a lower risk of ovarian failure in younger women [99,100]. The rate of amenorrhea has reported to be up to 37%, with permanent amenorrhea in up to 15% [101–103].

As a result of these toxicities, more recent studies in adults have examined protocols to reduce the toxicity of cyclophosphamide [104,105]. These have included studies examining lower total doses of cyclophosphamide [106] or shorter periods of so-called induction therapy with cyclophosphamide therapy (3–6 months of cyclophosphamide), followed by maintenance therapy of either azathioprine or MMF [107]. The Euro-Lupus trial demonstrated that low-dose intravenous cyclophosphamide (total dose of 3 g) followed by azathioprine was as effective as standard dosing of intravenous cyclophosphamide [95,108]. One additional strategy to reduce gonadal toxicity of cyclophosphamide is the administration of gonadotropin-releasing hormone agonists throughout the course of cyclophosphamide therapy [100,104,109]. However, permanent amenorrhea has been reported in patients treated with gonadotropin-releasing hormone agonists [109]. The mechanism of action of gonadotropin-releasing hormone agonists to protect ovarian function is unknown, but it may decrease the number of follicles that develop and thereby make them less susceptible to the effects of cyclophosphamide [110]. This may result in a decreased number of depleted follicles, which is usually seen following the use of alkylating agents. The gonadal toxicity of cyclophosphamide is particularly important in pSLE, however, it is not clear what the true gonadal toxicity of cyclophosphamide is in pSLE.

Both azathioprine and MMF have been studied as alternative immunosuppressive agents to cyclophosphamide. Azathioprine was the first of these agents to be studied. In 1984, prior to the NIH publication, in a meta-analysis Felson and colleagues demonstrated that a combination of prednisone and azathioprine was superior to prednisone alone in the treatment of proliferative LN [89]. A second meta-analysis, in 1997, following the NIH paper, confirmed the superiority of immunosuppressive agents in combination with prednisone compared with prednisone alone. Although they found that intravenous cyclophosphamide, in conjunction with oral prednisone, was more effective than oral prednisone alone for both total mortality and ESRD, cyclophosphamide was not found to be more effective than azathioprine for either mortality or ESRD [111]. The most recent meta-analysis, in 2004, showed that cyclophosphamide plus steroids reduced the risk for doubling of creatinine, but had no impact on overall mortality compared with steroids alone. This therapy was associated with an increased risk of ovarian failure. Azathioprine plus steroids reduced the risk for all-cause mortality compared with steroids alone,

but had no effect on renal outcomes. There was no difference between the two therapies for any outcome [112]. All of the meta-analyses examined only controlled trials.

Since the NIH study, there have been very few open-label studies or case series using azathioprine. In 2000, in 26 adult patients with proliferative LN, Nossent and colleagues demonstrated excellent renal survival of 92, 87 and 87% at 5, 10 and 15 years, respectively [113]. Similarly, in 2002, we demonstrated, in 27 pediatric patients with proliferative LN treated with azathioprine and prednisone, 92 and 84% 5- and 10-year renal survival with 94 and 91% 5- and 10-year patient survivals, respectively [114]. These results are comparable with the results reported in studies using cyclophosphamide. In a more recent study of patients who presented with renal failure, we found a relapse rate of 44%, which is identical to the reported relapse rate using intravenous cyclophosphamide from the NIH [96].

In 2004, a large controlled study compared the effect of maintaining patients with proliferative LN on azathioprine, MMF or intravenous cyclophosphamide. All patients received oral steroids and 3–6 months of intravenous cyclophosphamide to achieve remission. Azathioprine and MMF maintenance therapy was associated with a lower relapse rate, lower death rate and lower rate of ESRD compared with the patients maintained on intravenous cyclophosphamide [107]. In 2002, Mok and colleagues reported on 55 patients treated with prednisone and oral cyclophosphamide for 6–9 months, followed by oral azathioprine. At 12 months, 89% had complete or partial remission. The cumulative risk of renal flare was 6% at 1 year, 21% at 3 years and 32% at 5 years, with a median time to relapse of 43 months. At 10 years, 82% had stable renal function [115]. The time to flare was similar to the time to flare in the NIH study using intravenous cyclophosphamide and to our study of patients presenting in renal failure treated with azathioprine [96].

More recent studies have examined the use of MMF in proliferative LN. This agent has been shown to be of benefit in renal transplantation with an excellent safety profile. Multiple open-label studies in adults with SLE have shown MMF to be effective in patients with moderate-to-severe renal SLE who have failed to respond to or developed significant side effects with intravenous cyclophosphamide [116–118]. MMF was well tolerated in these studies. There have been only two reported case series of MMF therapy in pediatric patients with LN. The first reported a beneficial effect of MMF in patients with Class V LN but suggested that it was less efficacious in patients with proliferative LN [119]. The second smaller study of only two patients, both refractory to cyclophosphamide, reported remission following MMF [120].

Following these encouraging reports of the efficacy of MMF, randomized trials comparing MMF with cyclophosphamide were performed in adults with Class III, IV or V LN. The first controlled study, in 42 patients, demonstrated that MMF was equally effective as 6 months of oral cyclophosphamide followed by 6 months of azathioprine in inducing and maintaining remission at 12 months in adult patients with proliferative LN. The rates of complete/partial remission were 95 and 90% for MMF and cyclophosphamide/azathioprine groups, respectively, and the relapse rates were similar, at 15 and 11%, respectively [121]. In the subsequent follow-up, at a median of 63 months, the percentage of patients with a doubling of creatinine level was similar in the MMF group and the cyclophosphamide/azathioprine (6.3 vs 10.0%, respectively). In addition, the relapse-free survival rates were similar, although four patients in the cyclophosphamide/azathioprine group, but none in the MMF group, died or developed ESRD. In addition, MMF treatment was associated with fewer infections and fewer infections that required hospitalization [122]. In 2004, Contreras and colleagues (as described in the section on azathioprine) showed that MMF maintenance therapy, similar to what was seen with azathioprine, was associated with a lower relapse rate, death rate and lower rate of ESRD compared with patients maintained on intravenous cyclophosphamide. All patients received oral steroids and 3–6 months of intravenous cyclophosphamide to achieve remission prior to the maintenance phase. In addition, both azathioprine and MMF were associated with fewer hospitalizations, lower incidence of amenorrhea and fewer infections than in the patients maintained on intravenous cyclophosphamide [107].

The first reported randomized trial to compare initial therapy with MMF with intravenous cyclophosphamide monthly, reported in 2005, studied 44 patients with newly diagnosed proliferative LN. The partial/complete remission rates, rate of improvement of proteinuria and renal function were similar between the groups. All patients received similar doses of

corticosteroids [123]. The most recent publication examined 140 patients with Class III, IV or V LN, randomized to receive either MMF or intravenous cyclophosphamide. At 24 months, this study demonstrated that MMF was superior to intravenous cyclophosphamide in inducing remission and that it had a better safety profile. Three patients assigned to cyclophosphamide died, but none in the MMF group died, and there were also fewer severe infections and hospitalizations in the MMF group. However, MMF therapy was associated with a higher incidence of diarrhea. In this study, patients had longer-standing LN than in the first study (mean disease duration of 51 months), and if a satisfactory response was not seen at 12 weeks, patients were allowed to crossover to the other therapy [124]. However, there has been no reported long-term follow-up of patients treated with MMF.

One problem in comparing outcome studies is that many studies examine patients from different eras. A recent study showed that patients with newly diagnosed proliferative LN seen between 1980 and 1989 had a worse outcome as compared with patients seen between 1990 and 2000, despite similar treatments. The rates of ESRD were 40 and 17%, respectively. The authors suggested that the reason for the difference in development of ESRD was earlier diagnosis with earlier treatment in the patients seen between 1990 and 2000 [125]. There have been very few studies examining the outcome of proliferative LN more than 10 years after treatment. The largest study to date (in adult patients with SLE) reported survival rates of 84, 72, 62, 61 and 54% at 5, 10, 15, 20 and 25 years, respectively, with better rates in patients treated from 1976 to 1986 than in those treated from 1963 to 1975. Sepsis and myocardial infarction were the principal causes of late death, with most cases of renal failure occurring within 10 years of renal disease diagnosis. There was no difference in the outcome of patients treated with azathioprine or oral cyclophosphamide [126]. However, this was not a randomized trial and it is not clear why one treatment was selected over the other.

Two final important considerations in determining the choice of immunosuppressive agent to be used in proliferative LN are patient preference and flare rate. The only studies to examine this issue demonstrated that 98% of adult female patients would choose azathioprine over cyclophosphamide if both drugs conferred an equal probability of renal survival. Even if cyclophosphamide had better short-term renal survival, 31% were unwilling to switch from azathioprine to cyclophosphamide and 15% were unwilling to switch even for improved long-term renal survival. Risk-seeking women were more likely to prefer cyclophosphamide for the treatment of lupus nephritis than risk-averse women [127]. No similar study has been performed in the pediatric age group. As stated previously, the natural history of Class III and IV LN is to flare. Flare rates have been reported to vary between 27 and 66% in adult studies, with a mean rate of approximately 45% [94,96,128]. The highest flare rates have been reported to occur in patients aged less than 30 years at the time of nephritis onset [128]. There has been no study in pSLE describing flare rates but our experience and the reported flare rates in small studies suggest that flares are common in pediatric patients with proliferative LN. Overall, the data would suggest that patients treated with intravenous cyclophosphamide, azathioprine and MMF have similar flare rates.

Pediatric studies of cyclophosphamide in proliferative LN

A study from Malaysia of 31 patients with pSLE and proliferative LN treated with intravenous pulse cyclophosphamide showed a remission rate of only 39%, with persistent significant proteinuria in 58%. One patient developed ESRD and five patients died [129]. A study from Thailand of 17 patients with proliferative LN treated with intravenous cyclophosphamide had a 68% 5-year renal survival rate, with a 84% patient survival rate [130]. A study from Turkey of 29 patients with Class IV LN who were administered intravenous cyclophosphamide reported a 5-year renal survival rate of 76%, with a 86% 5-year patient survival rate. The relapse rate was 31%. All deaths occurred within the first year of LN diagnosis [131]. The 5-year renal survival rate of 34 patients with Class IV LN treated with intravenous cyclophosphamide reported by Bogdnovic and colleagues from the Balkans was 82%. A partial/complete remission was obtained in 59% of patients. The outcome was not influenced by the chronicity index [132]. As seen in adults with SLE, nephritis in African–American patients with pSLE is associated with increased morbidity and mortality [133]. The most recent study to examine this issue demonstrated that 49% of patients (67% of whom were African–American) developed ESRD at a mean of

2.8 years. The mortality rate was 17% [33]. Of note, although only 28% of patients had both nephritis and CNS disease, 58% of patients who died had both CNS and renal disease, as did 40% of patients who developed ESRD. Both the mortality rate and rate of ESRD were higher in this study than in the aforementioned studies.

Lehman and colleagues, from the USA, reported on the 3-year follow-up of 16 patients treated with intravenous cyclophosphamide. There was a decrease in mean daily prednisone dose by 60%, but at 36 months the mean daily dose was 14 mg/day. There was a decrease in proteinuria, although the mean protein excretion remained abnormal at 500 mg/day at the last follow-up. No data were given on remission rate [134]. Therefore, the overall 5-year renal survival rate of patients treated with intravenous cyclophosphamide was between 68 and 82%, with patient survival rates of approximately 85%. These results are similar to the results seen in adult studies with cyclophosphamide, MMF and azathioprine. A summary of renal and patient 5-year survival rates of published case series of patients with pSLE and renal involvement is shown in **Table 5**. Longer survival rates have rarely been reported.

When considering therapy of LN, it must be remembered that the nature history of proliferative LN is to flare and, therefore, in patients with pSLE, the cumulative toxicity of repeated courses of cyclophosphamide must be considered prior to initiating therapy with this agent. Furthermore, it is clear that azathioprine and MMF have a better safety record than cyclophosphamide with less gonadal toxicity [135]. Therefore, when the evidence does not demonstrate the superiority of intravenous cyclophosphamide in the treatment of proliferative LN (as outlined above) and azathioprine and MMF have a better safety profile, we suggest that the first immunosuppressive agent to be used in patients with proliferative LN should be either azathioprine or MMF, and not intravenous cyclophosphamide. All three agents appear to have similar flare rates following induction of remission. We suggest that intravenous cyclophosphamide should be reserved for patients who do not obtain a partial/complete remission after 6 months of therapy with one or both of the two oral agents. It should not be considered the gold standard of therapy of LN in pSLE. Currently, the major advantage of azathioprine over MMF is the cheaper cost and its longer use in pediatric patients. If a patient is intolerant of azathioprine or MMF, then a trial of the other agent is warranted prior to the use of cyclophosphamide. We do not suggest the use of oral cyclophosphamide over intravenous cyclophosphamide as it has a higher toxicity without any evidence of increased efficacy.

Antiphospholipid antibodies in pediatric SLE

A special section should be devoted to discuss the significance of aPL in pSLE. These antibodies consist of multiple specificities, of which the LAC and aCL are the most frequently measured and have the most clinical relevance. Although the importance of antibodies directed against anti-β2-glycoprotein-I (anti-β2GPI) has been extensively studied in adults, there have been fewer studies in pSLE [136–140]. The prevalence of aCL has been reported to be as high as 70%, although most studies indicate that they are present in 50–60% of patients with pSLE with the LAC present in 20–30% of patients [31,137–144]. The incidence of aPL has been reported to be as high as 65–70% when testing is carried out against other phospholipids in addition to aCL [141,145] However, the clinical relevance of antibodies to phospholipids other than aCL, β2GP1 or the lipids present in the LAC has yet to be proven, and most investigators suggest that LAC and aCL/β2GP1 are the antibodies that should be routinely measured to determine the risk of thrombosis [146–148]. ACL and β2GPI antibodies are generally present together in patients with SLE. Anti-β2GPI antibodies have been reported in up to 50% of patients with pSLE, but the measurement of these autoantibodies generally did not add to the knowledge derived from the measurement of LAC and aCL [139,140]. The only exception was the association of anti-β2GPI antibodies and stroke and persistent thrombocytopenia in one study, but the number of patients with stroke was very small [139]. Although the concept of β2GPI-dependent aCL has gained acceptance in adults with SLE, it has not been well studied in pSLE.

A large cohort study from our institute found that, in 85% of the patients with a thromboembolic event, the event was in the venous rather than the arterial circulation. All events occurred in the LAC-positive patients. All patients were treated with long-term anticoagulation and only one patient had a recurrence on therapeutic anticoagulation [34]. A smaller study from Pittsburgh, PA, USA, found that 24% of all patients with pSLE had thrombosis and, again, the majority of patients had a venous rather than an

arterial thrombosis. They also found an association with LAC and thrombosis as well as an association of the LAC and catastrophic events [141]. This high rate of aPL syndrome (APS) has been reported in only one study of adults with SLE, although in that study, the appearance of the first event occurred up to 15 years after diagnosis of SLE [149]. In a study using a smaller subset of the large HSC cohort, 58 patients were extensively investigated with multiple different assays. The strongest association of a thromboemolic event was with a positive LAC with weaker associations with aCL, anti-β2GP and antiprothrombin (PT) antibodies. The LAC had the highest sensitivity and specificity of any single test and the addition of studies to determine other aPLs did not add any additional diagnostic value to the LAC [140] Other investigators, in adults with SLE and in pSLE, have also shown that the LAC has the strongest association with thrombosis in SLE [31,150]. Interestingly, the thrombotic episode is frequently associated with a decrease in the aCL titers, which is presumed to be secondary to consumption [151]. In the Hopkins SLE cohort, the risk of developing a thromboembolic event within 20 years of SLE diagnosis was more than 40% in patients with the LAC and, although aCL was associated with the risk of a thromboembolic event, the LAC was the better predictor [152].

Overall, we recommend that all pediatric patients presenting with deep vein thrombosis, including cerebral vein thrombosis, even without any other clinical features of SLE or APS, should be screened for aPL, including the LAC. In addition, all patients with a thromboembolic event, even without evidence of overt SLE, should be screened for the presence of antinuclear antibodies and should have ongoing monitoring for the development of SLE over time [151–156]. Similarly, pediatric patients who present with Budd–Chiari syndrome frequently have the LAC and should be monitored for the development of SLE [157].

It is important to note that the LAC has been shown to consist of antibodies directed against β2GP1 and prothrombin [158,159]. However, the role of antiprothrombin antibodies only and thrombosis is not clear. The association of thrombosis and aCL is strongest in patients with high levels of immunoglobulin G aCL [160]. Most studies suggest that, in clinical practice testing for aCL and LAC, but not other aPL antibodies, is all that is required to determine patients at risk for APS [146]. The presence of the LAC has been also been associated with hemorrhage. These patients have evidence of not only the LAC but also reduced Factor II levels. It is the decreased Factor II activity that results in a prolonged PT in addition to the prolonged partial thromboplastin time with a net result of an increased risk of bleeding rather than thrombosis. The mechanism leading to the decreased Factor II level is not clear [161].

APS has been reported in 10–15% of cases of pSLE [143]. Patients generally present with evidence of venous thrombosis, although arterial thromboses, including stroke, transient ischemic attacks and thrombosis, of major vessels of pulmonary and abdominal vasculature may occur. Venous thromboses are more common than arterial thrombosis in pSLE, probably as the result of a relative paucity of atherosclerosis in the pediatric age group compared with a cohort of adults with SLE. There is a high -risk of recurrence without long-term anticoagulation, with a reported recurrence rate as high as 30% in one large adult study [34,143,162]. In patients with pSLE, the association between a thrombotic event and aPL is strongest in the presence of the LAC rather than other aPL including aCL [140,163]. On the arterial side, pediatric patients appear to be at risk of the development of splenic infarction with development of hyposplenism and the resulting increased risk of infection [164]. The best study of the incidence of APS in patients with LAC and aCL is a study in adults by Shah and colleagues, which showed that up to 50% of patients with LAC will develop APS [163]. Associated features of APS include hemolytic anemia, thrombocytopenia, valvular heart disease or Libbman-Sacks endocarditis and CVA, including vaso-occlusive retinopathy, while the association with osteonecrosis is controversial [31,144,165]. Recurrent fetal loss is rarely reported in pediatric APS, probably as a result of the relatively low incidence of pregnancies in this age group.

One final set of antibodies of potential importance in APS are anti-annexin antibodies. Current evidence suggests that annexin-V is protective against thrombosis by binding to phospholipids. Therefore, anti-annexin-V antibodies may prevent this binding and allow surface phospholipids to activate the coagulation system. Studies in adults with SLE have suggested a role for anti-annexin antibodies, in particular in the presence of atherosclerosis, in the development of thrombosis [138,149,166]. To date, there has not been any study in pediatric patients.

Further coagulation abnormalities that may predispose to thromboembolic events include acquired activated protein C resistance (APCR) and Factor V Leiden and prothrombin gene mutations. Acquired APCR has been demonstrated in 31% of patients with pSLE and was associated with the presence of LAC but not aCL. Although APCR was associated with an increased risk of thromboembolic events, it was not clear if this increased risk was the result of the association of APCR with the LAC or independent of this association [167]. In adult studies in SLE, both aCL/β2GPI and anti-PT antibodies have been correlated with LAC activity and these autoantibodies may cause APCR, and thereby increase the risk of a thromboembolic event. Other potential predisposing factors for thrombosis include Factor V Leiden, prothrombin gene mutations and low protein S levels. Heterozygous Factor V Leiden mutations have been shown to be associated with thrombosis in studies of patients with adult but not pSLE, while prothrombin gene mutations are not increased in either pediatric or adult SLE populations [34,168]. Although low free protein S levels have been reported in SLE, these low levels have not been associated with thrombosis in SLE patients [169].

It is currently recommended that patients with antiphospholipid antibodies should avoid estrogen-containing oral contraceptives because of an increased risk of thrombosis and chorea in these patients, although this issue is still not completely resolved [20,170,171]. However, most studies suggest that these medications do not appear to increase the risk of disease flare [171].

Pediatric primary antiphospholipid antibody syndrome

Asymptomatic thrombosis of the major vessels and pulmonary emboli may occur in the absence of overt SLE in the presence of aPL. When this occurs, the clinical syndrome is referred to as primary antiphospholipid antibody syndrome or pediatric primary APS (PAPS). Clinical features of PAPS include digital ischemia, stroke, hypertension, splenic infarction, peripheral arterial thrombosis, Budd–Chiari syndrome, deep vein thrombosis, pulmonary embolus, chorea, transverse myelitis and spinal cord infarction, optic neuritis and retinovascular thrombosis, Addison disease, polyvalvar cardiac disease, Evan's syndrome, thrombocytopenia and pulmonary vaso-occlusive disease [33,34,172–179]. Similar to what is observed in pSLE and APS, there is a strong association of LAC and aCL with pediatric PAPS [172]. The presence of aPL is a common thrombophilic defect in patients with pediatric stroke and cerebral sinus vein thrombosis [180,181]. Reports in adults with PAPS have shown that thrombocytopenia may be present in up to 25% of patients and the thrombocytopenia may be associated with thrombosis and/or disseminated intravascular coagulation [182,183]. The thrombocytopenia may be refractory to immunosuppressive therapies and some have advocated splenectomy for refractory patients, although, more recently, anti-B-cell therapy has been advocated (see future perspective). Most studies suggest that aPLs are more commonly seen in children than adults presenting with pulmonary embolus, and many of these children will develop overt SLE in follow-up [154,184]. Movement disorders, including chorea, dystonia and ballism, are other important presentations of pediatric PAPS [33,185,186]. This is particularly true with the decrease in rheumatic fever as a cause of chorea in children. Although uncommon, severe renal hypertension due to either renal arterial occlusion or renal thrombotic microangiopathy may be seen in pediatric PAPS and some patients may go on to develop overt SLE [187,188]. In adult patients with PAPS, renal involvement is characterized clinically by systemic hypertension, hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura and less commonly with isolated proteinuria or hematuria [187,188]. Pathologically small vessel vaso-occlusive lesions associated with fibrous intimal hyperplasia of interlobular arteries is the characteristic lesion [189]. Similarly to what is seen in SLE, pediatric patients with primary PAPS, including patients presenting with idiopathic cerebral ischemia, are at risk of developing SLE months to years later [33,190].

Catastrophic antiphospholipid antibody syndrome

A particularly worrisome presentation of patients with aPL is the development of catastrophic APS (CAPS). Less than 1% of adult patients with APS present with life-threatening CAPS. Although rarely seen in children, there have been case reports in the pediatric age group of patients who present with multiple thromboses and multiorgan failure [184,191–194]. Clinically, these patients have evidence of multiple thromboses, including renal artery/vein leading to renal failure, cardiac, gastrointestinal, pulmonary and cerebral thrombosis. Disseminated intravascular

coagulation is a frequent complication of CAPS, which requires a balance between the risk of thrombosis and the risk of hemorrhage. However, most reports demonstrated successful treatment of these patients with anticoagulation and immunosuppression [184].

In studies of adults with CAPS, neurological involvement is the main cause of death. The CNS pathology generally reveals thrombotic microangiopathy as well as small and large vessel occlusions in several brain areas [195]. The mortality of CAPS in adults was originally reported to be as high as 45%, however, more recent evidence has suggested an improved outcome. If patients survive the initial event, recurrence is unlikely, with only approximately 25% of the survivors developing a second evident with a higher survival rate [196]. Similar to the anecdotal reports in pediatrics, adult patients treated with both anticoagulation and immunosuppression have the best survival rate.

Expert view

There are many similarities between pediatric SLE and adult-onset SLE in clinical presentation, response to treatment and the production of autoantibodies. However, pSLE tends to be a more severe disease than its adult counterpart and there are likely differences in response to therapy and the potential for long-term toxicity. To date, there have been no therapeutic trials in pSLE and all therapy efficacy data have been extrapolated from adult to pediatric patients. This has led to the blind acceptance of data generated in adult studies without regard to the potential longer-term toxicities of the therapies in pSLE. Outcome measures, including the Systemic Lupus Erythematosus Daily Activity Index, European Consensus Lupus Activity Measure, British Isles Lupus Assessment Group Index and Systemic Lupus Activity Measure, have been validated for longitudinal use in pediatric patients [196–200]. However, their role in interventional studies is yet to be defined either in adult or pediatric studies [201,202]. Similarly, the SLICC-DI has been validated to assess damage in longitudinal studies in pediatric patients [200,202–205]. It has been suggested that the SLICC-DI should be adapted for pediatric use; however, the usefulness of a modification of the SLICC-DI requires further study, as the validation studies would suggest that the current SLICC-DI is a useful measure in pediatric SLE [206]. In addition, it has the advantage of being able to longitudinally follow patients into adulthood using the same tool.

The two most serious manifestations of SLE are CNS and renal involvement. CNS involvement can range from mild headache to coma. Despite many advances in neuroimaging techniques with SPECT, MRI, magnetic resonance spectroscopy and PET scanning, the diagnosis of CNS involvement generally remains a clinical one, with imaging techniques of greatest value in patients with vasculitis and to rule out other causes for CNS dysfunction. Great promise was held for the use of SPECT scanning to detect widespread CNS involvement but large, longitudinal studies have suggested that this technique is best used to differentiate SLE as a cause of CNS dysfunctional from other causes, such as idiopathic psychosis. This technique lacks specificity for clinically significant CNS involvement in patients known to have SLE. Patients with the most serious manifestations of psychosis, vasculitis and acute confusional state (organic brain syndrome) usually require treatment with high-dose corticosteroids and an immunosuppressive agent, such as azathioprine or cyclophosphamide. Most investigators tend to use cyclophosphamide rather than azathioprine. However, the choice of cyclophosphamide over azathioprine is based on anecdotal evidence and the adage that 'bad disease requires bad medicine'. We tend to use prednisone in high doses of 2 mg/kg/day up to a maximum of 60 mg/day, which is less than 1 mg/kg/day for a patient who weighs over 60 kg. Initially, it is divided and then consolidated and slowly tapered as per the protocol previously outlined in the section on renal involvement. Pulse methylprednisolone may be initially used and antipsychotic medications can be very helpful. Although most patients will recover from the acute presentation, CNS involvement remains a cause of significant morbidity.

Renal involvement, occurring in approximately 50–60% of patients, is the leading cause of morbidity and mortality. The WHO has developed a renal classification of renal pathology, most recently revised in 2003, which has been shown to be of both diagnostic and, more importantly, prognostic significance. The long-term outcome is generally dictated by the histology and therapy is guided by the histology. As a result, we suggest that all patients with a persistently abnormal urinalysis, hypertension or abnormal renal function test should undergo an early kidney biopsy to properly direct therapy. This would allow the clinician to be appropriately aggressive in the management of proliferative

nephritis and not over-treat patients with a milder lesion, such as Class I and II and the majority of patients with Class V nephritis. The presence of a proliferative lesion, Classes III and IV, requires aggressive high prednisone and an immunosuppressive. Most investigators have used intravenous cyclophosphamide as the immunosuppressive, despite the meta-analyses having failed to demonstrate the superiority of this agent over azathioprine. Our recent data of the long-term outcome of pediatric patients with proliferative lupus nephritis treated with either azathioprine or cyclophosphamide have shown that treatment with azathioprine, even in the presence of renal failure, is associated with an excellent outcome comparable with that obtained using cyclophosphamide in our own and other studies. It is clear that long-term treatment with cyclophosphamide is associated with an increase of malignancy, which is of particular concern in pediatric patients who will have a much longer lifespan (we hope), and thus more time to develop cyclophosphamide-induced cancer. In addition, as pediatric patients develop SLE prior to or at the beginning of child-bearing age the dose-dependent increased risk of infertility associated with cyclophosphamide is particularly significant. Azathioprine is not associated with infertility and is associated with a minimally, or nonexistent, increased risk of cancer. We therefore suggest that azathioprine, at a dose of 3 mg/kg/day (maximum 150 mg), should be used at the time of diagnosis of proliferative lupus nephritis in addition to high-dose corticosteroids. The development of leukopenia or lymphopenia may require the use of a lower dose of azathioprine. If patients are intolerant to azathioprine or fail to respond to this medication, we suggest the use of MMF. However, this may change and MMF may be the drug of choice in the future (see future perspective). Although the use of immunosuppressive agents and better overall management, including better blood pressure control with the use of ACE inhibitors and ARBs, have increased patient and renal survival rates, and both the remission and relapse rates of patients with proliferative LN can be significantly improved. New therapies and controlled trials are desperately needed.

As the mortality of acute pSLE has decreased, it has become apparent that patients with pediatric-onset SLE may develop premature atherosclerosis in early adulthood. This development, initially described as the bimodal mortality of SLE by Urowitz and colleagues, has been demonstrated to cause a 50-fold increase in deaths secondary to cardiovascular and cerebral vascular in women less than age 35 years of age [207]. Although it is not clear what factors lead to premature atherosclerosis, it is likely that a major risk factor is the chronic inflammation associated with SLE, as traditional risk factors and prednisone use alone cannot account for this increased burden of cerebral and cardiovascular disease. Studies are required to determine whether better control of SLE *per se*, including the aggressive use of antihypertensive agents, lipid-lowering agents and/or lifestyle interventions, are of the most benefit in decreasing premature atherosclerosis. These studies must be performed in pediatric patients and not extrapolated from data from studies in adults as, although the disease tends to be more aggressive in pediatric patients, the burden of atherosclerosis prior to development of SLE differs and, therefore, it is not clear whether the results of studies in adult patients are directly applicable to pediatric patients.

Future perspective

The next 5 years are likely to be a time of great promise, although it is not yet clear how significantly any new developments will alter the long-term outcome. In the past, the major strides in the treatment of SLE have come in the improved use of corticosteroids. Corticosteroids remain the mainstay of therapy and this is unlikely to change in the next 5 years. One promising new development may be the use of MMF rather than cyclophosphamide in the treatment of proliferative LN and significant CNS involvement. Most recent studies comparing these two agents demonstrate that MMF is as least as efficacious, if not superior, to intravenous cyclophosphamide in proliferative LN. However, these studies are only short term. There has not been any large controlled study of the use of azathioprine in SLE. Although it is likely that MMF and azathioprine have similar efficacies, it is yet to be proven. Currently, most rheumatologists and nephrologists are more likely to use MMF, despite its increased cost and lack of long-term safety data compared with azathioprine.

Newer, better-targeted therapies hold the promise of eliminating the autoreactive cells without the global side effect of nonspecific immunosuppression. The most widely suggested strategy is to selectively target B cells using either a monoclonal anti-B cell antibody or to target

receptors that are specific for B cells and that may be overexpressed on autoantibody-secreting cells. To date, there have only been uncontrolled studies using these strategies. The early reports with short-term follow-up of the use of rituximab, a chimeric antipan B-cell antibody directed against CD20 in patients with pediatric SLE have been encouraging, with a good response in the majority of patients. However, a significant number of patients developed severe adverse events, with a rate of 45% in the largest reported pediatric study. Many of these patients were on other immunosuppressive agents in addition to rituximab [208–214]. Although the studies using anti-CD20 therapy hold promise, the results are too preliminary to determine the exact role of targeting B cells. This therapy does, however, appear to be particularly effective in SLE patients with refractory autoimmune thrombocytopenia and hemolytic anemia, although its role in patients with major organ involvement requires large controlled studies [215,216].

Similar to what has been suggested in rheumatoid arthritis, it may be possible to target activation molecules on T cells in order to downregulate autoantibody production. To date, there have been no published data using this strategy. One final method to downregulate the immune system would be through anticytokine therapy. This strategy of targeting tumor necrosis factor (TNF) has been successful in rheumatoid arthritis. However, studies using anti-interleukin 10 therapy in SLE have been disappointing and most investigators would not use anti-TNF therapy in SLE. Overall, more targeted therapies hold great promise for the treatment of SLE but it is unlikely that they will have a major therapeutic impact in the next 5 years.

As previously stated, with the decreased acute mortality of pSLE, patients are living longer and developing new morbidities. The major morbidities, probably the result of both the chronic inflammation of SLE and treatment with corticosteroids, are premature atherosclerosis and osteoporosis. To date, most studies of atherosclerosis have focused on adult patients, but it is likely that this will become an increasingly recognized field of investigation. It is probable that over the next 5 years there will be a better understanding of the roles of chronic inflammation and traditional risk factors, including hyperlipidemia, in the development of atherosclerosis in pSLE. This will allow for better and individualized interventions to prevent what is likely to become an ever increasing cause of morbidity and mortality. Finally, it is likely that osteoporosis will become better recognized as a significant cause of morbidity that may be amenable to interventions. These potential inventions are likely to include an increasing emphasis on exercise accompanied by a better use of corticosteroids. It is not clear that the use of bisphosphanates will alter the outcome of corticosteroid-induced osteoporosis in this age group.

It is crucial that investigators in the pSLE community and granting agencies recognize that studies in patients with adult SLE cannot be directly extrapolated into pediatric patients and that large, multicentered studies are undertaken. We suggest that testing therapies that are shown to be of benefit in adult SLE are not 'me too studies', but are rather directed at a disease that is similar to, but not the same as adult SLE and in a developing body which may react differently, both therapeutically and with a different toxicity profile, to what is seen in adults.

Executive summary

- There needs to be greater awareness that pediatric patients with systemic lupus erythematosus (SLE) are not just smaller adult patients.
- Critical assessment of therapeutic trials, both controlled and uncontrolled, studying the use of immunosuppressive agents in proliferative lupus nephritis is required, and not just the blind acceptance of historical treatments.
- It must be recognized that pediatric SLE tends to be a more aggressive disease than adult SLE and usually requires the use of corticosteroids, and that younger patients generally require higher doses of corticosteroids.
- An increased emphasis on the prevention of long-term morbidities associated with both SLE and its therapy is required.
- A pediatric SLE network must be developed to study the long-term outcome of patients with pediatric SLE and for therapeutic trials.

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