**European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus – the SHARE initiative**

\*Noortje Groot1,2, \*Nienke de Graeff1, Tadej Avcin3, Brigitte Bader-Meunier4, Paul Brogan5, Pavla Dolezalova6, Brian Feldman7, Isabelle Kone-Paut8, Pekka Lahdenne9, Stephen D Marks5, Liza McCann 10, Seza Ozen11, Clarissa Pilkington5, Angelo Ravelli12, Annet van Royen1, Yosef Uziel13, Bas Vastert1, Nico Wulffraat1, \*\*Sylvia Kamphuis2, \*\*Michael W. Beresford 10,14

*1Wilhelmina Children's Hospital, Utrecht, The Netherlands; 2Sophia Children's Hospital, Erasmus University Medical Centre, Rotterdam, The Netherlands; 3University Children's Hospital Ljubljana, Ljubljana, Slovenia; 4Necker Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; 5Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; 6General University Hospital, 1st Faculty of Medicine, Charles University, Prague, Czech Republic; 7The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; 8Bicêtre Hospital, Paris, APHP, University of Paris Sud, France; 9Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland; 10Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom; 11Hacettepe University, Department of Pediatrics, Ankara, Turkey; 12Università degli Studi di Genova and Istituto Giannina Gaslini, Genoa, Italy; 13Meir Medical Center, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel; 14 Institute of Translational Medicine, University of Liverpool, Liverpool, UK.*

NB: \* Joint first authors, contributed equally to this work

\*\*Joint senior authors, contributed equally to this work

**Abstract:**

**Background**

Childhood-onset systemic lupus erythematosus (cSLE) is a rare, multisystem and potentially life-threatening autoimmune disorder with significant associated morbidity. Evidence-based guidelines are sparse and management is often based on clinical expertise. SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) was launched to optimize and disseminate management regimens for children and young adults with rheumatic diseases like cSLE.

**Objectives**

To provide evidence-based recommendations for diagnosis and treatment of cSLE. In view of extent and complexity of cSLE and its various manifestations, recommendations for lupus nephritis and antiphospholipid syndrome will be published separately.

**Methods**

Recommendations were generated using the European League Against Rheumatism (EULAR) standard operating procedure. An expert committee, consisting of paediatric rheumatologists and representation of paediatric nephrology from across Europe discussed evidence-based recommendations during two consensus meetings. Recommendations were accepted if >80% agreement was reached.

**Results**

A total of twenty-five recommendations regarding key approaches to diagnosis and treatment of cSLE were made. The recommendations include eleven recommendations on diagnosis, nine on disease monitoring, and five on general treatment. Topics included: appropriate use of SLE classification criteria, disease activity and damage indices; adequate assessment of autoantibody profiles; secondary macrophage activation syndrome; use of hydroxychloroquine and corticosteroid-sparing regimens; and the importance of addressing poor adherence. Ten recommendations were accepted regarding general diagnostic strategies and treatment indications of neuropsychiatric cSLE.

**Conclusions**

The SHARE-recommendations for cSLE and neuropsychiatric manifestations of cSLE have been formulated by an evidence-based consensus process to support uniform, high quality standards of care for children with cSLE.

**Introduction**

Childhood-onset SLE (cSLE) is a severe, chronic, systemic autoimmune disease that has great impact on the child or young person affected. cSLE shares its pathogenesis with adult-onset SLE, but generally has a more severe clinical phenotype (1-8).

With an incidence of 0.3 to 0.9 per 100,000 children-years and a prevalence ranging from 1.89 to 25.7 per 100,000 children worldwide (reviewed in (9-11)), including Europe (12-16), cSLE fulfils the definition of a rare disease in Europe (17). Its low prevalence makes clinical research challenging, resulting in a paucity of evidence-based data and subsequent guidelines for disease management. Consequently, the management of patients with cSLE differs widely between countries (18). Treatment approaches can vary between clinicians even within centres. To foster equity of access to the highest standards of care and uniformity of practice, evidence-based international guidelines are therefore urgently needed.

To achieve this, collaboration between countries is necessary. For this reason, the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) project was initiated (18). One of the key objectives of this project was to provide guidance regarding best practices for the diagnosis and management of paediatric rheumatic diseases (PRD). SHARE-recommendations for auto-inflammatory diseases and juvenile dermatomyositis have been published (19-21). Here, we present SHARE-recommendations for cSLE. In view of extent and complexity of cSLE, SHARE-recommendations for lupus nephritis and antiphospholipid syndrome will be published separately.

**Methods**

A European-wide panel of 16 paediatric rheumatologists and representation of paediatric nephrology was established to develop evidence-based recommendations. A project plan for the systematic literature search was written following the European League Against Rheumatism (EULAR) standardised operating procedure (22). SHARE was a European Union (EU)-funded project and as such there was a prerequisite for representative disease experts from across Europe to form the expert panel, with inclusion of a selected number of disease experts from outside the EU.

***Systematic literature search and study selection***

A systematic literature search, based on specific research questions was performed in PubMed/MEDLINE, EMBASE and Cochrane databases in July 2013 (see online Supplementary Table S1). A validated filter was used to specifically select articles on children and adolescents only (23). The filter was adapted for cSLE to exclude neonates, as neonatal lupus was beyond the scope of the review (see online Supplementary Table S2). The literature search also included lupus nephritis (LN) and paediatric antiphospholipid syndrome (APS). These topics will be discussed separately from this article.

***Validity assessment***

Two reviewers (NG, NdG) independently screened all articles according to the predefined inclusion and exclusion criteria.

Articles were reviewed independently by two cSLE experts from European panel (MWB, SK, TA, AR, IKP, BBM, CP). They assessed level of evidence and methodological quality of the articles (see online Supplementary Table S3 and S4) (24, 25). Data extraction was done by the experts using predefined data extraction forms adapted from classification tables for epidemiologic, diagnostic (26) and therapeutic (27) studies. If there were any discrepancies, a third expert was asked to give a final assessment.

***Establishment of recommendations***

The results of the literature review were mapped against the *a priori* research questions, and provisional recommendations were formulated (NG, NdG, SK, MWB). If no literature in children could be found to map against a particular recommendation, adult literature was consulted. The expert committee (TA, BBM, PB, PD, IKP, PL, LM, SO, CP, AR, AvR, YU, NW, SK, MWB) was presented with the provisional recommendations in web-based surveys (100% response rate) and gave their opinions on the statements. Recommendations were revised according to responses to the surveys and discussed at two sequential face-to-face consensus meetings in March 2014 (Genova, number of experts participating, n=15; moderators: BF and AR) and March 2015 (Barcelona, n=14; moderator: BF).

To reach consensus, the nominal group technique (NGT) was used, in which equal participation from group members is ensured (28). Recommendations were accepted when agreement was at least 80%. This process resulted in a final set of prioritised recommendations.

**Results**

Figure 1 summarizes the results of the literature search. A total of 9,341 articles were identified and reviewed regarding treatment and management of cSLE of which, 133 articles fulfilled the inclusion criteria. We identified 51 articles relating to diagnosis and management of cSLE generally, and 27 articles to neuropsychiatric manifestations of cSLE, all were scored by the experts (see online Supplementary table S5). The 55 articles pertaining to LN informed a specific set of complimentary recommendations that will be published separately.

The meetings resulted in 25 recommendations pertaining to the diagnosis and treatment of cSLE (Table 1) and 10 for neuropsychiatric cSLE (NP-cSLE) (Table 2). The recommendations in this paper can be used for all patients in whom cSLE is suspected or diagnosed.

The most severe symptom(s) or sign(s) should guide treatment decisions when considering these recommendations. For example, when a patient suffers from mild haematological involvement as well as severe neuropsychiatric disease, the latter should guide the treatment choice.

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 1. Recommendations for cSLE – Diagnostic procedures, management and treatment** | **L** | **S** | **Agreement (%)** |
| ***Diagnostic recommendations*** |
| 1. Based on the current evidence (mainly in adults) on the SLICC-criteria, the SLICC criteria can be used as classification criteria in cSLE
 | 3 | C | 100 |
| 1. In the presence of a positive ANA combined with at least two clinical SLICC criteria, or in the presence of a positive ANA combined with at least one clinical and one immunological SLICC criterion, referral to a paediatric rheumatologist is warranted
 | 3 | C | 100 |
| 1. When considering a diagnosis of cSLE, anti-Sm, anti-RNP-a, anti-Ro/SS-A and anti-La/SS-B should be included routinely
 | 3 | C | 100 |
| 1. In a clinical context, when a patient is ANA positive, but anti-dsDNA and ENA negative, a diagnosis of cSLE can still be made
 | 3 | C | 100 |
| 1. In cSLE patients, hereditary complement deficiencies should be considered, especially in young patients
 | 3 | C | 100 |
| 1. All cSLE patients should have a chest X-ray at diagnosis
 | 3 | C | 100 |
| 1. All cSLE patients should be screened for cardiac abnormalities using ECG and echocardiography at diagnosis
 | 3 | C | 100 |
| 1. cSLE patients with respiratory symptoms or signs (in the absence of acute infection) should have a pulmonary function test including CO diffusion
 | 3 | C | 100 |
| 1. Exertional intolerance in cSLE patients should be investigated. Initial investigations should include a chest X-ray, a pulmonary function test (with CO diffusion), echocardiography and an ECG
 | 3 | C | 100 |
| 1. In patients with cSLE, unexplained fever should trigger a search for infection and MAS
 | 3 | C | 93 |
| 1. When MAS is suspected, a bone marrow aspirate should be considered to facilitate MAS diagnosis and exclude other diagnoses. If MAS is suspected and the patient is clinically unstable, treatment should not be delayed if a bone marrow aspirate is not possible
 | 3 | C | 100 |
| ***Monitoring and management of cSLE*** |
| 1. Active disease should be regularly monitored by performing: a full clinical evaluation including body weight, height and blood pressure; urine dipstick testing; proteinuria estimation; blood tests including albumin; creatinine; eGFR; ESR; C3 and C4; anti ds-DNA; and complete blood cell count1
 | 2AB/3 | B-C/ C | 100 |
| 1. Clinical evaluation should usually occur every 2–4 weeks for the first 2–4 months after diagnosis or flare, and then according to the response to treatment1
 | 3 | C | 100 |
| 1. Children receiving systemic corticosteroids should be checked regularly for linear growth
 | 2A | B | 100 |
| 1. All children with cSLE should have disease activity assessed regularly using a standardized disease activity measure such as the SLEDAI-2k or pBILAG-2004
 | 4 | D | 100 |
| 1. All children with cSLE should have disease damage assessed yearly using a standardized disease damage measure such as the paediatric SDI
 | 3 | C | 100 |
| 1. All cSLE patients should have access to an ophthalmologist
 | 3 | C | 100 |
| 1. Annual eye screening should be considered for cSLE patients taking hydroxychloroquine
 | 3 | C | 100 |
| 1. Sun-protection may be beneficial in patients with skin manifestations and should be considered1
 | 3 | C | 100 |
| 1. In lupus, a coordinated transition programme including paediatric and adult specialists is crucial for ensuring continuity of care and adherence to treatments in order to optimize long-term outcome including prevention of fatalities1
 | 3 | C | 80 |
| ***Treatment recommendations*** |
| 1. All children with lupus should be on hydroxychloroquine routinely
 | 2A | B | 100 |
| 1. In all decisions of treatment change or modification, compliance should be actively checked
 | 3 | C | 100 |
| 1. When it is not possible to taper the prednisone dose, a DMARD should be added to the therapy
 | 3 | C | 100 |
| 1. Mild/moderate haematological involvement: when haemolysis is present and Hb is lower than normal, a DMARD should be added to the therapy
 | 3 | C | 100 |
| 1. If rituximab is required, the recommended dose is either 750 mg/m2/dose (up to a maximum of 1 gram) at day 1 and day 15, or 375 mg/m2/dose once a week for 4 doses
 | 3 | C | 100 |
| *1This statement is based on the EULAR recommendations for adults with SLE (29-31)**L, level of evidence; for diagnostic and observational studies:1A, Meta-analysis of cohort studies; 1B, Meta-analysis of case-control studies; 2A, Cohort studies; 2B, Case-control studies; 3, Non-comparative descriptive studies; 4: Expert opinion; and for treatment studies: 1A, meta-analysis of randomised controlled trial; 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study; 4 expert opinion (25-27); S, strength of recommendation: A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion (22), Agreement indicates % of experts agreeing on the recommendation during the final voting round of the consensus meeting.* *Abbreviations: cSLE: childhood-onset Systemic Lupus Erythematosus; SLICC: Systemic Lupus International Collaborating Clinics; ANA: Anti-nuclear antibodies; anti-dsDNA: anti double-stranded DNA; ENA: Extractable Nuclear Antigens; ECG: electrocardiogram; CO: carbon monoxide; MAS: Macrophage Activation Syndrome; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; SLEDAI-2k: Systemic Lupus Erythematosus Disease Activity Index 2000; pBILAG-2004: paediatric British Isles Lupus Assessment Group index 2004; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology; Damage Index DMARD: Disease-Modifying Anti Rheumatic Drug; Hb: haemoglobin; EULAR: European League Against Rheumatism* |

***General diagnostic recommendations***

Prompt, accurate diagnosis of cSLE in a specialist centre is crucial to enable timely initiation of appropriate treatment, including multi-disciplinary care. However, there are no validated diagnostic criteria for cSLE. Despite some differences regarding symptoms at onset, pattern of organ involvement and severity of disease between cSLE and adult-onset disease (3, 32), their similarities mean that the established ACR classification criteria for SLE are widely used for cSLE (33). In 2012, new classification criteria for SLE were published (34). To date, two studies have assessed the performance of these Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE in children (6, 7). Both concluded that although some specificity may be lost, the SLICC-criteria had better sensitivity than the ACR-criteria. Evidence to date indicates the SLICC-criteria may well be preferable in cSLE, and should be used to aid referral to, or at least consultation with a paediatric rheumatologist. Similarly, they may help prompt referral, even if a child does not yet meet full criteria, since these are classification and not diagnostic criteria.

A hallmark of SLE is the presence of autoantibodies, particularly those directed towards nuclear autoantigens (antinuclear antibodies, ANA). Next to ANA, autoantibodies including anti-dsDNA, anti-Sm, anti-RNP, anti-Ro/SS-A, and anti-La/SS-B antibodies (collectively referred to as ‘ENA’ (Extractable Nuclear Antigens)) are prevalent in cSLE: dsDNA 54%-93%; anti-Sm 17%-52%; anti-RNP 22%-50%; anti-Ro/SSA 33%-54% Anti-La/SSB 14%-32% (5, 35-41). As such, including all of these antibodies in the diagnostic work-up when considering cSLE was strongly recommended. However there are no antibodies with specific predictive qualities (e.g. disease severity, organ involvement, age of onset) despite extensive efforts to find them (42-50). Notably, patients negative for anti-dsDNA antibodies and/or ENA can still be diagnosed with cSLE.

Hereditary complement deficiencies can predispose to lupus or lupus-like disease at an early age. Early recognition of these deficiencies should facilitate adequate treatment of disease and comorbidities including infections, which are especially important as these patients seem to have a higher mortality (51, 52). Therefore, screening for complement deficiencies via CH50, AP50, C3 and C4 (or other validated classic and alternative complement pathway assay) is important in cSLE, especially in young lupus patients. It was also recognised that there are other causes of monogenic lupus outside of the complement pathway, thus normal complement screening assay results do not preclude this possibility (53, 54).

***Cardiopulmonary involvement***

Although unusual in cSLE, cardiac and pulmonary involvement do occur, but are often asymptomatic initially (55-63). Respiratory symptoms or signs such as exertional intolerance could be a sign of pulmonary or cardiac pathology. However, there is a wide differential diagnosis that must be considered and use of appropriate diagnostic procedures should consequently be performed to find out whether cardiopulmonary involvement is due to cSLE.

Early recognition of cardiopulmonary involvement is important when trying to prevent subsequent organ damage. Therefore, a baseline echocardiography and electrocardiogram (ECG) screen in every cSLE patient for cardiopulmonary involvement is advised. Additionally, intermittent monitoring for any future progression or new involvement of these organ systems over time can be considered, as it is not clear how many children with asymptomatic cardiopulmonary involvement become symptomatic.

***Macrophage Activation Syndrome***

Macrophage activation syndrome (MAS) is a rare but severe, potentially life-threatening complication of cSLE, characterized by high fever, associated in some patients with organ involvement (neurologic symptoms, hepatomegaly, splenomegaly), pancytopenia, coagulopathy, elevation of liver enzymes, ferritin and triglycerides (64, 65). Preliminary recommendations for timely diagnosis and correct classification of MAS in cSLE have been developed (64). Patients can develop MAS at any time during their disease. Distinguishing sepsis from MAS can be difficult, as they may share features such as fever, cytopenias and hepatic involvement, both resulting in systemic inflammation. There are differences, as for example ferritin levels in MAS tend to increase dramatically, whereas hyperferritinaemia is generally more modest in sepsis (66, 67). A bone marrow aspirate should be performed to assess the cause of cytopenias and to detect possible hemophagocytosis. This will help in making a diagnosis of MAS. As MAS can be rapidly progressive and life-threatening, the threshold for diagnostic procedures should be low. However, if the patient is clinically unstable, treatment should not be delayed if a bone marrow aspirate is not possible.

***Monitoring and general management***

The frequency of visits to the paediatric outpatient clinic is dependent on clinical presentation, disease severity, as well as the age of the patient. Visits should be regular, especially at diagnosis and following flares and a basic set of investigations is recommended for each visit (68, 69). Consensus was reached on preliminary criteria for global flares in cSLE (70). Further validation studies are needed to confirm the usefulness of the cSLE flare criteria in research and for clinical care.The recommended frequency of visits as well as the important clinical parameters that should be checked at each visit is similar to the recommendations for adult-onset disease (29-31). In addition, regular height and weight monitoring is important, as well as pubertal assessment. Growth impairment can occur in children with cSLE, which can be difficult to overcome and may lead to a lower final height due to continuous disease activity and/or corticosteroid use. Similarly, these factors can contribute to delayed pubertal development. Pre-pubertal and peri-pubertal patients receiving a high cumulative dose of corticosteroids are specifically at risk for both growth impairment and pubertal delay, which must be proactively assessed (71, 72).

It is strongly recommended that disease activity, response to treatment, and disease damage should be regularly and comprehensively assessed using standardized tools to monitor disease progression. Many tools are available for this purpose (73-75). For example, disease activity can be monitored with the paediatric British Isles Lupus Assessment Group index (pBILAG) or the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2k) (73, 75-77). Disease damage should also be comprehensively assessed annually, for example using the paediatric version of the SLICC/American College of Rheumatology Damage Index (pSDI) (71).

A broad range of ocular manifestations including retinopathy or optic nerve disease can occur in cSLE. Additionally, two of the most commonly used drugs for SLE, corticosteroids and hydroxychloroquine, can affect the eyes (78-80). Therefore, it is recommended that patients have access to the expertise of paediatric ophthalmology. Paucity of evidence regarding ophthalmological risks due to long-term corticosteroids and hydroxychloroquine use means that annual examination of the eyes should be considered in the paediatric age group (81).

Despite minimal published evidence supporting the benefits of sun-protection in cSLE patients, sunscreens are widely recommended to prevent photosensitive rashes and as part of general disease management. One study in eleven adult SLE patients showed that some, but not all types of sunscreen prevented the development of UV-radiation induced skin lesions (82).

Adolescent patients need to be supported through the transition process and prepared for transfer of their care to the adult services once they reach adulthood. During adolescence, patients need to develop self-management skills and become responsible for their own health (83-86). One of the major challenges during the transitional process is non-adherence to treatments (84, 87), which should be addressed frequently at out-patient clinics. EULAR recommendations for this transitional process have been published, to support professionals in designing a coordinated transition programme (88).

***General treatment recommendations***

It is recommended that all children with lupus should be on hydroxychloroquine routinely. A systematic review of 95 articles analysing the beneficial and adverse effects of antimalarial therapies such as HCQ in adults with SLE showed a broad spectrum of beneficial effects, such as a higher remission rate, less relapses and less accrual of damage. Additionally, hydroxychloroquine has a favourable safety profile (89). Adult studies show that long-term use of hydroxychloroquine is relatively safe, although the risk of retinopathy increases with the increasing cumulative dose (89). Unfortunately, no such evidence is available for children with cSLE, but studies in patients with juvenile idiopathic arthritis show that doses up to 6 mg/kg/day (based on lean body weight) are safe to use (90).

Lack of adherence has been associated with a higher disease activity and more damage (91-93). Rates of non-adherence can be as high as 50% and disease severity does not guarantee medication adherence (94). Therefore, adherence should be checked whenever a patient shows poor response to a treatment, measuring medication (trough) levels may be helpful to detect non-adherence. When a patient experiences side effects from a drug, choice of therapy will need to be reassessed and switched if necessary. If disease severity is such that tapering of oral prednisolone is not possible despite adequate compliance to oral prednisone and hydroxychloroquine, addition of a disease modifying anti-rheumatic drug (DMARD) is recommended to improve disease control and permit subsequent corticosteroid tapering. Examples of DMARDs often used include mycophenolate mofetil, azathioprine, methotrexate, or cyclophosphamide in severe cases.

The use of rituximab has been described in six studies including a total of 115 individual patients with cSLE. All patients had acute, life-threatening symptoms or symptoms that did not respond to standard treatment. Two dose regimens were described, which both proved to be effective and safe in the majority of the patients (95-100).

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 2. Recommendations for Neuropsychiatric cSLE (NP-cSLE) – Diagnostic procedures and treatment** | **L** | **S** | **Agreement (%)** |
| ***Diagnostic recommendations*** |
| 1. The nomenclature and case definitions for NP-cSLE syndromes proposed by the ACR *ad hoc* committee should be used to classify and describe NP-SLE syndromes in cSLE
 | 3 | C | 100 |
| 1. In cSLE, patients with new or unexplained symptoms or signs suggestive of neuropsychiatric disease, initial diagnostic work-up should include work-up as performed in patients without SLE
 | 3 | C | 100 |
| 1. In a patient with a suspected diagnosis of NP-cSLE or worsening NP-cSLE symptoms, underlying factors including infections, hypertension, metabolic abnormalities or adverse effects of medication should be excluded
 | 3 | C | 100 |
| 1. Depending upon the type of neuropsychiatric manifestation, the diagnostic work-up may include lumbar puncture and CSF analysis (primarily to exclude CNS infection), EEG, neuropsychological assessment of cognitive function, consultation with an ophthalmologist, nerve conductional studies, and neuroimaging (MRI) to assess nervous system structure and function1
 | 3 | C | 100 |
| 1. A normal MRI of the CNS does not exclude NP-cSLE1
 | 3 | C | 100 |
| 1. Cognitive impairment should be tested either in collaboration with a neuropsychologist, or using validated tests for cognitive impairment in cSLE, like the ped-ANAM
 | 3 | C | 100 |
| ***Treatment recommendations*** |
| 1. When neuropsychiatric manifestations are caused by an immune or inflammatory process and non-SLE related causes are excluded, corticosteroids and immunosuppressive therapy are indicated
 | 3 | C | 100 |
| 1. Anti-epileptic drugs are usually not necessary after a single seizure in the absence of MRI lesions and definite epileptic abnormalities on EEG following recovery from the seizure1
 | 3 | C | 100 |
| 3. Long-term anti-epileptic therapy should be considered for recurrent seizures1 | 3 | C | 93 |
| 1. There is a need for paediatric NP-cSLE research regarding treatment
 | 4 | D | 100 |
| *1This statement is based on the EULAR recommendations for adults with NP-cSLE (29, 101)**L, level of evidence; for diagnostic and observational studies:1A, Meta-analysis of cohort studies; 1B, Meta-analysis of case-control studies; 2A, Cohort studies; 2B, Case-control studies; 3, Non-comparative descriptive studies; 4: Expert opinion; and for treatment studies: 1A, meta-analysis of randomised controlled trial; 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasi-experimental study; 3, descriptive study; 4 expert opinion(25-27); S, strength of recommendation: A, based on level 1 evidence; B, based on level 2 or extrapolated from level 1; C, based on level 3 or extrapolated from level 1 or 2; D, based on level 4 or extrapolated from level 3 or 4 expert opinion (22), Agreement indicates % of experts agreeing on the recommendation during the final voting round of the consensus meeting.* *Abbreviations: NP-cSLE: Neuropsychiatric childhood-onset Systemic Lupus Erythematosus; ACR: American College of Rheumatology; CSF: Cerebrospinal fluid; CNS: Central nervous system; EEG: electroencephalogram; MRI: Magnetic Resonance Imaging; ped-ANAM: Pediatric Automated Neuropsychological Assessment Metrics; DMARD: Disease-Modifying Anti-rheumatic Drug; EULAR: European League Against Rheumatism* |

***Diagnostic recommendations***

NP-cSLE can be a common manifestation of lupus in children (102-109). To promote uniformity and comparability between NP-SLE manifestations in children and adults and in view of the limited available evidence in NP-cSLE, it is recommended that the ACR nomenclature and case definitions for NP-SLE (110) are also used in cSLE. It must be taken into account however that the ACR nomenclature was designed for adults and some of the diagnostic or screening tests listed here, cannot be used for children. As is the case in adult-onset NP-SLE, no single clinical, laboratory, neuropsychological or imaging test can be used in children to differentiate NP-cSLE from other causes of neuropsychiatric manifestations. There have been some small studies aiming at identification of specific biomarkers or imaging techniques for neuropsychiatric involvement in cSLE, but large, controlled studies are lacking (111-123). Therefore, the recommendation regarding the diagnostic evaluation of neuropsychiatric symptoms is adopted from the adult EULAR recommendations (29, 101).

It is important to make a detailed and thorough assessment of any patient with suspected NP-cSLE. In the context of a suspected NP-cSLE diagnosis or worsening of neuropsychiatric disease, an initial comprehensive work-up should include all other potential underlying causes, including infections, hypertension, metabolic abnormalities or adverse effects of medication. A systematic approach is recommended, with the specific symptoms guiding the type of diagnostic procedure.

Importantly, not all NP-cSLE manifestations can be detected with conventional magnetic resonance imaging (MRI) techniques (124, 125). In addition, conventional MRI techniques (as well as novel MRI imaging modalities) may be unspecific for CNS involvement due to cSLE or to other causes. Formal neuropsychiatric testing by a neuropsychologist can be used to ascertain the presence of neurocognitive dysfunction. However, as a neuropsychologist is not always available, a helpful screening tool is the Paediatric Automated Neuropsychological Assessment Metrics (Ped-ANAM), which can be used by non-specialists to screen patients for possible neurocognitive dysfunction (126, 127)

***Treatment recommendations***

The evidence for the treatment of NP-cSLE in children is especially limited. Recommendations are therefore based principally on adult recommendations for the management of NP-SLE (101), adapted for use in children by the expert panel. It was noted that this remains an important area for future clinical research. When non-SLE related causes for neuropsychiatric symptoms or signs are excluded, corticosteroids and immunosuppressive therapy are indicated (101).

Recurrent seizures in SLE may benefit from antiepileptic treatment. However, one single seizure without evidence for epileptic activity on electroencephalogram (EEG) in the brain is usually not an indication for antiepileptic treatment. Undertaking a careful evaluation seeking and treating the underlying cause, including anti-inflammatory treatment of potential NP-cSLE, most often suffices to prevent further seizures.

**Discussion**

A total of 35 recommendations for diagnosis, management and treatment for cSLE (25 recommendations) and NP-cSLE (10 recommendations) have been formulated. All recommendations were accepted with >80% agreement.

These recommendations are intended to help specialists with decisions regarding the general care for patients with cSLE. Notably, recommendations regarding the management of nephritis in cSLE and paediatric APS will be published separately.

It must be noted that good quality evidence regarding diagnosis and treatment in cSLE is limited. Due to lack of robust evidence underpinning some statements, the expert panel refrained from being too specific regarding diagnostic procedures, monitoring intervals or specific drug treatments. This emphasises the need for more research on diagnostic procedures, as well as treatment in this population. International collaboration will be vital, as large cohorts are difficult to achieve.

In conclusion, the SHARE project has resulted in recommendations on diagnosis, management and treatment of cSLE and NP-cSLE, based on best available evidence and expert opinion. These recommendations should facilitate the optimization of the management of this rare disease.

**References**

1. Bandeira M, Buratti S, Bartoli M, Gasparini C, Breda L, Pistorio A, et al. Relationship between damage accrual, disease flares and cumulative drug therapies in juvenile-onset systemic lupus erythematosus. Lupus. 2006;15(8):515-20.

2. Brunner HI, Gladman DD, Ibanez D, Urowitz MD, Silverman ED. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis and rheumatism. 2008;58(2):556-62.

3. Hersh AO, von Scheven E, Yazdany J, Panopalis P, Trupin L, Julian L, et al. Differences in long-term disease activity and treatment of adult patients with childhood- and adult-onset systemic lupus erythematosus. Arthritis and rheumatism. 2009;61(1):13-20.

4. Livingston B, Bonner A, Pope J. Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: a meta-analysis. Lupus. 2011;20(13):1345-55.

5. Ramirez Gomez LA, Uribe Uribe O, Osio Uribe O, Grisales Romero H, Cardiel MH, Wojdyla D, et al. Childhood systemic lupus erythematosus in Latin America. The GLADEL experience in 230 children. Lupus. 2008;17(6):596-604.

6. Sag E, Tartaglione A, Batu ED, Ravelli A, Khalil SM, Marks SD, et al. Performance of the new SLICC classification criteria in childhood systemic lupus erythematosus: a multicentre study. Clin Exp Rheumatol. 2014;32(3):440-4.

7. Fonseca AR, Gaspar-Elsas MI, Land MG, de Oliveira SK. Comparison between three systems of classification criteria in juvenile systemic lupus erythematous. Rheumatology. 2015;54(2):241-7.

8. Mina R, Brunner HI. Pediatric lupus--are there differences in presentation, genetics, response to therapy, and damage accrual compared with adult lupus? Rheumatic diseases clinics of North America. 2010;36(1):53-80, vii-viii.

9. Hiraki LT, Feldman CH, Liu J, Alarcon GS, Fischer MA, Winkelmayer WC, et al. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. Arthritis and rheumatism. 2012;64(8):2669-76.

10. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol. 2010;6(9):538-46.

11. Pineles D, Valente A, Warren B, Peterson MG, Lehman TJ, Moorthy LN. Worldwide incidence and prevalence of pediatric onset systemic lupus erythematosus. Lupus. 2011;20(11):1187-92.

12. Huemer C, Huemer M, Dorner T, Falger J, Schacherl H, Bernecker M, et al. Incidence of pediatric rheumatic diseases in a regional population in Austria. J Rheumatol. 2001;28(9):2116-9.

13. Kaipiainen-Seppanen O, Savolainen A. Incidence of chronic juvenile rheumatic diseases in Finland during 1980-1990. Clin Exp Rheumatol. 1996;14(4):441-4.

14. Lopez P, Mozo L, Gutierrez C, Suarez A. Epidemiology of systemic lupus erythematosus in a northern Spanish population: gender and age influence on immunological features. Lupus. 2003;12(11):860-5.

15. Nightingale AL, Farmer RD, de Vries CS. Incidence of clinically diagnosed systemic lupus erythematosus 1992-1998 using the UK General Practice Research Database. Pharmacoepidemiol Drug Saf. 2006;15(9):656-61.

16. Pelkonen PM, Jalanko HJ, Lantto RK, Makela AL, Pietikainen MA, Savolainen HA, et al. Incidence of systemic connective tissue diseases in children: a nationwide prospective study in Finland. J Rheumatol. 1994;21(11):2143-6.

17. Series OR. List of rare diseases and synonyms listed in alphabetical order: Orphanet; 2016 [cited 2016 20-01-2017]. Available from: <http://www.orpha.net/orphacom/cahiers/docs/GB/List_of_rare_diseases_in_alphabetical_order.pdf>.

18. Wulffraat NM, Vastert B, consortium S. Time to share. Pediatr Rheumatol Online J. 2013;11(1):5.

19. Enders FB, Bader-Meunier B, Baildam E, Constantin T, Dolezalova P, Feldman BM, et al. Consensus-based recommendations for the management of juvenile dermatomyositis. Ann Rheum Dis. 2017;76(2):329-40.

20. Giancane G, Ter Haar NM, Wulffraat N, Vastert SJ, Barron K, Hentgen V, et al. Evidence-based recommendations for genetic diagnosis of familial Mediterranean fever. Ann Rheum Dis. 2015;74(4):635-41.

21. ter Haar NM, Oswald M, Jeyaratnam J, Anton J, Barron KS, Brogan PA, et al. Recommendations for the management of autoinflammatory diseases. Ann Rheum Dis. 2015;74(9):1636-44.

22. Dougados M, Betteridge N, Burmester GR, Euller-Ziegler L, Guillemin F, Hirvonen J, et al. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. Ann Rheum Dis. 2004;63(9):1172-6.

23. Leclercq E, Leeflang MM, van Dalen EC, Kremer LC. Validation of search filters for identifying pediatric studies in PubMed. J Pediatr. 2013;162(3):629-34 e2.

24. Higgins JPT GS. T.C. Cochrane Handbook for Systematic Reviews of Interventions2013.

25. Whiting P, Rutjes AW, Dinnes J, Reitsma J, Bossuyt PM, Kleijnen J. Development and validation of methods for assessing the quality of diagnostic accuracy studies. Health Technol Assess. 2004;8(25):iii, 1-234.

26. Zhang W, Doherty M, Pascual E, Bardin T, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006;65(10):1301-11.

27. Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006;65(10):1312-24.

28. Delbecq AL vdVA. A group process model for problem identification and program planning. J Appl Behav Sci. 1971;7:466-92.

29. Bertsias G, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis. 2008;67(2):195-205.

30. Bertsias GK, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JH, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012;71(11):1771-82.

31. Mosca M, Tani C, Aringer M, Bombardieri S, Boumpas D, Brey R, et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis. 2010;69(7):1269-74.

32. Tarr T, Derfalvi B, Gyori N, Szanto A, Siminszky Z, Malik A, et al. Similarities and differences between pediatric and adult patients with systemic lupus erythematosus. Lupus. 2015;24(8):796-803.

33. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis and rheumatism. 1997;40(9):1725.

34. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis and rheumatism. 2012;64(8):2677-86.

35. Abdwani R, Rizvi SG, El-Nour I. Childhood systemic lupus erythematosus in Sultanate of Oman: demographics and clinical analysis. Lupus. 2008;17(7):683-6.

36. Bader-Meunier BBM AJ, Haddad E, Cochat P et. al. Initial presentation of childhood-onset systemic lupus erythematosus: a French multicenter study. 2005. 2005;J pediatr(146).

37. Buoncompagni A, Barbano GC, Pistoia V, Fasce L, Micalizzi C, Gusmano R, et al. Childhood systemic lupus erythematosus: a review of 30 cases. Clin Exp Rheumatol. 1991;9(4):425-30.

38. Chiang LL, Lin YT, Chan HY, Chiang BL. Differential manifestations of prepubescent, pubescent and postpubescent pediatric patients with systemic lupus erythematosus: A retrospective study of 96 Chinese children and adolescents. Pediatr Rheumatol Online J. 2012;10(1):12.

39. Hiraki LT, Benseler SM, Tyrrell PN, Hebert D, Harvey E, Silverman ED. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: a longitudinal study. J Pediatr. 2008;152(4):550-6.

40. Olowu W. Childhood-onset systemic lupus erythematosus. J Natl Med Assoc. 2007;99(7):777-84.

41. Watson L, Leone V, Pilkington C, Tullus K, Rangaraj S, McDonagh JE, et al. Disease activity, severity, and damage in the UK Juvenile-Onset Systemic Lupus Erythematosus Cohort. Arthritis and rheumatism. 2012;64(7):2356-65.

42. Campos LM, Kiss MH, Scheinberg MA, Mangueira CL, Silva CA. Antinucleosome antibodies in patients with juvenile systemic lupus erythematosus. Lupus. 2006;15(8):496-500.

43. Hinze CH, Suzuki M, Klein-Gitelman M, Passo MH, Olson J, Singer NG, et al. Neutrophil gelatinase-associated lipocalin is a predictor of the course of global and renal childhood-onset systemic lupus erythematosus disease activity. Arthritis and rheumatism. 2009;60(9):2772-81.

44. Jesus AA, Campos LM, Liphaus BL, Carneiro-Sampaio M, Mangueira CL, Rosseto EA, et al. Anti-C1q, anti-chromatin/nucleosome, and anti-dsDNA antibodies in juvenile systemic lupus erythematosus patients. Rev Bras Reumatol. 2012;52(6):976-81.

45. Jesus AA, Silva CA, Carneiro-Sampaio M, Sheinberg M, Mangueira CL, Marie SK, et al. Anti-C1q antibodies in juvenile-onset systemic lupus erythematosus. Ann N Y Acad Sci. 2009;1173:235-8.

46. Jurencak R, Fritzler M, Tyrrell P, Hiraki L, Benseler S, Silverman E. Autoantibodies in pediatric systemic lupus erythematosus: ethnic grouping, cluster analysis, and clinical correlations. J Rheumatol. 2009;36(2):416-21.

47. Lehman TJ, Hanson V, Singsen BH, Kornreich HK, Bernstein B, King K. The role of antibodies directed against double-stranded DNA in the manifestations of systemic lupus erythematosus in childhood. J Pediatr. 1980;96(4):657-61.

48. Tang X, Huang Y, Deng W, Tang L, Weng W, Zhang X. Clinical and serologic correlations and autoantibody clusters in systemic lupus erythematosus: a retrospective review of 917 patients in South China. Medicine (Baltimore). 2010;89(1):62-7.

49. Wu FQ, Zhao Q, Cui XD, Zhang W. C1q and anti-C1q antibody levels are correlated with disease severity in Chinese pediatric systemic lupus erythematosus. Rheumatol Int. 2011;31(4):501-5.

50. Wu JF, Yang YH, Wang LC, Lee JH, Shen EY, Chiang BL. Antinucleosome antibodies correlate with the disease severity in children with systemic lupus erythematosus. J Autoimmun. 2006;27(2):119-24.

51. Al Mayouf SM; Abanomi H EA. Impact of C1q deficiency on the severity and outcome of childhood systemic lupus erythematosus. International Journal of Rheumatic Diseases. 2011;14:81-5.

52. Pickering MC, Botto M, Taylor PR, Lachmann PJ, Walport MJ. Systemic lupus erythematosus, complement deficiency, and apoptosis. Adv Immunol. 2000;76:227-324.

53. Crow YJ. Lupus: how much "complexity" is really (just) genetic heterogeneity? Arthritis and rheumatism. 2011;63(12):3661-4.

54. Bader-Meunier B, Cave H, Jeremiah N, Magerus A, Lanzarotti N, Rieux-Laucat F, et al. Are RASopathies new monogenic predisposing conditions to the development of systemic lupus erythematosus? Case report and systematic review of the literature. Semin Arthritis Rheum. 2013;43(2):217-9.

55. Ahmed AM E-SM. Asymptomatic cardiac involvement in children with systemic lupus erythematosus. J Med Sci. 2006;6(6):944-9.

56. Al-Abbad A-JA CD, Sanatani S, Sandor GGS, Meear M, Petty RE, Malleson PN. Echocardiography and pulmonary function testing in childhood onset systemic lupus erythematosus. Lupus. 2001;10:32-7.

57. Cerveri I, Fanfulla F, Ravelli A, Zoia MC, Ramenghi B, Spagnolatti L, et al. Pulmonary function in children with systemic lupus erythematosus. Thorax. 1996;51(4):424-8.

58. Ciftci E, Yalcinkaya F, Ince E, Ekim M, Ileri M, Orgerin Z, et al. Pulmonary involvement in childhood-onset systemic lupus erythematosus: a report of five cases. Rheumatology. 2004;43(5):587-91.

59. de Jongste JC, Neijens HJ, Duiverman EJ, Bogaard JM, Kerrebijn KF. Respiratory tract disease in systemic lupus erythematosus. Arch Dis Child. 1986;61(5):478-83.

60. El-Dessoky El Shahawy E MA, Algoubashy AA, Abo-Warda MH et al. Pleuropulmonary manifestations in juvenile onset systemic lupus erythematosus: Assessment by pulmonary function tests and multidetector computed tomography. The Egyptian Rheumatologist. 2011;33:163-9.

61. Gazarian M, Feldman BM, Benson LN, Gilday DL, Laxer RM, Silverman ED. Assessment of myocardial perfusion and function in childhood systemic lupus erythematosus. J Pediatr. 1998;132(1):109-16.

62. Trapani S, Camiciottoli G, Ermini M, Castellani W, Falcini F. Pulmonary involvement in juvenile systemic lupus erythematosus: a study on lung function in patients asymptomatic for respiratory disease. Lupus. 1998;7(8):545-50.

63. Beresford MW, Cleary AG, Sills JA, Couriel J, Davidson JE. Cardio-pulmonary involvement in juvenile systemic lupus erythematosus. Lupus. 2005;14(2):152-8.

64. Parodi A, Davi S, Pringe AB, Pistorio A, Ruperto N, Magni-Manzoni S, et al. Macrophage activation syndrome in juvenile systemic lupus erythematosus: a multinational multicenter study of thirty-eight patients. Arthritis and rheumatism. 2009;60(11):3388-99.

65. Bennett TD, Fluchel M, Hersh AO, Hayward KN, Hersh AL, Brogan TV, et al. Macrophage activation syndrome in children with systemic lupus erythematosus and children with juvenile idiopathic arthritis. Arthritis and rheumatism. 2012;64(12):4135-42.

66. Assari R, Ziaee V, Mirmohammadsadeghi A, Moradinejad MH. Dynamic Changes, Cut-Off Points, Sensitivity, and Specificity of Laboratory Data to Differentiate Macrophage Activation Syndrome from Active Disease. Dis Markers. 2015;2015:424381.

67. Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2008;50(6):1227-35.

68. Mina R, Klein-Gitelman MS, Nelson S, Eberhard BA, Higgins G, Singer NG, et al. Validation of the systemic lupus erythematosus responder index for use in juvenile-onset systemic lupus erythematosus. Ann Rheum Dis. 2014;73(2):401-6.

69. Mina R, Klein-Gitelman MS, Ravelli A, Beresford MW, Avcin T, Espada G, et al. Inactive disease and remission in childhood-onset systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2012;64(5):683-93.

70. Brunner HI, Mina R, Pilkington C, Beresford MW, Reiff A, Levy DM, et al. Preliminary criteria for global flares in childhood-onset systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2011;63(9):1213-23.

71. Gutierrez-Suarez R, Ruperto N, Gastaldi R, Pistorio A, Felici E, Burgos-Vargas R, et al. A proposal for a pediatric version of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index based on the analysis of 1,015 patients with juvenile-onset systemic lupus erythematosus. Arthritis and rheumatism. 2006;54(9):2989-96.

72. Rygg M, Pistorio A, Ravelli A, Maghnie M, Di Iorgi N, Bader-Meunier B, et al. A longitudinal PRINTO study on growth and puberty in juvenile systemic lupus erythematosus. Ann Rheum Dis. 2012;71(4):511-7.

73. Brunner HI, Higgins GC, Klein-Gitelman MS, Lapidus SK, Olson JC, Onel K, et al. Minimal clinically important differences of disease activity indices in childhood-onset systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2010;62(7):950-9.

74. Brunner HI, Silverman ED, Bombardier C, Feldman BM. European Consensus Lupus Activity Measurement is sensitive to change in disease activity in childhood-onset systemic lupus erythematosus. Arthritis and rheumatism. 2003;49(3):335-41.

75. Lattanzi B, Consolaro A, Solari N, Ruperto N, Martini A, Ravelli A. Measures of disease activity and damage in pediatric systemic lupus erythematosus: British Isles Lupus Assessment Group (BILAG), European Consensus Lupus Activity Measurement (ECLAM), Systemic Lupus Activity Measure (SLAM), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Physician's Global Assessment of Disease Activity (MD Global), and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI; SDI). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S112-7.

76. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29(2):288-91.

77. Marks SD, Pilkington C, Woo P, Dillon MJ. The use of the British Isles Lupus Assessment Group (BILAG) index as a valid tool in assessing disease activity in childhood-onset systemic lupus erythematosus. Rheumatology. 2004;43(9):1186-9.

78. Al Mayouf SM AHA. Ocular manifestations of SLE in children. Saudi Med J. 2003;24(9):964-6.

79. Hoes JN, Jacobs JW, Boers M, Boumpas D, Buttgereit F, Caeyers N, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis. 2007;66(12):1560-7.

80. Marmor MF, Kellner U, Lai TY, Lyons JS, Mieler WF, American Academy of O. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. Ophthalmology. 2011;118(2):415-22.

81. Rheumatology ACo. Position Statement: Screening for Hydroxychloroquine Retinopathy. 2011.

82. Stege H, Budde MA, Grether-Beck S, Krutmann J. Evaluation of the capacity of sunscreens to photoprotect lupus erythematosus patients by employing the photoprovocation test. Photodermatol Photoimmunol Photomed. 2000;16(6):256-9.

83. Tucker LB, Cabral DA. Transition of the adolescent patient with rheumatic disease: issues to consider. Rheumatic diseases clinics of North America. 2007;33(3):661-72.

84. Lawson EF, Hersh AO, Applebaum MA, Yelin EH, Okumura MJ, von Scheven E. Self-management skills in adolescents with chronic rheumatic disease: A cross-sectional survey. Pediatr Rheumatol Online J. 2011;9(1):35.

85. Hersh AO, Pang S, Curran ML, Milojevic DS, von Scheven E. The challenges of transferring chronic illness patients to adult care: reflections from pediatric and adult rheumatology at a US academic center. Pediatr Rheumatol Online J. 2009;7:13.

86. Falcini F, Nacci F. Systemic lupus erythematosus in the young: the importance of a transition clinic. Lupus. 2007;16(8):613-7.

87. Felsenstein S, Reiff AO, Ramanathan A. Transition of care and health-related outcomes in pediatric onset systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2015.

88. Foster HE, Minden K, Clemente D, Leon L, McDonagh JE, Kamphuis S, et al. EULAR/PReS standards and recommendations for the transitional care of young people with juvenile-onset rheumatic diseases. Ann Rheum Dis. 2016.

89. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. Ann Rheum Dis. 2010;69(1):20-8.

90. Ziering CL, Rabinowitz LG, Esterly NB. Antimalarials for children: indications, toxicities, and guidelines. J Am Acad Dermatol. 1993;28(5 Pt 1):764-70.

91. Uribe AG, Alarcon GS, Sanchez ML, McGwin G, Jr., Sandoval R, Fessler BJ, et al. Systemic lupus erythematosus in three ethnic groups. XVIII. Factors predictive of poor compliance with study visits. Arthritis and rheumatism. 2004;51(2):258-63.

92. Rojas-Serrano J, Cardiel MH. Lupus patients in an emergency unit. Causes of consultation, hospitalization and outcome. A cohort study. Lupus. 2000;9(8):601-6.

93. Koneru S, Kocharla L, Higgins GC, Ware A, Passo MH, Farhey YD, et al. Adherence to medications in systemic lupus erythematosus. J Clin Rheumatol. 2008;14(4):195-201.

94. M. R. Adherence to Pediatric Medical Regimens. Handbook of Child Psychology and Developmental Science. 7 ed. New York: John Wiley & Sons Inc. ; 2010. p. 596-.

95. Willems M, Haddad E, Niaudet P, Kone-Paut I, Bensman A, Cochat P, et al. Rituximab therapy for childhood-onset systemic lupus erythematosus. J Pediatr. 2006;148(5):623-7.

96. Polido-Pereira J, Ferreira D, Rodrigues AM, Nascimento C, Costa P, Almeida M, et al. Rituximab use in pediatric autoimmune diseases: four case reports. Ann N Y Acad Sci. 2009;1173:712-20.

97. Podolskaya A, Stadermann M, Pilkington C, Marks SD, Tullus K. B cell depletion therapy for 19 patients with refractory systemic lupus erythematosus. Arch Dis Child. 2008;93(5):401-6.

98. Nwobi O, Abitbol CL, Chandar J, Seeherunvong W, Zilleruelo G. Rituximab therapy for juvenile-onset systemic lupus erythematosus. Pediatr Nephrol. 2008;23(3):413-9.

99. Marks SD, Patey S, Brogan PA, Hasson N, Pilkington C, Woo P, et al. B lymphocyte depletion therapy in children with refractory systemic lupus erythematosus. Arthritis and rheumatism. 2005;52(10):3168-74.

100. Watson L, Beresford MW, Maynes C, Pilkington C, Marks SD, Glackin Y, et al. The indications, efficacy and adverse events of rituximab in a large cohort of patients with juvenile-onset SLE. Lupus. 2015;24(1):10-7.

101. Bertsias GK, Ioannidis JP, Aringer M, Bollen E, Bombardieri S, Bruce IN, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis. 2010;69(12):2074-82.

102. Parikh S, Swaiman KF, Kim Y. Neurologic characteristics of childhood lupus erythematosus. Pediatr Neurol. 1995;13(3):198-201.

103. Sibbitt WL, Jr., Brandt JR, Johnson CR, Maldonado ME, Patel SR, Ford CC, et al. The incidence and prevalence of neuropsychiatric syndromes in pediatric onset systemic lupus erythematosus. J Rheumatol. 2002;29(7):1536-42.

104. Turkel SB, Miller JH, Reiff A. Case series: neuropsychiatric symptoms with pediatric systemic lupus erythematosus. J Am Acad Child Adolesc Psychiatry. 2001;40(4):482-5.

105. Yu HH, Lee JH, Wang LC, Yang YH, Chiang BL. Neuropsychiatric manifestations in pediatric systemic lupus erythematosus: a 20-year study. Lupus. 2006;15(10):651-7.

106. Lim LS, Lefebvre A, Benseler S, Peralta M, Silverman ED. Psychiatric illness of systemic lupus erythematosus in childhood: spectrum of clinically important manifestations. J Rheumatol. 2013;40(4):506-12.

107. Loh WF, Hussain IM, Soffiah A, Lim YN. Neurological manifestations of children with systemic lupus erythematosus. Med J Malaysia. 2000;55(4):459-63.

108. Singh S, Gupta MK, Ahluwalia J, Singh P, Malhi P. Neuropsychiatric manifestations and antiphospholipid antibodies in pediatric onset lupus: 14 years of experience from a tertiary center of North India. Rheumatol Int. 2009;29(12):1455-61.

109. Brunner HI, Jones OY, Lovell DJ, Johnson AM, Alexander P, Klein-Gitelman MS. Lupus headaches in childhood-onset systemic lupus erythematosus: relationship to disease activity as measured by the systemic lupus erythematosus disease activity index (SLEDAI) and disease damage. Lupus. 2003;12(8):600-6.

110. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis and rheumatism. 1999;42(4):599-608.

111. Avcin T, Benseler SM, Tyrrell PN, Cucnik S, Silverman ED. A followup study of antiphospholipid antibodies and associated neuropsychiatric manifestations in 137 children with systemic lupus erythematosus. Arthritis and rheumatism. 2008;59(2):206-13.

112. dos Santos MC, Okuda EM, Ronchezel MV, Leon EP, Trindade VS, Bastos WA, et al. Verbal ability impairment in juvenile systemic lupus erythematosus. Rev Bras Reumatol. 2010;50(4):362-74.

113. Mortilla M, Ermini M, Nistri M, Dal Pozzo G, Falcini F. Brain study using magnetic resonance imaging and proton MR spectroscopy in pediatric onset systemic lupus erythematosus. Clin Exp Rheumatol. 2003;21(1):129-35.

114. Prismich G, Hilario MO, Len CA, Terreri MT, Quaresma MR, Alonso G, et al. Use of single photon emission computed tomography and magnetic resonance to evaluate central nervous system involvement in patients with juvenile systemic lupus erythematosus. Braz J Med Biol Res. 2002;35(7):805-10.

115. Reiff A, Miller J, Shaham B, Bernstein B, Szer IS. Childhood central nervous system lupus; longitudinal assessment using single photon emission computed tomography. J Rheumatol. 1997;24(12):2461-5.

116. Russo R, Gilday D, Laxer RM, Eddy A, Silverman ED. Single photon emission computed tomography scanning in childhood systemic lupus erythematosus. J Rheumatol. 1998;25(3):576-82.

117. Szer IS, Miller JH, Rawlings D, Shaham B, Bernstein B. Cerebral perfusion abnormalities in children with central nervous system manifestations of lupus detected by single photon emission computed tomography. J Rheumatol. 1993;20(12):2143-8.

118. Dong J, Li H, Wang JB, Yao Y, Yang QR. Predictors for neuropsychiatric development in Chinese adolescents with systemic lupus erythematosus. Rheumatol Int. 2012;32(9):2681-6.

119. Falcini F, De Cristofaro MT, Ermini M, Guarnieri M, Massai G, Olmastroni M, et al. Regional cerebral blood flow in juvenile systemic lupus erythematosus: a prospective SPECT study. Single photon emission computed tomography. J Rheumatol. 1998;25(3):583-8.

120. Mostafa GA, Ibrahim DH, Shehab AA, Mohammed AK. The role of measurement of serum autoantibodies in prediction of pediatric neuropsychiatric systemic lupus erythematosus. J Neuroimmunol. 2010;227(1-2):195-201.

121. Mostafa GA, Nazif HK, El-Shahawi HH, Abd El-Aziz MM, Hassan MA. Antineuronal antibodies and electroneurophysiological studies in pediatric patients with neuropsychiatric systemic lupus erythematosus. Pediatr Allergy Immunol. 2009;20(2):192-9.

122. Papero PH, Bluestein HG, White P, Lipnick RN. Neuropsychologic deficits and antineuronal antibodies in pediatric systemic lupus erythematosus. Clin Exp Rheumatol. 1990;8(4):417-24.

123. Press J, Palayew K, Laxer RM, Elkon K, Eddy A, Rakoff D, et al. Antiribosomal P antibodies in pediatric patients with systemic lupus erythematosus and psychosis. Arthritis and rheumatism. 1996;39(4):671-6.

124. Al-Obaidi M, Saunders D, Brown S, Ramsden L, Martin N, Moraitis E, et al. Evaluation of magnetic resonance imaging abnormalities in juvenile onset neuropsychiatric systemic lupus erythematosus. Clin Rheumatol. 2016;35(10):2449-56.

125. Gulati G, Jones JT, Lee G, Altaye M, Beebe DW, Meyers-Eaton J, et al. Blood Brain Barrier Permeability is altered in patients with Systemic Lupus Erythematosus: A Novel Imaging Approach. Arthritis Care Res (Hoboken). 2016.

126. Brunner HI, Klein-Gitelman MS, Zelko F, Thomas EC, Hummel J, Nelson SM, et al. Validation of the Pediatric Automated Neuropsychological Assessment Metrics in childhood-onset systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2013;65(3):372-81.

127. Vega-Fernandez P, Vanderburgh White S, Zelko F, Ruth NM, Levy DM, Muscal E, et al. Cognitive Performance Scores for the Pediatric Automated Neuropsychological Assessment Metrics in Childhood-Onset Systemic Lupus Erythematosus. Arthritis Care Res (Hoboken). 2015;67(8):1119-27.