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

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ABSTRACT

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 optimise and disseminate management regimens for children and young adults with rheumatic diseases like cSLE. Here, we 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. Recommendations were generated using the EULAR (European League Against Rheumatism) 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. A total of 25 recommendations regarding key approaches to diagnosis and treatment of cSLE were made. The recommendations include 11 on diagnosis, 9 on disease monitoring and 5 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. 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.

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INTRODUCTION

Childhood-onset systemic lupus erythematosus (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 0.3–0.9 per 100 000 children-years and a prevalence ranging from 1.89 to 25.7 per 100 000 children worldwide (reviewed in refs[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 SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) 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. SHARE recommendations for autoinflammatory 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 (LN) and antiphospholipid syndrome (APS) 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 EULAR (European League Against Rheumatism) 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 LN and paediatric 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 tables 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 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 summarises the results of the literature search. A total of 9341 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 S1). 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.

General diagnostic recommendations

Prompt, accurate diagnosis of cSLE in a specialist centre is crucial to enable timely initiation of appropriate treatment, including multidisciplinary 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 29] their similarities mean that the established American College of Rheumatology (ACR) classification criteria for SLE are widely used for cSLE.[30] In 2012, new classification criteria for SLE were published.[31] 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.

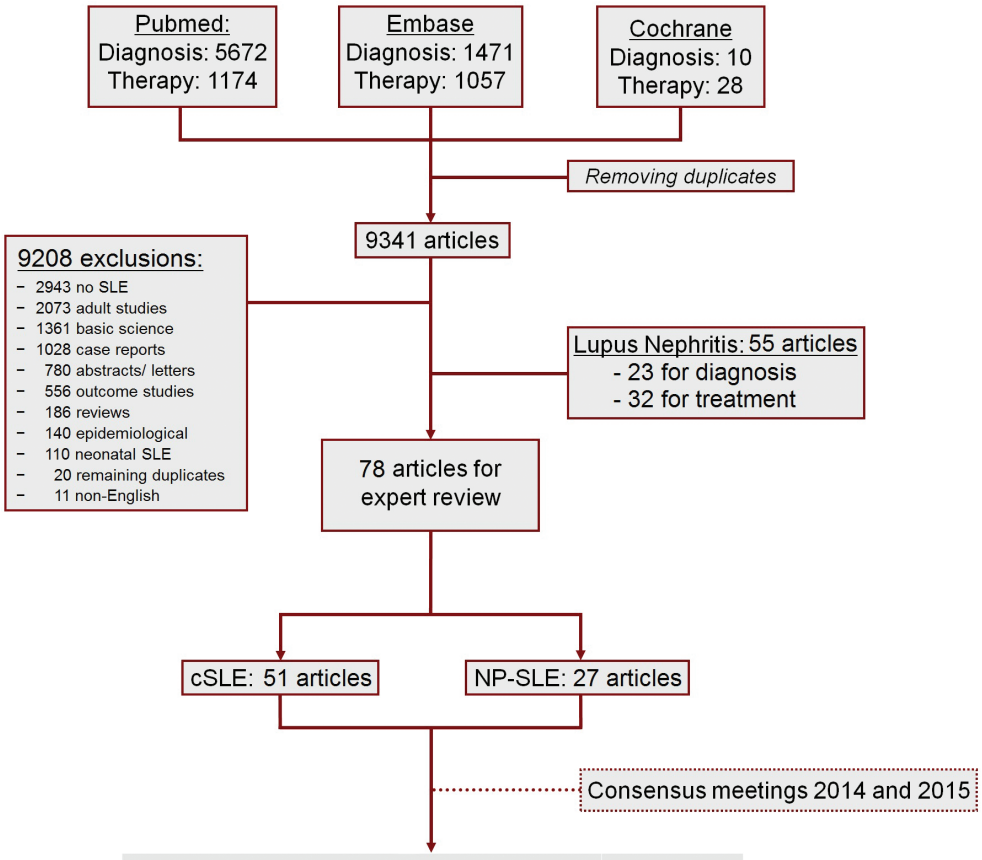
A hallmark of SLE is the presence of autoantibodies, particularly those directed towards nuclear autoantigens (antinuclear antibodies, ANA). Next to ANA, autoantibodies including anti-double-stranded DNA (anti-dsDNA), anti-Sm, anti-RNP, anti-Ro/SS-A and anti-La/SS-B (collectively referred to as 'ENA' (extractable nuclear antigens)) are prevalent in cSLE: dsDNA 54%–93%; anti-Sm 17%–52%; anti-RNP 22%–50%; anti-Ro/SS-A 33%–54%; anti-La/SS-B 14%–32%.[5 32–38] 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 (eg, disease severity, organ involvement, age of onset) despite extensive efforts to find them.[39–47] 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.[48 49] 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 patients with lupus. 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.[50 51]

Cardiopulmonary involvement

Although unusual in cSLE, cardiac and pulmonary involvement does occur, but is often asymptomatic initially.[52–60] 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 ECG screen in every patient with cSLE 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.



Recommendations regarding:	Number
cSLE	
Diagnosis	11
Management	9
Treatment	5
NP-cSLE	
Diagnosis	6
Management	4

Figure 1 Summary of the literature search. cSLE, childhood-onset systemic lupus erythematosus; LN, lupus nephritis; NP-cSLE, neuropsychiatric cSLE; NP-SLE, neuropsychiatric SLE; SLE, systemic lupus erythematosus.

Macrophage activation syndrome

Macrophage activation syndrome (MAS) is a rare but severe, potentially life-threatening complication of cSLE, characterised by high fever, associated in some patients with organ involvement (neurological symptoms, hepatomegaly, splenomegaly), pancytopenia, coagulopathy, elevation of liver enzymes, ferritin and triglycerides.[61 62] Preliminary recommendations for timely diagnosis and correct classification of MAS in cSLE have been developed.[61] 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.[63 64] A bone marrow aspirate should be performed to assess the cause of cytopenias and to detect possible haemophagocytosis. 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.[65 66] Consensus was reached on preliminary criteria for global flares in cSLE.[67] 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.[68–70] 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

Table 1 Recommendations for cSLE—diagnostic procedures, management and treatment

	Level of evidence	Strength	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
2. 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
3. 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
4. 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
5. In patients with cSLE, hereditary complement deficiencies should be considered, especially in young patients.	3	C	100
6. All patients with cSLE should have a chest X-ray at diagnosis.	3	C	100
7. All patients with cSLE should be screened for cardiac abnormalities using ECG and echocardiography at diagnosis.	3	C	100
8. Patients with cSLE with respiratory symptoms or signs (in the absence of acute infection) should have a pulmonary function test including CO diffusion.	3	C	100
9. Exertional intolerance in patients with cSLE 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
10. In patients with cSLE, unexplained fever should trigger a search for infection and MAS.	3	C	93
11. 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-dsDNA; and complete blood cell count.*	2AB/3	B-C/ C	100
2. 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 treatment.*	3	C	100
3. Children receiving systemic corticosteroids should be checked regularly for linear growth.	2A	B	100
4. All children with cSLE should have disease activity assessed regularly using a standardised disease activity measure such as the SLEDAI-2k or pBILAG-2004.	4	D	100
5. All children with cSLE should have disease damage assessed yearly using a standardised disease damage measure such as the paediatric SDI.	3	C	100
6. All patients with cSLE should have access to an ophthalmologist.	3	C	100
7. Annual eye screening should be considered for patients with cSLE taking hydroxychloroquine.	3	C	100
8. Sun protection may be beneficial in patients with skin manifestations and should be considered.*	3	C	100
9. 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 optimise long-term outcome including prevention of fatalities.*	3	C	80
Treatment recommendations			
1. All children with lupus should be on hydroxychloroquine routinely.	2A	B	100
2. In all decisions of treatment change or modification, compliance should be actively checked.	3	C	100
3. When it is not possible to taper the prednisone dose, a DMARD should be added to the therapy.	3	C	100
4. 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
5. If rituximab is required, the recommended dose is either 750 mg/m^2/dose (up to a maximum of 1 g) at day 1 and day 15, or 375 mg/m^2/dose once a week for four doses.	3	C	100

*This statement is based on the EULAR recommendations for adults with SLE.[68–70]
Level of evidence: for diagnostic and observational studies: 1A, meta-analysis of cohort studies;1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasiexperimental study; and for treatment studies: 1A, meta-analysis of randomised controlled trial; 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]; Strength of recommendation: A, based on level 1 evidence; 3, descriptive study; 4, expert opinion.[25–27] Agreement indicates per cent of experts agreeing on the recommendation during the final voting round of the consensus meeting.
ANA, antinuclear antibodies; anti-dsDNA, anti-double-stranded DNA; CO, carbon monoxide; cSLE, childhood-onset systemic lupus erythematosus; DMARD, disease-modifying antirheumatic drug; eGFR, estimated glomerular filtration rate; ENA, extractable nuclear antigens; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; Hb, haemoglobin; MAS, macrophage activation syndrome; pBILAG-2004, paediatric British Isles Lupus Assessment Group index 2004; SDI, SLICC/American College of Rheumatology Damage Index; SLEDAI-2k, Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC, Systemic Lupus International Collaborating Clinics.

and/or corticosteroid use. Similarly, these factors can contribute to delayed pubertal development. Prepubertal and peripubertal 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 standardised tools to monitor disease progression. Many tools are available for this purpose.[73–75] For example, disease activity can be monitored with the paediatric

Table 2 Recommendations for NP-cSLE—diagnostic procedures and treatment

	Level of evidence	Strength	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
2. In patients with cSLE 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
3. 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
4. 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 function.*	3	C	100
5. A normal MRI of the CNS does not exclude NP-cSLE.*	3	C	100
6. 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
2. Antiepileptic 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 seizure.*	3	C	100
3. Long-term antiepileptic therapy should be considered for recurrent seizures.*	3	C	93
4. There is a need for paediatric NP-cSLE research regarding treatment.	4	D	100

*This statement is based on the EULAR recommendations for adults with NP-cSLE.[68 123]
Level of evidence: for diagnostic and observational studies: 1A, meta-analysis of cohort studies; 1B, randomised controlled study; 2A, controlled study without randomisation; 2B, quasiexperimental study; and for treatment studies: 1A, meta-analysis of randomised controlled trial; 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] Strength of recommendation: A, based on level 1 evidence; 3, descriptive study; 4, expert opinion.[25–27] Agreement indicates percent of experts agreeing on the recommendation during the final voting round of the consensus meeting.
ACR, American College of Rheumatology; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalogram; EULAR, European League Against Rheumatism; NP-cSLE, neuropsychiatric childhood-onset systemic lupus erythematosus; NP-SLE, neuropsychiatric systemic lupus erythematosus; Ped-ANAM, Pediatric Automated Neuropsychological Assessment Metrics; SLE, systemic lupus erythematosus.

British Isles Lupus Assessment Group index or the Systemic Lupus Erythematosus Disease Activity Index 2000.[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.[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 (HCQ), 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 HCQ 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 patients with cSLE, sunscreens are widely recommended to prevent photosensitive rashes and as part of general disease management. One study in 11 adult patients with SLE showed that some, but not all types of sunscreen prevented the development of ultraviolet 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 outpatient 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 HCQ 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, HCQ has a favourable safety profile.[89] Adult studies show that long-term use of HCQ 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 HCQ, addition of a disease-modifying antirheumatic 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]

Diagnostic recommendations

NP-cSLE can be a common manifestation of lupus in children.[101–108] 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[109] 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.[110–122] Therefore, the recommendation regarding the diagnostic evaluation of neuropsychiatric symptoms is adopted from the adult EULAR recommendations.[68 123]

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 MRI techniques.[124 125] In addition, conventional MRI techniques (as well as novel MRI imaging modalities) may be unspecific for central nervous system 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 Pediatric Automated Neuropsychological Assessment Metrics, 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,[123] 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.[123]

Recurrent seizures in SLE may benefit from antiepileptic treatment. However, one single seizure without evidence for epileptic activity on electroencephalogram 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 optimisation of the management of this rare disease.

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Correction notice This paper has been amended since it was published Online First. Owing to a scripting error, some of the publisher names in the references were replaced with 'BMJ Publishing Group'. This only affected the full text version, not the PDF. We have since corrected these errors and the correct publishers have been inserted into the references.

Contributors MWB and SK are senior authors. NW and BV designed the SHARE initiative. NG and NdG performed the systematic literature review, supervised by MWB and SK. Validity assessment of selected papers was done by MWB, SK, TA, AR, IKP, BBM and CP. Recommendations were formulated by NG, MWB and SK. The expert committee consisted of TA, BBM, PB, PD, IKP, PL, LM, SO, CP, AR, AvR, YU, NW, SK, MWB and SDM; they completed the online surveys and/or participated in the subsequent consensus meetings. NG, NdG, SK and MWB prepared the consensus meetings, and NG and NdG chaired the meetings and took minutes. AR and BF facilitated the consensus procedure using nominal group technique. NG, SK and MWB wrote the manuscript, with contribution and approval of all coauthors.

Competing interests None declared.

Patient consent The study did not involve human subjects.

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

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