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Practice Guideline

Interdisciplinary Clinical Practice Guidelines for patient-centred management of juvenile-onset systemic lupus erythematosus

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ABSTRACT

Objectives: To develop updated interdisciplinary clinical practice guidelines for the management of juvenile-onset systemic lupus erythematosus (jSLE) in a patient-centred, treat-to-target (T2T) approach.

Methods: Recommendations were developed based on T2T principles around shared decision-making by a multidisciplinary team of experts including paediatric and adult rheumatologists, paediatric nephrologists, neurologists, cardiologists, pneumologists, radiologists, immunologists, and infectious disease specialists, geneticists, and ophthalmologists from Germany, Switzerland, Austria, the United Kingdom and Ireland, a psychologist, and a patient representative. The process followed the standard operating procedures of the German AWMF (Association of the Scientific Medical Societies in Germany). The team conducted an extensive literature review (2012-2024) of 40 clinically selected Population/Intervention/Comparison/Outcome questions. Overarching principles (OAP), overarching treatment strategies (OATS), and recommendations were formulated and explored in 2 online preconsensus meeting Delphi surveys with the experts. The results were discussed in 3 virtual consensus meetings using a modified nominal group technique to discuss, modify and vote on the OAP, OATS, and recommendations. All final document was approved by 2 external reviewers and the AWMF.

Results: We reached consensus on 45 recommendations on the general assessment, diagnosis, monitoring, nonpharmacologic, and pharmacologic management of jSLE. We highlight organ-specific manifestations, such as central nervous system disease, jSLE-related antiphospholipid antibody syndrome, and juvenile lupus nephritis, and consider disease severity for treatment recommendations.

Conclusions: We have developed updated interdisciplinary clinical practice guidelines to facilitate a patient-centred T2T approach to the management of patients with jSLE.

INTRODUCTION

Systemic lupus erythematosus with onset in childhood or adolescence (hereafter referred to as juvenile SLE or jSLE) is a rare, complex immune-mediated disease with a broad spectrum of organ manifestations. Like adult SLE, juvenile-onset SLE (jSLE) is characterised by a heterogeneity of clinical manifestations and courses with periods of remission and relapse [1,2]. Children and youth living with jSLE on average have higher disease activity and a worse prognosis than adults [3].

The majority of jSLE patients continue to require immunomodulatory drugs and glucocorticoids (GCs) into adulthood [4]. jSLE patients have a significantly increased premature risk of developing atherosclerosis and GC-related toxicity [5]. Standardised mortality rates in jSLE are similar to adult-onset SLE [6] with a 2.6-fold higher risk of death compared to the general population. The main causes of death are infections, kidney involvement, and cardiovascular complications [7]. Despite the high morbidity and mortality, there is a paucity of research and evidence leading to off-label treatment. The disease heterogeneity mandates a patient-centred and multidisciplinary management approach. Treat-to-target (T2T) concepts are currently being developed by international task forces for jSLE [8,9].

Since the SHARE (Single Hub and Access point for Paediatric Rheumatology in Europe) initiative in 2017, no updated recommendations have been formulated. The novelty of these

WHAT IS ALREADY KNOWN ON THIS TOPIC

- In 2017, consensus guidelines on juvenile systemic lupus erythematosus (SLE) by European experts were published separately for nonrenal SLE and lupus nephritis by an international team (SHARE [Single Hub and Access point for Paediatric Rheumatology in Europe])
- Treat-to-target (T2T) approach is a therapeutic goal in adult and juvenile SLE
- Adult guidelines include grading of disease severity (mild-moderate-severe)

WHAT THIS STUDY ADDS

- We have consented the first multidisciplinary guidelines on juvenile-onset SLE (jSLE) with expertise from 10 different subspecialties and patient input, in which recommendations for mild, moderate and severe disease manifestations are given in a patient-centred T2T approach.
- Our guidelines comprise recommendations for renal, neuropsychiatric and nonrenal-nonneuropsychiatric jSLE and antiphospholipid antibody syndrome in a holistic approach.
- This T2T concept integrates goals set by patients and their families into a comprehensive therapeutic management plan.
- We suggest the combination of medication (biologicals/disease-modifying antirheumatic drugs [DMARDs]; DMARD and DMARD) when therapeutic goals are not reached to optimize drug therapy and reduce steroid toxicity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This study will influence treatment recommendations and decisions in daily practice to improve outcome of patients with jSLE worldwide.

consensus guidelines on jSLE is the focus on the multidisciplinary management approach for children and adolescents. The work represents the concerted effort of paediatric and adult rheumatologists and nephrologists, paediatric neurologists, and 7 other subspecialities, as well as a patient representative. We aimed to establish a structured approach for diagnosis and management that could inform the work of interdisciplinary clinical teams in daily practice. We also incorporated shared decision-making as a hallmark of a state-of-the-art T2T approach to jSLE care. The recommendations include secondary antiphospholipid antibody syndrome (APS), while the topics of cutaneous, neonatal, and monogenetic jSLE were excluded.

These present guidelines built on the 2017 SHARE recommendations [10–12]. Our update includes detailed recommendations for juvenile lupus nephritis that are closely aligned with the recently published KDIGO recommendations for glomerular diseases [13,14]. As published evidence for the treatment of jSLE remains scarce by 2025, our recommendations take into account the EULAR recommendations for adults [15] to facilitate a process of presenting evidence-based recommendations to the community wherever applicable.

METHODS

Involvement of experts and representatives of other national (paediatric) societies in this consensus guideline

The German Societies for Pediatric Rheumatology (GKJR), Pediatric Nephrology (GPN), Pediatric Immunology Working Group (API), Association for Child and Adolescent Health Professionals (BVKJ), German Society for Infectious Diseases (DGPI), German Society for Pediatric Endocrinology (DGKED), German Society for Pediatrics and Adolescent Medicine (DGKJ), German Society for Pediatric Cardiology and Congenital Heart Defects (DGPK), German Society for Rheumatology and Clinical Immunology (DGRh), German Ophthalmological Society (DOG), German Rheumatism League (RheumaLiga), Society for Human Genetics (GfH), Society for Pediatric and Adolescent Rheumatology (GKJR), Society for Neuropediatrics (GNP), Society for Pediatric Pneumology (GPP), and Society for Pediatric Radiology (GPR).

Development of PICO questions

Prior to the literature search, the guideline coordinators worked together with a group of paediatric nephrologists to develop 5 key themes: Overarching Principles of Diagnosis and Treatment, Nonrenal SLE, Neuropsychiatric jSLE, Renal jSLE, and overarching treatment strategies. Each overarching topic was assigned to a designated patient-partnered, multidisciplinary working group. Each group developed and agreed on the most relevant questions for their topic, which formed the basis of the literature search. Based on this, a total of 40 PICO (Population/Intervention/Comparison/Outcome) questions were collected and provided to the 4 working groups as a basis for future recommendations within the new guidelines.

Literature search

The search was divided into 2 strategies including 1 for nonrenal SLE such as neuropsychiatric lupus and 1 for lupus nephritis due to the high amount of published SLE-related evidence. Different search strategies were developed and tested using a variety of synonyms. The keywords used were ‘juvenile systemic lupus erythematosus AND (therapy OR diagnosis)’; the search limits were ‘humans’, ‘all child 0-18 years’, and ‘clinical trial’. Exclusion criteria were antiphospholipid syndrome, focus on other diseases, cutaneous SLE, case reports with fewer than 10 participants, median age over 30 years, incidence/prevalence, national data, experimental reports (eg, in vitro studies), not clinically applicable, outcome of interest not reported, full text not available, abstract not available, and full text not written in English or German. Publications on therapy, diagnostics, genetics, and epidemiology/ethnics were included. After manual exclusion of studies, the team analysed 60 studies as sources and assessed them for methodological quality (see Figs 1 and 2 [9,16–18] in the Supplementary Appendix). The cut-off date was the period between August 2012 and June 2021. Based on the literature provided, each working group conducted its own literature search on the respective PICO questions, extending the cut-off date to June 2024. Based on the selected studies, each working group provided answers to their respective PICO questions and divided the core statements into ‘overarching principles’ and ‘recommendations’. The secondary APLS working group was added during the guideline development process after the initial literature search.

Delphi process and structured consensus building

The core statements with overarching principles (OAP) and recommendations were made available to the participants of the consensus conference with the corresponding explanatory background texts in 2 Delphi processes using digital voting. The digital vote (yes/no/hold) with the option to provide alternative

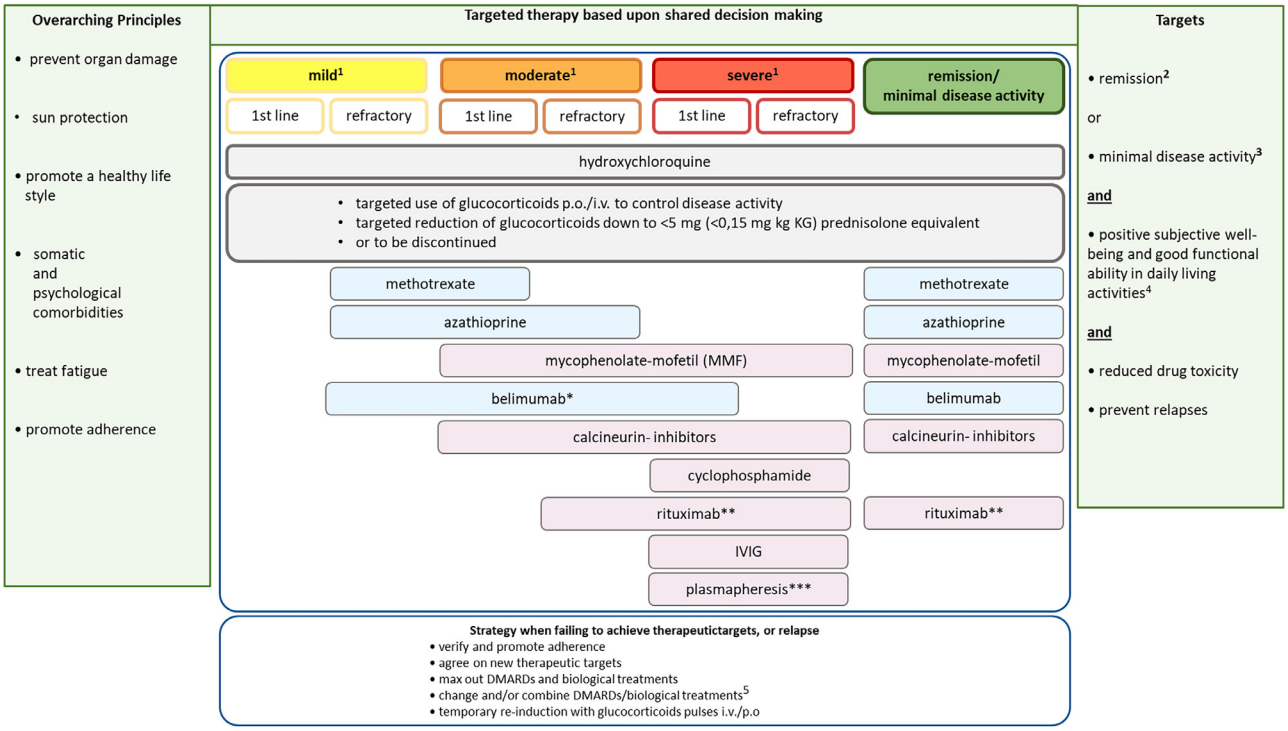

Figure 1. Treatment recommendations for nonrenal juvenile SLE. Blue, in-label; pink, off-label medications. [1]Disease activity (mild, moderate, severe) must be regularly assessed, documented, and evaluated and adjusted accordingly, ideally using the cSLEDAI (SLEDAI-2K without serological activity). Since the SLEDAI is a dichotomous scale primarily capturing organ manifestations, the disease activity assessment should also include the physician's evaluation using a visual analogue scale (VAS) [16,17]. It is crucial that treatment is not based solely on one organ, but rather considers the diversity of manifestations. Thus, both remission and disease activity should be captured in an overarching manner [9]. Categorisation for adults adapted for use in paediatric patients: Mild manifestation: Constitutional symptoms/mild arthritis/erythema <9% of body surface area (BSA), thrombocytopenia 50-100/nL; SLEDAI ≤6. Moderate manifestation: RA (rheumatoid arthritis)-like arthritis/erythema 9-18% BSA/cutaneous vasculitis ≤18% BSA; thrombocytopenia 20-50/nL; serositis; SLEDAI 7-12. Severe manifestation: Organ involvement (nephritis, central nervous system [CNS], myelitis, pneumonitis, mesenteric vasculitis, myocarditis); thrombocytopenia <20/nL; TTP (thrombotic thrombocytopenic purpura)-like disease, acute hemophagocytic syndrome; SLEDAI >12. [2]Remission in juvenile SLE (jSLE): Clinical remission with glucocorticoids (GCs) cLEDAI = 0, disease activity by physician (VAS 0-3) <0.5, prednisone equivalent 0.15 mg/kg body weight (BW), max 5 mg, hydroxychloroquine, DMARDs, and biologics as maintenance therapy. Clinical remission without GCs is defined as cLEDAI = 0, physician's global disease activity assessment (VAS 0-3) <0.5, hydroxychloroquine, DMARDs, and biologics as maintenance therapy. Maintenance therapy can be performed if dose changes are made not due to disease activity, but to improve adherence, adjust for weight, reach the target dose, or reduce side effects [16]. [3]Childhood lupus low disease activity state (cLLDAS): (SLEDAI)-2K ≤4 without activity in major organ systems and no new disease activity since the last evaluation and disease activity assessment by the physician ≤1 (scale 0-3), and prednisone dose ≤0.15 mg/kg BW/d, ≤7.5 mg/d maximum while on therapy with antimalarials, immunomodulatory drugs (DMARDs), and biologics. Maintenance therapy can be continued if dose changes are made not due to disease activity, but to improve adherence, adjust for weight, reach the target dose, or reduce side effects [9]. Note: The consensus group has decided on a target maximum dose of ≤5 mg/d prednisone equivalent, as opposed to ≤0.15 mg/kg/d, 7.5 mg/d/maximum in the cLLDAS definition. This decision was made before the PReS publication [16], where remission was defined by the target minimum dose of 0.1 mg/kg/d, ≤5 mg (Smith et al, 2024) [16]. Thus, the target prednisone equivalent dose for remission and cLLDAS is theoretically the same, though the prednisone equivalent of 5 mg would be 0.1 mg/kg/d. [4]The patient perspective must be regularly captured and incorporated into targeted treatment as part of therapy response. We recommend assessing subjective well-being and daily functionality (eg, well-being VAS for patient and parents, daily functionality using CHAQ [18]. *Belimumab as an adjunct therapy is currently approved and recommended for children aged 5 years and older for refractory serologically active manifestations without severe organ involvement, such as skin, musculoskeletal manifestations, and fatigue, and is not approved for the treatment of NP-SLE/renal manifestations. **Consider switching to obinutuzumab (if RTX serum sickness or inadequate B-cell depletion occurs). ***Plasmapheresis in combination with CYC, IVIG, or RTX (note: optimal order of PLEX ≥ RTX or IVIG, and interval between RTX or IVIG ≥ PLEX). For severe or therapy-resistant NP-SLE manifestations (encephalopathy, psychosis, seizures, NP-SLE vasculitis), the combination of PLEX, IVIG, and rituximab is a possible therapeutic option. [5]Established DMARD combinations: (A) MMF or AZA with RTX, IVIG, PLEX, CNI, MTX, and BELI or (B) CY with RTX, BELI, IVIG, and PLEX; start of consolidation therapy at the earliest 4 weeks post CY and depending on leucocyte counts. *Belimumab as add-on therapy is currently approved and recommended in children aged 5 years and older only for refractory serologically active manifestations without severe organ involvement, such as skin, musculoskeletal manifestations, and fatigue, and is not recommended for the treatment of NP-SLE/renal manifestations. **Switch to obinutuzumab if necessary (if RTX serum sickness or insufficient B-cell depletion occurs). ***Plasmapheresis in combination with CYC, IVIG, or RTX (CAVE: observe optimal sequence PLEX ≥ RTX or IVIG or distance RTX or IVIG ≥ PLEX). [#]In severe or refractory NP-SLE manifestations (encephalopathy, psychosis, seizures, NP-SLE vasculitis), the combination of PLEX, IVIG, and rituximab is a possible treatment option. AZA, azathioprine; BEL, belimumab; cAPLS, catastrophic antiphospholipid syndrome; CNI, calcineurin inhibitor; CYC, cyclophosphamide; DMARD, disease-modifying antirheumatic drug; IVIG, i.v. Immunoglobulins at 2 g/kg/BW; MMF, mycophenolate mofetil; MTX, methotrexate; PLEX, plasmapheresis; RTX, rituximab; TTP, thrombotic thrombocytopenic purpura.

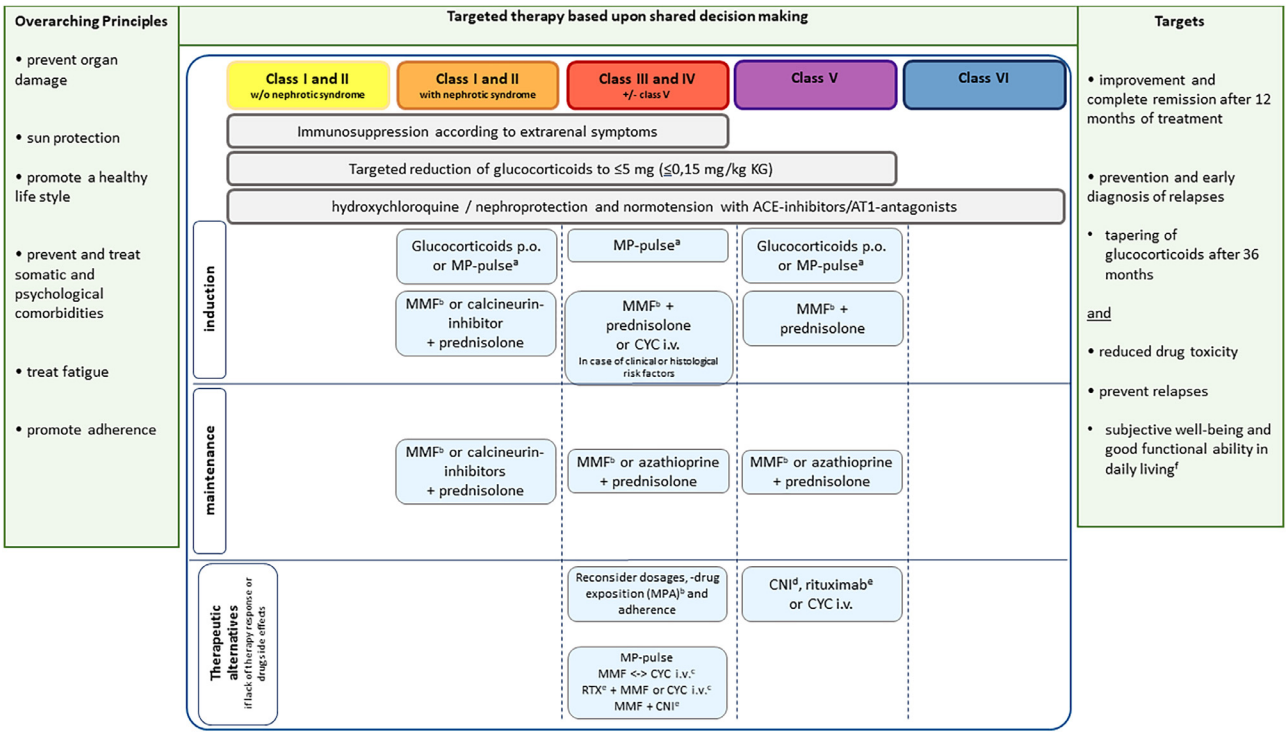

Figure 2. Treatment recommendations for juvenile lupus nephritis. [a]3 × 10 to 30 mg/kg BW, max. 1g. [b]In order to ensure an optimal response to therapy, an MPA-AUC >45 mg × h/L should be targeted in patients undergoing MMF therapy. [c]eg, for nonadherence. [d]Only with eGFR>30 mL/min/1.73 m^2. [e]If necessary, switch to obinutuzumab (if serum sickness or insufficient B cell depletion under RTX). [f]The patient's perspective must be regularly recorded and included in the targeted treatment, including an element of treatment response. We recommend recording subjective well-being and functional ability in everyday life (eg, well-being VAS patient and parents, functional ability in everyday life CHAQ [18]). AUC, area under the curve; AZA, azathioprine; CHAQ, childhood; CNI, calcineurin inhibitor (cyclosporin A or tacrolimus); CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; MPA, mycophenolate acid; RTX, rituximab; VAS, visual analogue scale.

content or wording where a proposed recommendation was not accepted and was made available to all participants of the guideline group (100% participation). Each member was required to cast one vote for each option. Recommendations and statements for which consensus strength reached at least 75% were included and discussed via nominal group technique in 3 consensus conferences. Drs M. Nothacker and F. Schwier (AWMF) acted as neutral moderators of the consensus process. The final 40 recommendations were adopted by consensus or strong consensus.

External review and adoption

The guideline manuscript was submitted to the following experts for external review: Prof. Dr Martin Aringer, Dresden, Germany (adult rheumatologist), and Prof. Dr Hermine Brunner, Cincinnati, OH, USA (paediatric rheumatologist), and subsequently agreed in writing by the guideline group. Finally, the guideline was formally adopted by the boards of the participating professional societies and organisations between November and December 2024. The guideline is currently in the process of formal endorsement by the European Reference Network (ERN) RITA.

RESULTS

The consensus group agreed on 2 core statements, 11 OAP (Table 1), and 15 overarching treatment strategies (OATS) (Table 4), complemented by 8 principles for organ-specific disease diagnostics and monitoring (Table 2). Recommendations for specific organ manifestations were formulated: 7 for neuropsychiatric lupus (Table 3), 9 for lupus nephritis (Table 6), and 5 for APS (Table 7). Finally, 7 recommendations were consented for the therapeutic management of jSLE.

OAP for general management of jSLE

The OAP emphasise the importance of early diagnosis and an interdisciplinary treatment approach involving a multidisciplinary team with expertise in jSLE (Table 1).

The focus must be on minimising disease activity, achieving remission, and preventing organ damage and is consistent with current T2T approaches to jSLE treatment. The emphasis on the quality of life, functional capacity, and age-appropriate development is particularly important for paediatric patients. The cornerstone of the T2T approach is to establish a culture of shared decision-making between the multidisciplinary team, jSLE patients, and caregivers. The multidisciplinary team must be able to empower children and adolescents with jSLE and their families by providing information that is tailored to the families' literacy, values, preferences, and goals. By understanding patient-related disease characteristics, associated risks, and treatment options, patients and parents can be encouraged to actively participate in complex treatment decisions. Similarly, the team must incorporate the concerns of children, adolescents, and their families into the treatment goals and therapy options [19].

This approach was shown to improve adherence and outcomes [20]. This is also true for the inclusion of psychosocial support and comprehensive patient education. These aspects are

Table 1
Overarching principles in jSLE

Overarching principles	Consensus strength
1. The diagnosis of jSLE is a clinical one. jSLE should be diagnosed early in the course of the disease and managed in a multidisciplinary fashion. The ACR/EULAR 2019 classification criteria should be used to support this diagnosis.[a]	100%
2. Children and adolescents with jSLE should be treated by a multidisciplinary team with expertise in the management of the disease. Paediatric rheumatologists should be involved in the management along with paediatric nephrologists and/or paediatric neurologists, depending on the organ manifestation.	95%
3. The goal of treatment is to minimise disease activity and, if possible, achieve remission, prevent organ damage and relapse, and reduce drug toxicity and secondary complications. Prevention of comorbidities should be part of the treatment plan. Comorbidities should be identified and treated at an early stage.[b]	100%
4. Therapeutic management should enable children and adolescents with jSLE to achieve an optimal quality of life, functional ability in daily life, participation, and age-appropriate development. Management is based on the treatment goals agreed upon by the multidisciplinary team with patients and their families (shared decision-making). Agreed treatment goals include both therapeutic aims and strategies.[c]	100%
5. Children and adolescents with jSLE and their parents should have low-threshold access to a psychosocial team that works together hand-in-hand with the treating physicians.	95%
6. Children and adolescents with jSLE and their families should receive comprehensive and individualised information about their disease and treatment options. Access to patient organisations should be facilitated.[d]	88%
7. Children and adolescents with jSLE and their families should be educated about a healthy lifestyle for cardiovascular and bone health. This includes exercise, healthy eating, obesity prevention, nicotine abstinence and stress management.	100%
8. Optimal protection through vaccination is important for children and adolescents with jSLE. According to the German Federal Commission for Vaccination (STIKO), basic and indication-based vaccinations with inactivated vaccines should always be up to date. During treatment with immunosuppressants, children and adolescents should not receive live vaccines; in justified individual cases, this can be done after an individual benefit-risk assessment. Treatment of SLE should not be delayed by vaccination.	94%
9. Adherence to treatment and medications should be openly discussed and be part of treatment monitoring.[e]	95%
10. From the onset of puberty, teenagers with jSLE should be counselled by a gynaecologist on family planning, contraception and pregnancy, emphasising individual risk factors, according to EULAR recommendations.[f]	
11. Adolescents with jSLE should be transitioned to adult rheumatology care in a timely, coordinated, and well-informed manner to ensure continuity of care and optimal treatment outcomes.	100%

ACR, American Colleague of Rheumatology; EULAR, European League against Rheumatism; jSLE, juvenile-onset systemic lupus erythematosus.
[a] The ACR/EULAR criteria have only been recently evaluated in paediatric patients [21,22].
[b-e] In accordance with the recently published treat-to-target principles in jSLE [11].
[f] According to the 2017 published guidelines by Andreoli at al [23].

Table 2
Recommendations for organ-specific disease manifestations

Recommendations for organ-specific disease manifestations	Consensus strength
1. Disease activity in jSLE should be measured and documented at least every 3 months using validated tools.[a]	93%
2a. When newly diagnosed, children and adolescents with jSLE should undergo a thorough clinical examination, laboratory testing, pulmonary function testing, echocardiography, ECG, abdominal ultrasound, and an EEG. cMRI and neuropsychological testing should be considered.	88%
2b. Children and adolescents with jSLE and musculoskeletal involvement should undergo basic diagnostic imaging (ultrasound, MRI) based on clinical findings. In the presence of myositis, testing for myositis-specific/myositis-associated autoantibodies should be considered.	84%
2c. In children and adolescents with jSLE and suspected haematological involvement, the following laboratory tests should be ordered: complete and differential blood count, blood smear, haemolysis parameters, direct Coombs test, and other cell-directed autoantibodies as appropriate. Bone marrow aspiration and/or biopsy may be required in some patients.	95%
2d. In children and adolescents with jSLE and suspected cardiac involvement, ECG and echocardiography, BNP or NT-proBNP, and troponin testing should be obtained. For specific indications, transesophageal echocardiography or cardiac MRI with contrast medium should be considered.	100%
2e. In children and adolescents with jSLE and suspected pulmonary involvement, chest X-rays and pulmonary function tests, including body plethysmography and diffusion capacity/DLCO, should be performed at baseline. For specific indications, further diagnostic procedures, such as a chest CT, bronchoscopy, and/or biopsy should be considered.	100%
2f. Children and adolescents with jSLE and evidence of significant therapy-refractory pancytopenia, evidence of ongoing lymphoproliferation, persistent fever and hyperferritinaemia, a macrophage activation syndrome/secondary HLH, and other forms of immune dysregulation should be considered. Specific differential laboratory tests and diagnostic imaging should be performed.	100%
2g. In children and adolescents with jSLE and other gastrointestinal involvement, including enteritis/pancreatitis/hepatitis/ protein-losing enteropathy, targeted diagnostic evaluation, including upper and lower gastrointestinal endoscopy, should be considered based on clinical symptoms and other findings. In case of liver involvement, additional advanced diagnostics should be performed.	95%

BNP, B-type natriuretic peptide; cMRI, conventional magnetic resonance imaging; CT, computed tomography; DLCO, Diffusing Capacity of the Lungs for Carbon Monoxide; ECG, electrocardiogram; EEG, electroencephalogram; HLH, hemophagocytic lymphohistiocytosis; jSLE, juvenile-onset systemic lupus erythematosus; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro B-type natriuretic peptide; T2T, treat-to-target.
[a] These recommendations have been developed from the SHARE (Single Hub and Access point for Paediatric Rheumatology in Europe) guidelines (2017) and points to consider from the T2T recommendations [11]; however, there are no controlled studies evaluating these recommendations. These above recommendations have been formulated together with expert subspecialists (eg, cardiologists, gastroenterologists, pneumologists, haematologists).

Table 3
Recommendations for CNS-specific disease manifestations

Recommendations for CNS-specific disease manifestations	Consensus strength
3a. The diagnostic evaluation and treatment of patients with suspected or confirmed NP-SLE should be managed by an interdisciplinary team, including paediatric neurologists and child and adolescent psychiatrists. Diagnosis and therapy should target manifestations directly attributable to jSLE, such as vascular ischaemic and thrombotic manifestations, diffuse inflammatory manifestations, lupus-associated diseases, including autoimmune encephalitis, demyelinating diseases, and infections, or adverse reactions to medications.	81%
3b. The diagnostic evaluation of children and adolescents with jSLE and suspected NP-SLE manifestations should include lumbar puncture and CSF analysis, a cMRI, and EEG testing.	100%
4. In children and adolescents with jSLE, concern for NP-SLE and evidence of etiologically uncertain cMRI lesions, the indication for advanced diagnostic evaluation for possible vasculitis of large or small cerebral vessels should be considered. This may include MR angiography, conventional angiography (DSA), transcranial Doppler ultrasound examination, or (brain) biopsy.	95%
5. The type and frequency of follow-up examinations (including cMRI) of NP-SLE disease and jSLE should be determined in interdisciplinary team meetings.	90%
6. Headache, as the most common symptom of NP-SLE involvement in jSLE, requires special attention. In particular, we recommend that changes in intensity (acute severe headache) and frequency (persistent headache), as well as recalcitrance to analgesic therapy, be investigated in a multidisciplinary approach.	100%
7. School performance, attention, and affective symptoms should be assessed and recorded at regular intervals in children and adolescents with jSLE. Neuropsychological testing or standardised questionnaires may supplement the diagnostic evaluation. If abnormal results are found, a thorough neuropsychological and/or psychiatric evaluation should be performed.	89%
8. Seizures in jSLE patients should be evaluated by a multidisciplinary team. Treatment should follow neuropediatric/epileptologic standards.	83%

cMRI, conventional magnetic resonance imaging; CNS, central nervous system; CSF, cerebrospinal fluid; DSA, digital subtraction angiography; EEG, electroencephalogram; jSLE, juvenile-onset systemic lupus erythematosus; MR, magnetic resonance; NP-SLE, neuropsychiatric systemic lupus erythematosus.

underrepresented in current clinical practice guidelines but play a crucial role in the overall well-being of patients. Openly addressing adherence as part of treatment monitoring is an important point, as nonadherence with treatment can be a common problem in chronic diseases during adolescence. Emphasising a healthy lifestyle, particularly with regard to cardiovascular and bone health, is very important given the increased risk of cardiovascular disease in jSLE patients. The issue of vaccination is of great importance due to the inherent risk of infection, partly related to immunosuppression in jSLE patients. Vaccination is one of the most important preventive measures against serious viral and bacterial infections. A well-prepared transition to adult rheumatology is crucial for continuity of care and long-term treatment outcomes, including counselling on family planning, contraception, and pregnancy for teenagers with jSLE.

The following core statements on the definition and classification of jSLE were unanimously accepted.

- jSLE is a complex systemic autoimmune disease characterised by inflammation and a heterogeneous clinical picture with onset before the age of 18 years.
- The classification of the heterogeneous clinical signs and symptoms of neuropsychiatric manifestations in childhood and adolescence remains based on the 1999 ACR classification criteria, which have not been validated for jSLE.

Principles of diagnostics and monitoring according to the organ manifestation

The management of jSLE patients is highly dependent on their individual organ manifestations. Therefore, the panel focused on the major organ manifestations, with specific recommendations for central nervous system (CNS) and renal SLE discussed below. The recommendations were formulated in collaboration with the relevant specialists in the consensus group (Table 2).

Neuropsychiatric jSLE

An estimated one-quarter of children and adolescents with jSLE have neuropsychiatric jSLE (NP-SLE) manifestation during the course of their disease. The variance in incidence data [24] can be explained by different study designs and ethnicities, but almost importantly by the wide clinical variability of NP-SLE [25–28]. Most NP-SLE manifestations become symptomatic in the first 2 years of jSLE disease [26,28]. The main challenges in the management of NP-SLE are the variability of the clinical presentation and the differential diagnosis. Therefore, the group agreed upon conventional magnetic resonance imaging of the brain and spine plus neuropsychological testing as initial screening. In case of new onset of symptoms of the central or peripheral nervous system symptoms or psychiatric symptoms, the possibility of neuropsychiatric involvement of jSLE should be considered and evaluated. The most common symptoms are headache, seizures, focal neurologic deficits (stroke), cognitive deficits, encephalopathy/altered consciousness, anxiety, and depression. In particular, the differential diagnosis of lupus headache and cognitive impairment can be challenging (Table 3).

OATS for jSLE

The expert group developed and agreed on overarching therapeutic principles according to T2T.

The overall treatment goal is to achieve remission. If this cannot be achieved, childhood lupus low disease activity state (cLLDAS) (low lupus disease activity) [9] is considered an alternative treatment goal. It is important that the management/care team and the patient and family agree on treatment goals that are documented and regularly reviewed. Treatment goals include both clinical and patient-defined criteria by affected children, adolescents, and their families. As part of the goal setting process, not only the primary clinical goals should be discussed with the children, adolescents, and parents as part of the target agreements but also the recommended therapeutic

strategies. Joint treatment planning in the sense of shared decision-making is based on the individual characteristics of the children and adolescents concerned and should also be discussed with them [11]. Patients whose defined treatment target has not been achieved within a certain time frame should be seen earlier in the outpatient clinic if necessary (Table 4).

Infections

Patients with jSLE are at increased risk for infections. These are a leading cause of hospitalisation, morbidity, and especially mortality in jSLE [4,29]. In a recent nationwide study in China with 54 338 jSLE patients, 0.7% died, 37% of whom died from pneumonia [30]. Infections correlate closely with long-term damage. Significantly elevated CRP levels are a warning sign of a bacterial infection, as these are uncommon in active SLE except for patients with arthritis or serositis. The typically increased type I interferon activity in SLE has an inhibitory effect on CRP production [31]. Immunosuppression impacts the sensitivity of classic markers of inflammation, such as CRP; these may increase with delay or not at all, leading to misdiagnosis [32].

Therapeutic management for jSLE

The treatment recommendations and overall treatment strategies for jSLE are summarised in Figure 1. Iterative, standardised assessments of disease activity are the basis for guiding and adjusting therapeutic management over the course of the disease. Although criteria for global flares and clinically relevant improvement are preliminary for jSLE, our expert panel agreed on the SLEDAI2k as a standardised, validated disease activity tool following the definition of very low disease activity [9,33] and remission [11] as a reachable treatment goal [34].

Regarding medication (Table 5), GCs sparing is considered an essential goal. Control of disease activity should primarily be achieved by optimising disease-modifying antirheumatic drug therapy or adding effective biologic therapies.

The consensus group has decided to follow the current EULAR recommendations [35] of a low-dose prednisone equivalent of ≤5 mg/d prednisone, considering clinical and serological disease activity. At the same time, the PReS 2023 consensus decision will be included in the definition of cLLDAS of 0.15 mg/kg body weight (BW)/d as the minimum dose to be aimed for, albeit with a reduction in the absolute maximum daily dose from 7.5 mg to 5 mg. Following the consensus meeting, the PReS recommended definition of remission in jSLE with a target minimum dose of 0.1 mg/kg BW/d prednisolone or ≤5mg prednisolone/d [16] was published. This new PReS recommendation was discussed extensively, and the consensus decision was to recommend a minimum dose of 0.15 mg/kg/d. We agree with the PReS task force that the lowest possible

Table 4
Overarching treatment strategies

T2T—implementation in everyday clinical practice	Consensus strength
1. Therapy is based on the individual characteristics of the patient. The treatment team agrees on treatment goals with the children, adolescents, and families in a participatory decision-making process. Treatment goals should be documented according to the 'treat-to-target' principle, regularly reviewed, and the treatment strategy adjusted accordingly.[a]	100%
2. The coordinating care team should regularly monitor disease activity, treatment response, and disease damage using disease-specific, validated measurement tools, and regularly document the global medical assessment of the disease.[b]	100%
3. Patient/parent ratings of well-being, fatigue, and pain (using a visual analogue scale [VAS]), as well as health-related quality of life and functional capacity, should be recorded regularly and considered in treatment decisions.[c]	100%
4. The overriding goal is to achieve remission. If this is not achieved, cLLDAS (low disease activity) can be accepted as an alternative treatment goal.[d]	100%
5. Relapse should be prevented. Agreed treatment goals should be achieved and maintained.[e]	88%
6. Children and adolescents with jSLE should be screened at least annually for depression and anxiety using validated instruments (eg, PHQ-9 and GAD-7) and treated (psychologically/psychiatrically) if necessary. Lupus activity and medication side effects should be considered in the differential diagnosis.	100%
Drug therapy	
7. Glucocorticoids should be used in a targeted manner according to disease activity and should generally not be administered for longer than 3 to 6 months at a daily dosage exceeding 0.15 mg/kg BW or 5 mg (prednisolone equivalent), whichever one is lower.[e]	100%
8. All children and adolescents with jSLE should receive continuous hydroxychloroquine.[f]	100%
Early diagnosis and treatment of comorbidities	
9. Kidney health should be monitored regularly (see Table 6), and medications should be adjusted according to glomerular function.	100%
10. Blood pressure should be measured at each visit, and any hypertension should be treated with medication.[g]	95%
11. Children and adolescents with jSLE and hyperlipidaemia should be treated with lipid-lowering therapy, especially in the presence of other cardiovascular risk factors such as hypertension or obesity (see LL Hyperlipidemia and KDIGO 2023).[h]	100%
12. The team should educate children, adolescents, families, and all others involved in care about the risk of infection and the warning signs of potentially life-threatening sepsis.	100%
13. Patients with jSLE and their families need to be informed about the increased risk of infection and the symptoms to watch for. Primary care providers (paediatricians/family doctors) and providers in reference centres should be aware of this increased risk and promptly initiate antimicrobial therapy when in doubt.	100%
14. The risk of sepsis is increased in patients with jSLE. If there is concern for sepsis, we recommend early initiation of antibiotic therapy.	100%
15. The risk of atypical and opportunistic infections is increased in patients with jSLE. Therefore, we recommend prompt initiation of appropriate treatment in the event of clinical concern, which may include antiviral and antifungal medications.	100%

BW, body weight; cLLDAS, low lupus disease activity; GAD-7, Generalized Anxiety Disorder-7; jSLE, juvenile-onset systemic lupus erythematosus; PHQ-9, Patient Health Questionnaire-9; T2T, treat-to-target; VAS, visual analogue scale.

[a-f] These recommendations have been developed and formulated from and in accordance with the SHARE (Single Hub and Access point for Paediatric Rheumatology in Europe) guidelines [10] and key issues from the T2T recommendations [11]; however, there are no controlled studies evaluating these recommendations.

[g,h] In accordance with current KDIGO guidelines 2024.

Table 5
Recommendations for the therapeutic management of jSLE

Recommendations for the therapeutic management of jSLE	Consensus strength
10a. Hydroxychloroquine (HCQ) is an essential immunomodulator for the treatment of jSLE and should always be part of the therapeutic management.	95%
10b. An ophthalmologic examination should be performed within 6 months of starting hydroxychloroquine (≤5 mg/kg body weight). Retinopathy screening should be repeated after 5 years of treatment and annually.[a]	100%
11a. Glucocorticoid (GC) therapy in jSLE should follow a T2T strategy, with the aim of administering the lowest effective dose possible. Systematic monitoring of GC therapy should be performed using quality indicators (see Table 5). The therapeutic aim is to reduce the GC dose to ≤0.15 mg/kg BW or a maximum of 5 mg (prednisolone equivalent), whichever is lower, in patients with low disease activity or remission. Both clinical and serologic disease activity should be taken into account. In patients in whom GC reduction is not possible, DMARD therapy should be optimised.[b]	100%
11b. In patients with acute and severe jSLE manifestations, methylprednisolone pulse therapy (10-30 mg/kg body weight, IV with a maximum dose of 1 g/d for 3-5 days) should be considered at an early stage.[c]	80%
12. The following steroid-sparing agents should be considered in jSLE patients: azathioprine, belimumab, calcineurin inhibitors, methotrexate, and mycophenolic acid/MMF.[d]	100%
13a. For the treatment of severe organ manifestations or life-threatening progression of jSLE, combination regimens of immunosuppressive therapies in addition to GC should be considered: mycophenolic acid/MMF, cyclophosphamide/CYC, rituximab, calcineurin inhibitors, immunoglobulins, and plasmapheresis (see also footnote 5 of Fig 1).	100%
13b. In female jSLE patients, pregnancy and its challenges with regard to jSLE treatments should be addressed. jSLE patients should be aware that certain medications must be discontinued and be replaced if they wish to become pregnant (or are pregnant). These include mycophenolic acid/MMF, methotrexate, and cyclophosphamide/CYC.[e]	100%

BW, body weight; CYC, cyclophosphamide; DMARD, disease-modifying antirheumatic drug; jSLE, juvenile-onset systemic lupus erythematosus; MMF, mycophenolate mofetil; RCT, randomised controlled trial; T2T, treat-to-target.
[a] Adapted from the German guidelines for adult [38].
[b] Adapted from Fanourakis et al 2023 as well as Smith et al 2023 [11,15].
[c] Data on methylprednisolone pulses vs oral corticosteroids are scarce and do not show advantages; however, it has been shown that long-term treatment with lower oral doses of GC demonstrate less side effects, and these lower doses are usually accompanied by IV pulse therapy upfront [39].
[d] Except from belimumab (TULIP trial), no RCT exists for each of these medications, and only azathioprine is approved for SLE.
[e] Adapted from the EULAR recommmendations on pregnancy [23].

prednisone dose should be aimed for, although a tolerable lowest glucocorticoid dose cannot yet be clearly defined [11]. Therefore, the recommended target prednisolone equivalent dose in this guideline is the same for remission and for accepted low disease activity (cLLDAS).

It is essential to follow a structured approach in the event of therapeutic failure or relapse (see Figs 1 and 2). Regular monitoring of the patients, review of treatment targets, patient adherence, and optimisation or modification of drug dosage or modifications are essential. The combination of immunomodulatory therapies should also be considered. If cyclophosphamide is used for severe organ manifestations, the Eurolupus dosing regimen should be used for both renal and nonrenal jSLE. Regarding novel treatment options, including biologics, belimumab is the only agent with a positive paediatric randomised controlled trial (RCT) (PLUTO) and paediatric FDA/European Medicines Agency labelling for childhood SLE. Rituximab is quite widely used, but off-label for refractory, organ-threatening paediatric SLE (nephritis, severe cytopenias, NP-SLE); its use is supported by case series and registries, but not by a formal paediatric SLE RCT approval. A new B cell–depleting medication (obinutuzumab) has yielded promising results based on adult lupus nephritis (LN) RCT data (REGENCY trial [36]) and is currently being investigated in paediatric trials. There is an evolving field of new targeted medication for SLE requiring alternative methods for paediatric drug development and approval to make them accessible for jSLE patients [37].

Lupus nephritis

Juvenile LN occurs in up to 80% of children and adolescents with SLE and is often initially asymptomatic [40]. The incidence of LN is higher in children and adolescents than in adults, and the severity of the disease is more pronounced. Children and adolescents of Asian, African/Caribbean, or Hispanic descent have an increased risk of kidney involvement. In addition to proliferative LN (class III or IV), non-Caucasian origin, low socioeconomic status, delayed diagnosis, reduced estimated glomerular filtration rate (eGFR) at the time of diagnosis, hypertension, and less intensive induction therapy are risk factors for the development of chronic kidney disease (CKD) [41–43]. Today, however, the renal outcome of proliferative LN treated with intensified induction therapy is comparable to that of non-proliferative LN [44,45]. The incidence of kidney failure requiring dialysis and/or transplantation, which is associated with an increased mortality rate, is up to 15% in juvenile LN over observation periods of 3 to 20 years [4,44,46–49].

Resolution of proteinuria at 12 months is the best single predictor of long-term renal outcome [44], although up to 50% of patients who do not achieve this therapeutic goal still have long-term stable kidney function [50]. A reduction in proteinuria (with normalisation and/or stabilisation of eGFR) and a reduction in proteinuria of at least 25% within 3 months and a reduction in proteinuria of at least 50% (partial clinical response) at 6 months can be expected based on previous retrospective studies in patients with LN [44,45,47]. In patients with initial proteinuria in the nephrotic range (>2 g creatinine/g protein or > 1 g/m^2 body surface area per day), the above-mentioned periods should be extended by 6 to 12 months, as the recovery of proteinuria is slower. Consideration of a very high but steadily decreasing proteinuria can avoid premature, unindicated changes in therapy.

Based on the above findings, the primary therapeutic goal in LN is continuous improvement and complete remission at 12 months, ie, normalisation of proteinuria (<0.2 g/g creatinine) and eGFR (>90 mL/min/1.73 m^2), unless irreversible chronic lesions are already present. Secondary therapeutic goals are the

Table 6
Recommendations for juvenile LN

Recommendations for juvenile LN	Consensus strength
14a. In patients with signs of kidney involvement (protein-to-creatinine ratio >0.5 g/g and/or decrease in eGFR with or without glomerular haematuria), a kidney biopsy should be considered. Kidney biopsy should be repeated if the findings may influence therapy or allow an assessment of the renal prognosis.[a]	100%
14b. Patients with active class III or IV (± class V) LN should receive immunosuppressive treatment consisting of glucocorticoids (GC) in combination with mycophenolate mofetil (MMF), or, in the case of unfavourable clinical or histologic risk factors, intravenous cyclophosphamide (CYC).[b]	100%
14c. To optimise drug therapy, we recommend therapeutic drug monitoring in patients with class III or IV LN on MMF treatment with determination of the total exposure (area-under-the-concentration-vs-time-curve, AUC) of mycophenolic acid (MPA) in a 12-hour dosing interval.[c] We recommend aiming for an MPA-AUC > 45 mg × h/L to optimise the effectiveness of MMF therapy in children with class III or IV LN.[c]	78%
14d. As part of the induction therapy, patients with severe active disease (class III or IV LN) should be started on high-dose GC (intravenous methylprednisolone pulses 10-30 mg/kg body weight, maximum 1 g/dose).[d]	100%
14e. In patients with active LN class III or IV, maintenance therapy with MMF should be given in the event of a response to induction therapy (Table 5), or alternatively with AZA, in combination with low-dose prednisone. Gradual withdrawal of immunosuppressive therapy (starting with GC) may be considered after 3 years.[e]	100%
14f. If there is no response to induction therapy in class III or IV LN, the drug dosage, drug exposure (mycophenolic acid), and adherence should be checked. Repeat kidney biopsy to differentiate acute from chronic disease may be considered.In addition to optimising the drug dosage, the following options should be considered: • Reinduction with IV methylprednisolone pulse (may be combined with the following options). • Switching from MMF to IV CYC (nonadherence) and vice versa • Adding rituximab in combination with MMF or CYC In addition, combination therapy with MMF and a calcineurin inhibitor (CNI)[f] may be considered, if eGFR >30 mL/min/1.73 m^2.	100%
14g. In class I, II, and VI LN, no specific immunosuppressive therapy should be initiated unless nephrotic syndrome is present in combination with class I or II LN. In the case of pure class V LN, a combination therapy of MMF with GC should be used for induction and a therapy with MMF or AZA for maintenance treatment, respectively. Alternative options include treatment with CNI, rituximab or intravenous CYC in the event of treatment-emergent side effects or an inadequate or no response.[g]	100%
14h. Patients with hypertension and/or proteinuria (>0.5 g/g creatinine) should be treated with inhibitors of the renin-angiotensin-aldosterone system (RAAS) up to the maximum tolerated or approved dose.[h]	95%
14i. Oedema in lupus nephritis should be treated.[i]	94%

AZA, azathioprine; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IV, intravenous; LN, lupus nephritis; PDN, prednisolone/prednisone; RCT, randomised controlled trial.

[a] Clinical presentation of LN may be mild despite significant renal involvement and early diagnosis of LN matters to initiate effective treatment and avoid progressive CKD [53].

[b] Data from uncontrolled studies in patients with active LN class III or IV (± class V) suggest equivalent renal outcomes in patients receiving mycophenolate mofetil (MMF) compared to intravenous cyclophosphamide (CYC) when given in combination with glucocorticoids (GCs) which is inline with the reports from RCTs in adults with proliferative LN [45,54,55]. Intravenous CYC should be considered in patients with risk factors such as nonadherence, severely impaired kidney function (eGFR <30 mL/min/1.73 m²) or prognostically unfavourable histology (crescents or necrosis in >25% of the glomeruli) as patients with severely impaired kidney function were excluded in clinical trials on MMF treatment.

[c] Therapeutic drug monitoring (TDM) should be considered within the first 3 months after starting therapy, but not earlier than 1 week after starting therapy [56]. It may may be helpful in the event of potential MMF-associated side effects in order to verify an MPA exposure significantly above the target value of >45 mg × h/L, which would allow a dose reduction without risk of loss of efficacy [57,58]. The MPA exposure can be estimated using a limited sampling strategy, ie, calculating the total exposure based on the MPA concentration in mg/L [=µg/mL] using fewer blood samples (before (C0), as well as 1 (C1) and 2 hours (C2) eMPA-AUC0-12 = 8.70 + 4.63*C0 + 1.90*C1 + 1.52*C2) [59]. TDM may also be useful after switching therapy, particularly to drugs that interact with the metabolism of MPA and facilitate dose adjustments during continued therapy.

[d] In patients with severe active disease (class III or IV LN) intravenous methylprednisolone pulses before starting oral glucocorticoid therapy allow to achieve a rapid anti-inflammatory effect, while in less severe cases high-dose oral GCs appear to be efficient.

[e] In patients with proliferative LN, MMF, AZA, cyclosporine A (CsA), and intravenous CYC in combination with oral PDN were used with decreasing frequency for maintenance therapy in observational and registry studies [44,55,60]). Two retrospective studies showed a slight superiority of MMF compared to AZA with regard to the prevention of relapses of LN [60]. In these studies, glucocorticoid exposure was higher in patients treated with AZA compared to the MMF group, which should theoretically lead to lower glucocorticoid toxicity in the MMF group. Given the adverse effects of long-term immunosuppression a stepwise withdrawal of immunosuppressive treatment (GCs first) may be considered after 3 years as suggested for adults with LN [14].

[f] Such as MMF (2-3 g/1.73 m² per day), CYC, and CNI (TAC and CyA) are recommended as monotherapy or 'multitarget' therapy [15,61]. B cell–depleting therapies such as RTX or obinutuzumab, even if not approved, should be considered either as monotherapy or as add-on therapy to MMF or CYC; complete depletion of circulating B cells is considered to be prognostically favourable for renal outcome [62,63]. As data on the efficacy and safety of treating LN with belimumb is lacking and belimumab is not approved for this indication European Medicines Agency (EMA), this option cannot be recommended at present.

[g] The prognosis of classes I and II LN is good even without immunosuppressive therapy; therefore, specific immunosuppressive therapy is usually not indicated [64]. However, a change of class of LN may occur [65]. In rare cases, a class I or II LN is accompanied by a nephrotic syndrome. In these cases, treatment with GCs in combination with MMF or AZA appears to be efficient. In the case of class VI LN, treatment is purely nephroprotective (see chapter 'Antihypertensive, antiproteinuric and nephroprotective therapy') because the scarring changes can then no longer be influenced by immunosuppression. The study situation for children and adolescents with class V LN is very limited. As reliable data on class V LN are lacking we follow recommendations stemming from data in adults [14], ie, combination therapy of MMF with low-dose PDN for induction and MMF or AZA for maintenance and a CNI (CsA, TAC), RTX, or intravenous CYC as alternative options—in the event of treatment side effects or nonresponders [14].

[h] Consistent antihypertensive therapy should preferably be carried out with inhibitors of the renin-angiotensin-aldosterone system (RAAS) (ACE inhibitors, ATII receptor antagonists), as these have an antiproteinuric and nephroprotective effect [66]. In addition, diuretics (eg, hydrochlorothiazide, furosemide, torasemide), calcium antagonists, and β-blockers are used. The aim is to adjust both the systolic and diastolic office blood pressure as well as the mean blood pressure in the 24-hour ambulatory blood pressure measurement (ABDM) to below the 75th percentile in patients without proteinuria and below the 50th percentile of the age and gender norm in patients with proteinuria [67]. With suboptimal blood pressure control, annual screening for left ventricular hypertrophy using echocardiography is recommended. In addition, as with other glomerular diseases, RAAS inhibitors should also be used in normotensive patients with persistent proteinuria (>0.5 g/g creatinine) due to their antiproteinuric effect [14].

[i] In patients with persisting oedema, a maximum sodium intake of around 2 to 3 mmol/kg per day (2000 mg/d in older children) should be aimed for; this corresponds to the daily requirement. In the case of severe oedema and/or hyponatraemia <135 mmol/L, fluid restriction is also recommended [68]. Diuretics, preferably loop diuretics, can also be used. Thiazide diuretics and/or aldosterone antagonists (eg, spironolactone) can be combined with loop diuretics as they have a synergistic effect. Attention should be paid to adverse effects such as hyponatraemia, hypo- or hyperkalaemia, and a decrease in eGFR due to intravascular volume depletion.

prevention of relapse, which is expected to occur in approximately one-third of children and adolescents with active LN class III or IV, and the resulting organ damage, as well as disease and/or therapy-related complications, such as growth disturbance, osteopenia, infertility, infections, CKD, and cardiovascular damage. In the case of proliferative LN (class III or IV), this requires an initial intensive immunosuppressive therapy over a period of 3 to 6 months (induction therapy), followed by maintenance therapy. One goal of maintenance therapy is to reduce GCs by adding immunosuppressive drugs, such as mycophenolate mofetil or azathioprine (target dose of prednisone ≤5 mg/d), and to phase out GCs after 36 months in case of stable remission (Table 6).

An inadequate response is defined as a lack of continuous improvement in proteinuria during induction therapy with a reduction in protein/creatinine ratio to <50% of baseline or <0.5 g/g and normalisation of eGFR or eGFR >60 mL/min/1.73 m^2 with initial eGFR <60 mL/min/1.73 m^2 within 3 to 6 months. It is important to consider the trend of the laboratory results, which should be recorded at close intervals. In the absence of a response, immediate intervention and intensification of immunosuppression is indicated, as this may lead to irreversible nephron loss, progressive CKD, and kidney failure. It should be noted that persistent proteinuria may also be due to chronic structural kidney damage, ie, fibrosis, which does not improve with increased immunosuppression. Therefore, in such cases, a repeat biopsy should be considered. Finally, treatment with renin-angiotensin-aldosterone system inhibitors, especially in patients with persistent proteinuria or hypertension, is of utmost importance in slowing the progression of the disease, as has been observed in other forms of glomerulonephritis [51]. The goal is to use the maximum tolerated doses to minimise proteinuria and achieve a mean arterial blood pressure based on 24-hour ambulatory blood pressure measurement below the 75th percentile in children without proteinuria and below the 50th percentile in those with proteinuria (urine protein-to-creatinine ratio >0.5 g/g) [52].

Table 7
Recommendations for secondary APS in jSLE

Recommendations for secondary APS in jSLE	Consensus strength
9a. All children and adolescents with jSLE should be tested for the presence of lupus anticoagulant, anti-cardiolipin IgM/IgG, and/or anti-2-glycoprotein IgM/IgG at baseline (repeat testing at 12 weeks if positive) or at any time if APS is suspected.	100%
9b. Initiate primary prophylaxis with low-dose aspirin in patients with jSLE and evidence of aPL, especially in high-risk patients (see Table 5).	100%
9c. In patients with jSLE and secondary APS manifesting as venous thrombosis, treatment with a vitamin K antagonist should be initiated after initial heparin therapy has been completed. Direct oral anticoagulants should not be considered as first-line therapy.[a]	100%
9d. Patients with jSLE with secondary APS manifesting as arterial thrombosis should be started on long-term therapy with a vitamin K antagonist, if necessary, in combination with low-dose aspirin. Direct oral anticoagulants should not be considered as first-line therapy.[b]	100%
9e. Because catastrophic APS (CAPS) has a high mortality, combination therapy with anticoagulation, high-dose immunosuppression, intravenous immunoglobulins, and plasma exchange or immunoadsorption should be started immediately. Treatment should be planned and implemented in collaboration with a reference centre.	88%

aPL, antiphospholipid; APS, antiphospholipid syndrome; IgM/IgG, immunoglobulin M/immunoglobulin G; jSLE, juvenile-onset systemic lupus erythematosus.

[a,b] All recommendations are based on the SHARE (Single Hub and Access point for Paediatric Rheumatology in Europe) recommendations on APS [10], at that time direct oral anticoagulants (DOACs)were not approved for children. Current data on DOACs in adult patients with APS suggest that they should not be used and we therefore followed this recommendation.

Secondary APS in jSLE

APS is a systemic autoimmune disease characterised by the presence of antiphospholipid antibodies, especially anticardiolipin antibodies and anti-beta2-glycoprotein antibodies, as well as lupus anticoagulant positivity, and the occurrence of thrombotic events, pregnancy complications, haematologic, nephrologic, cardiologic, dermatologic, neurologic, and other manifestations. The revised Sapporo classification criteria for adults specifically address thrombosis and pregnancy complications [69]. Therefore, they can only be used to a very limited extent for the classification of APS in children. The new classification criteria for adult-onset APS also include microvascular disease, heart valve damage, and thrombocytopenia, thus encompassing a broader spectrum of symptom variability in APS [70]. Catastrophic APS, characterised by microvasculopathy, is a life-threatening disease that affects at least 3 organ systems in a very short period of time [71]. Recommendations for the presence of APS in jSLE are provided below (Table 7).

DISCUSSION

To develop these state-of-the-art clinical practice guidelines for the management of juvenile lupus erythematosus, a multidisciplinary task force of jSLE experts from the 3 German-speaking countries joined efforts. To ensure the broadest possible representation in this truly broad multidisciplinary panel, experts in paediatric rheumatology, nephrology, neurology, endocrinology, cardiology, infectious diseases, radiology, and pulmonology contributed after being delegated by their respective professional organisations. A molecular geneticist, an ophthalmologist, a psychologist, and 2 adult rheumatologists contributed. Most importantly, a patient representative was the core of the expert panel. The current set of recommendations takes into account the severity of lupus activity, ie, mild, moderate, and severe, and includes treatment recommendations for the different stages of the disease. One major challenge for these updated clinical practice guidelines is the lack of controlled trials for the paediatric age, which explains why evidence-based recommendations for jSLE are difficult to generate.

For a highly complex systemic disease with a spectrum of symptoms such as jSLE, the clinical challenge is to address its heterogeneity by providing a structured, personalised treatment approach using a T2T strategy. In addition, our consensus group decided to combine treatment goals defined by a multidisciplinary medical team with shared decision-making by patients and their families as a solid basis for individualised therapeutic strategies that need to be re-evaluated regularly. It is essential that affected children, adolescents, and their families are informed about treatment options and understand the benefits and risks. The perspectives and needs of affected children and adolescents must be taken into account when discussing treatment options. Shared decision-making involves the joint development of an individualised treatment strategy, which may be implemented by the children and adolescents themselves. This approach may promote adherence to a given treatment regimen.

The goals of jSLE management are to achieve remission or alternatively cLLDAS/VLDA, prevent relapses, minimise morbidity, sequelae, and drug toxicity, particularly by limiting steroid exposure, and allow children and adolescents to enjoy a good quality of life and participation. In the event of nonresponse to treatment or relapse, adherence should be openly discussed and, if possible, re-evaluated before treatment is modified. Our treatment recommendations do not include immunosuppressive agents for which little or no data have been published in the context of jSLE. In refractory cases, it may be necessary to use such molecules off-label, ie, JAK inhibitors, anifrolumab, as well as the more recent targeted cell therapy, such as CAR T cells.

Our expert panel anticipates that the increasing number of immunomodulators for the comprehensive management of jSLE with a T2T approach will require international recommendations under the auspices of the ERN RITA within the next years. This emphasises the need for international collaborative research initiatives and, in particular, the need for registries in which clinical data are gathered. Registry-based safety and efficacy data would support informed decision-making, which combination of medications might be the best for an individual patient.

In the meantime, these truly patient-centred consented practice guidelines will empower paediatric rheumatologists, nephrologists, neurologists, other involved health professionals, policymakers, and patients with a state-of-the-art management of jSLE.

Competing interest

All authors declare they have no competing interests.

CRediT authorship contribution statement

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