***Working title: (limit 3000 words)***

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

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## Abstract

### Background
Lupus nephritis (LN) occurs in 50-60% of patients with childhood-onset systemic lupus erythematosus (cSLE), leading to significant morbidity. Timely recognition of renal involvement and appropriate treatment are essential to prevent renal damage.

### Objectives
To provide evidence-based recommendations for diagnosis and treatment of LN in childhood.

### Methods
The SHARE (Single Hub and Access point for paediatric Rheumatology in Europe) initiative was launched in 2012 to generate diagnostic and management regimens for children and adolescents with rheumatic diseases such as cSLE. Recommendations were developed using the European League Against Rheumatism (EULAR) standard operating procedure. A European-wide expert committee including representation of paediatric nephrology formulated recommendations using the nominal group technique.

### Results
Six recommendations regarding diagnosis and twenty recommendations covering treatment choices and goals were accepted for the different classes of LN, described in the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system. Treatment goal should be complete renal response. Treatment of class I LN should mainly be guided by other symptoms. Class II LN should be treated initially with low-dose prednisone, only adding a DMARD after 3 months of persistent proteinuria or prednisone dependency. Induction treatment of class III/IV LN should be mycophenolate mofetil (MMF) or intravenous cyclophosphamide combined with corticosteroids; maintenance treatment should be MMF or azathioprine for at least 3 years. In pure class V LN, MMF with low-dose prednisone can be used as induction and MMF as maintenance treatment.

### Conclusions
Evidence-based recommendations for diagnosis and treatment of LN have been generated to support uniform and high quality care for all children with SLE.

## Introduction

In 2012, the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) initiative was launched with the aim to optimise and disseminate diagnostic and management regimens for children and adolescents with rheumatic diseases, including childhood-onset Systemic Lupus Erythematosus (cSLE) (1). SLE in children is rare, with a prevalence ranging from 1.89 to 25.7 per 100,000 children and an incidence of 0.3 to 0.9 per 100,000 children-years worldwide (reviewed in (2-4)). cSLE and SLE share the same pathogenesis, but in general, cSLE appears to have a more severe phenotype (5-8). 50%-60% of patients with cSLE will develop lupus nephritis (LN) (5-8). Timely and accurate recognition of renal involvement combined with appropriate treatment choices will optimise clinical outcome and decrease renal-associated morbidity and mortality (1).

Consensus treatment recommendations for (proliferative) LN in children are currently available (9, 10), but have not included a systematic literature search focused on cSLE studies, nor did they focus on recommendations regarding diagnosis of LN or treatment in non-proliferative LN.

SHARE-recommendations for paediatric antiphospholipid syndrome, juvenile dermatomyositis, familial Mediterranean fever and auto-inflammatory diseases have been published (11-13)(+ref APS). SHARE-recommendations for diagnosis and treatment of cSLE – not including LN - have also been published (REF cSLE). Here, the SHARE-recommendations for LN are presented. These recommendations should support medical specialists caring for children with LN in carrying out a stepwise diagnostic process and guide them in the decision making process regarding LN therapies.

## Methods

SHARE is a European Union (EU)-funded project; therefore representative paediatric rheumatologists from across Europe formed a panel of 16 members, with representation of paediatric nephrology. A selected number of disease experts from outside the EU have also contributed to the project. The European League Against Rheumatism (EULAR) standardised operating procedure for developing best practice recommendations was followed (14).

### *Systematic literature search and study selection*

A systematic literature search, based on specific research questions was performed in the electronic databases PubMed/MEDLINE, EMBASE and Cochrane databases in July 2013 (see online Supplementary Table S1), using a validated filter to search articles pertaining to children and adolescents only (15). All titles and abstracts were screened independently by two reviewers (NG and NdG). Articles fulfilling the inclusion criteria were sent to the experts for validity assessment and data-extraction (Supplementary Table S2). Notably, the literature search included terms regarding cSLE and paediatric APS, these topics are discussed separately from this paper (ref APS, cSLE). Here, we report the results of the identified studies regarding LN in cSLE.

### *Validity assessment*

All articles were analysed by the expert panel (two independent reviewers per article, MWB, SK, TA, AR, IKP, BBM, CP) using standardized data extraction and scoring forms. Any discrepancies were resolved by a third expert (SK or MWB) to reach consensus. Adapted classification tables for diagnostic (16) and therapeutic (17) studies were used to determine the level of evidence and strength of each recommendation (14) (see online Supplementary Tables S3 and S4).

### *Establishment of recommendations*

Based on the evidence from the literature search, provisional statements regarding diagnosis and treatment of LN were formulated (NG, NdG, SK, MWB). Adult literature was consulted if no evidence in children could be found to map against a particular recommendation. The provisional statements were presented to the expert committee (n=15) in an online survey (100% response rate). Recommendations were revised according to responses and discussed at two sequential face-to-face consensus meetings in March 2014 (Genova, number of experts participating, n=16) and March 2015 (Barcelona, n=14). Nominal group technique was used to reach consensus (18). Final recommendations were formulated during these meetings. Recommendations were accepted when a predefined $\geq$80% of the experts agreed.

## Results

### *Literature review*

The results of the literature search are summarized in figure 1. The initial literature search yielded a total of 9341 articles regarding diagnosis, treatment and management of cSLE. After screening on title and abstract and assessing the full text for relevance, 55 articles fulfilled inclusion criteria for LN in cSLE and were scored by the experts (see online Supplementary Table S5).

### Recommendations for Lupus Nephritis – Diagnosis *(Table 1)*

Renal symptoms that could be indicative of LN are renal dysfunction (acute kidney injury, acute on chronic kidney disease), hypertension, macroscopic or microscopic haematuria and/or proteinuria. However, proteinuria is not always related to LN. Orthostatic proteinuria or postural proteinuria is the most common cause of proteinuria in teenagers, and should therefore be excluded as a cause of mild proteinuria in patients with (suspected) cSLE (19, 20). If proteinuria is not orthostatic, confirmation and classification of renal involvement with consultation with paediatric nephrologist is recommended, proceeding to a percutaneous renal biopsy.

The International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification system is commonly used to classify LN (9, 21) (see online Supplementary Table S6). Studies using the ISN/RPS classification system showed that class of nephritis is associated with severity of renal disease and (long-term) renal outcome. Therefore, treatment strategies of LN are based upon the class LN nephritis as identified by using the ISN/RPS 2003 classification system (22, 23).

Assessment of renal biopsies can be challenging and requires expertise. A renal pathologist experienced in LN should be consulted for the evaluation of these biopsies (24). Even so, misclassification of a renal biopsy is possible. For example, patients diagnosed with class I or II LN should not generally have proteinuria after 3 months of treatment. If proteinuria persists after 3 months, the possibility of misclassification of the biopsy or progression to class III or IV LN must be considered (25). To avoid unnecessary repeat biopsy, the expert group recommends re-evaluating the initial biopsy as a first step.

### Recommendations for Lupus Nephritis – Treatment *(Table 2, Figure 2)*

As clinical symptoms are not reliable enough to reflect severity of renal disease, a renal biopsy is needed to guide treatment strategy. Treatment strategies for the different classes of LN are discussed below; an overview summarizing all treatment strategies is shown in Figure 2. It is acknowledged that renal biopsy is not always possible, for instance due to the patient's critical clinical condition or due to lack of resources to safely perform the procedure. Nephrotic syndrome, hypertension and impaired renal function are all correlated with class III/IV LN (26-

28). In cases when a renal biopsy cannot be performed, these symptoms should be considered as reflecting class III/IV LN and treated likewise.

The long-term aim for treatment of LN should be complete renal response, with early morning urine protein:creatinine ratio (UP:UC) of <50mg/mmol or urine albumin:creatinine ratio of 35 mg/mmol and normal or near-normal renal function (estimated Glomerular Filtration Rate (eGFR) <80 ml/min/1.73m$^2$). Within 6–12 months after initiation of treatment, partial renal response, defined as a ≥50% reduction in proteinuria to at least sub-nephrotic levels and normal or near-normal renal function should be achieved (9).
Several studies have reported on the anti-proteinuric effect of angiotensin-I converting enzyme inhibitors (ACE-I) or angiotensin-II receptor blockers (ARB) in renal disease. Evidence in adult-onset SLE patients shows that these inhibitors of the renin-angiotensin system have a protective effect on the kidneys in case of proteinuria (29, 30). Therefore, additional treatment with ACE-I and/or ARB in children with lupus nephritis and proteinuria should be advocated. A paediatric nephrologist should be consulted to guide the use of ACE-I or ARB.

*ISN/RPS Class I and II LN*

Class I LN is more common in cSLE compared to SLE in adults, but no specific articles on treatment of class I LN were found in the literature search. Based on literature in adults and expert opinion, class I LN could be treated with low dose oral corticosteroid therapy (31). If other organ systems are involved and class I LN has been found, treatment choice should be guided by these other clinical features. If class I LN is the only clinically active feature, adding other disease modifying anti-rheumatic drugs (DMARDs) to the therapy is generally not necessary (Table 2, Figure 2).
Similarly, class II LN generally responds well to low dose (<0.5mg/kg/day) oral corticosteroid therapy, tapered over a 3-6-month period. If proteinuria is persistent or corticosteroid dose cannot be effectively weaned, the biopsy should first be re-evaluated by a renal pathologist experienced in LN to exclude possible misclassification. Adding a DMARD to the treatment or switching to another DMARD effective for LN (e.g. MTX to AZA) is recommended (Table 2, figure 2) (32-34). Notably, if treatment of class II LN remains unchanged despite the lack of renal response or prednisone dependency, renal impairment or even renal failure may develop (35). There is little evidence for a specific DMARD in class I/II LN. Only case series or cohorts with limited number of patients are available and report the use of, mycophenolate mofetil (MMF), tacrolimus and cyclophosphamide (CYC) with variable effects (36-38).

*ISN/RPS Class III and IV LN with or without class V LN*

Class III or IV LN, also known as proliferative LN, are the most common and severe forms of LN in cSLE (6, 26, 27, 39-41). Combination of class III or IV LN with class V LN is prevalent. As class III and IV LN in general show a less favourable disease course than class V LN, treatment strategies as advised for proliferative LN should be followed in case of combined class III or IV with class V LN.

<u>Induction treatment:</u>
In adults, evidence for induction treatment of class III and IV LN is based on several randomized controlled trials (RCT) (42, 43). Equal efficacy and toxicity ratios for low-dose intravenous (I.V.) CYC (500 mg/pulse, 6 pulses given every 2 weeks) and high-dose CYC (750 mg/m$^2$/pulse (maximum dose 1200 mg/pulse), 6 monthly pulses) (42). When comparing high dose I.V. CYC to MMF (1000 mg/day, maximum dose 3000 mg/day), the renal outcomes were similar (43). Recently, a network meta-analysis including only RCTs investigated comparative efficacy and toxicity of I.V. CYC, MMF, calcineurin inhibitors (CNI), Azathioprine

(AZA), Rituximab and plasma exchange alone or in combination for induction and/or maintenance treatment of proliferative LN in adults. They concluded that induction treatment with MMF, CNI, or a combination thereof, when added to corticosteroids, were the most effective treatments compared to I.V. CYC (44).
No RCTs have been performed in children, but the literature search yielded several observational cohort studies and case series describing treatment of class III and IV LN. In the majority of these articles I.V. CYC is used as induction treatment, with good results in the majority of patients (45-53). Three studies compared I.V. CYC induction therapy to AZA in proliferative LN, one of these studies included patients with acute renal failure at diagnosis. The efficacy of both AZA and I.V. CYC were similar (47, 49, 51). Notably, the patients with acute renal failure at diagnosis had an excellent renal outcome (49).
One small study compared MMF to I.V. CYC in 13 patients with Class III LN. Complete or partial remission was achieved by more patients in the MMF group than in the I.V. CYC group (52). A study in 11 patients concluded that MMF is well tolerated as induction treatment (54). Initial MMF monotherapy combined with ciclosporin after 4 weeks was a safe and effective therapy for 16 patients, with a follow-up of 12 months (55).
When combining the high-quality evidence from RCT for LN in adult-onset SLE with the evidence from smaller case series and observational cohort studies in cSLE, the expert group recommends MMF (1200-1800mg/m2/day, maximum 1500 mg twice daily) or I.V. CYC in combination with high-dose prednisone (1-2 mg/kg/day, maximum 60 mg/day) for induction treatment of proliferative LN in cSLE (10, 42-60). The dosing of I.V. CYC (high or low-dose, see above) is left to the discretion of the treating physician. The toxicity profile of MMF is more favourable when compared to I.V. CYC and may be preferred above I.V. CYC for this reason. In case of suspected non-compliance to oral medication, I.V. CYC should be considered (Table 2, Figure 2) (43, 58).

Maintenance treatment

RCT in adults showing that both MMF and AZA are good options for maintenance treatment in class III and IV LN (56, 57, 61, 62), although a higher relapse rate is seen in patients treated with AZA (56, 57, 62). In addition, the recent network meta-analysis mentioned above showed that MMF was the most effective strategy to maintain remission for proliferative LN (44).
Studies of proliferative LN in cSLE show similar results for MMF and AZA as in adults. Some studies show better outcomes for MMF, others for AZA (47-49, 51, 52, 54, 55, 63, 64). The expert group therefore advises to use MMF (1200 mg/m$^2$/day, maximum dose 3000 mg/day) or AZA (2-3 mg/kg/day, maximum dose 150 mg/day) as maintenance treatment for LN in cSLE. Of note, AZA is associated with a higher flare risk in a meta-analysis of adult LN RCT (61). I.V. CYC can also be effective as maintenance treatment (45-47, 50, 51, 53, 63, 64), but is not advised due to higher toxicity when compared to MMF or AZA (e.g. increased risk of a reduced ovarian reserve/premature ovarian failure, inhibition of spermatogenesis, increased risk of bladder carcinoma) (65).
Duration of maintenance treatment in LN in the cSLE case series or observational cohort studies from our literature search was variable (1 to 5 years). Adult proliferative LN RCT studying maintenance therapy treat patients up to 3 years with good results (57, 62). The expert panel agreed that adopting this time frame, while accepting that more evidence is necessary to support this statement, was the best strategy (Table 2, Figure 2)

Corticosteroid use in class III/IV LN

Corticosteroids are generally used concomitantly with induction/maintenance regimen for class III/IV LN but comparative studies regarding corticosteroid dose and oral versus I.V. use are not available. The EULAR/ERA-EDTA as well as the ACR guideline for treatment of proliferative LN in adult-onset SLE recommend I.V. methylprednisolone pulse therapy as part

of the initial treatment strategy, followed by oral prednisone (0,5-1 mg/kg/day) and tapered to the minimal amount necessary to control disease. This recommendation is based on expert opinion and extrapolation from controlled studies (9, 66). Consensus treatment plans of CARRA for induction therapy of proliferative LN in cSLE include three different dosing regimens combining oral corticosteroids with I.V. methylprednisolone-pulses based on expert opinion and by evidence from gene-expression arrays suggesting that I.V. methylprednisolone pulses but not oral prednisone have the potential to eliminate the interferon-alpha gene expression signature in cSLE (10). However, there are no clinical data available reporting that eliminating the interferon-alpha gene expression signature is associated with a better renal outcome.
As there is no robust evidence for the ideal dosing strategy of corticosteroids in proliferative LN in SLE or cSLE, the expert group has not specified this in a recommendation. Most studies in cSLE report the use of oral prednisone 1-2 mg/kg/day (maximum 60 mg/day) as initial dosing in proliferative LN where children < 30 kg mostly are dosed up to 2 mg/kg/day (38, 47, 48, 52, 53, 64). I.V. methylprednisolone pulse therapy (30 mg/kg/dose I.V. for 3 consecutive days, maximum 1000 mg/dose) may be added to induction treatment before start of oral prednisone, especially in case of severe disease (e.g. impaired GFR (<80 ml/min/1.73m2), nephrotic range proteinuria (> 3,5 g/24 hr), biopsy-proven crescentic glomerulonephritis). An example for a prednisone-tapering schedule that may be used is tapering by 10 to 20 percent at one-week or two-week intervals based on clinical improvement (42, 43, 58, 62).

*ISN/RPS class V LN*

When comparing the use of corticosteroids with I.V. CYC to corticosteroids alone, the combination therapy was superior in the only RCT for adults with pure class V LN available. (67). A pooled analysis of patients with pure class V LN included in two RCTs showed that MMF was equally efficacious when compared to I.V. CYC as induction treatment (68). Patients with class V LN with or without class III or IV LN were also included in RCT for LN in adults, showing no difference between the use of MMF or high dose I.V. CYC as induction treatment (58). Evidence for treatment strategies in the literature search for children with class V LN was very limited. Recently Hugle et al. reported good renal outcome in a cohort (n=30) of cSLE with pure class V LN. 33% of the total cohort were treated with DMARDs (AZA, CSP, MMF) (69).
When combining the evidence of SLE and cSLE, the expert group recommends the use of MMF in combination with low-dose oral prednisone (0.5 mg/kg/day) as induction treatment for pure class V LN in cSLE. MMF or AZA are recommended as maintenance treatment. CNI (ciclosporin, tacrolimus), rituximab or I.V. CYC are recommended as alternative options or for non-responders (43, 67-69). (Figure 2, Table 2)

*Renal flares and refractory disease*

In general when a patient is not responding to the prescribed treatment as expected or develops a flare of disease, noncompliance for medication should first be explored. Lack of adherence to therapy can be as high as 50%, and has been associated with higher persistent disease activity and poorer renal outcomes (70-73). In addition, the aim of LN treatment is complete renal response but RCT in adult LN have shown that time is needed to reach this response and can be awaited for at least 3-6 months after start of treatment (43). However, if a patient shows hardly any response within 3 months of induction treatment, it is generally accepted to change the principle induction agent.
Renal flares have been reported to occur in up to 50% of cSLE patients during maintenance treatment (41, 74, 75). After excluding noncompliance to medication, restarting or increasing the dose of corticosteroids (oral prednisone or I.V. methylprednisolone pulses) and a switch

of DMARD should be considered. Defining renal response criteria or other outcomes of renal disease is outside the scope of this article. An overview is given in the CARRA consensus treatment plans for proliferative LN (10).
In persistent active or refractory cases of lupus nephritis class III and IV with or without class V LN, treatment should be changed to another therapeutic agent, for example when treating with MMF this should be changed to rituximab or I.V. CYC. As mentioned before, adherence must be assessed and dosing of current treatment must be optimized before this switch. With regard to rituximab, two RCTs in adults testing rituximab for LN did not reach the primary endpoint, therefore rituximab is not recommended as primary treatment for LN (76, 77). However in observational studies of LN in adults rituximab has been successfully used as rescue treatment for refractory LN (78, 79). Only very limited evidence for the use of rituximab for LN in cSLE was found in the literature search (37, 48). Recently, an observational cohort study in cSLE reported the effects of rituximab treatment in 63 children, LN was the indication to start rituximab treatment in 36% of the patients. Rituximab was well-tolerated and improved disease activity in these children with a significant reduction in oral corticosteroid dose (80). The expert group recommends that rituximab should be considered as treatment option in refractory LN, in addition to the DMARD currently used.
CNI (tacrolimus, ciclosporin) can be considered as a treatment option for LN in selected cases, albeit with the consideration of potential nephrotoxicity especially related to ciclosporin after long-term use (81).

**Discussion**

Six recommendations regarding diagnosis, and twenty recommendations regarding treatment for LN in children were accepted with over 93% agreement among a European-wide group of cSLE experts, including expertise from paediatric nephrology.

Recommendations for treatment of LN in cSLE are available (9, 10). The cSLE subcommittee of Childhood Arthritis and Rheumatology Research Alliance (CARRA), a North American based research collaboration specifically for paediatric rheumatic diseases, have published consensus treatment plans for newly diagnosed class III and IV LN in cSLE (10). These treatment plans correspond well with the SHARE LN recommendations. For example, the CARRA cSLE subcommittee advises to use MMF or I.V. CYC as induction treatment, similarly to the SHARE recommendations. Differences exist specifically regarding the use of concomitant corticosteroid use, as pointed out in the results section above. The EULAR/ERA-EDTA have also published recommendations for the management of adult and paediatric lupus nephritis but these recommendations have mainly focussed on evidence obtained in studies with LN in adults. Notably, these recommendations underline the importance of a well-coordinated transition programme in the care for children with LN (9). The expert group fully supports this recommendation, but as specific EULAR-guidelines for transition programmes for young people with rheumatic diseases have recently been published (82), we have refrained from this subject in the SHARE guidelines.
The SHARE recommendations are the first to specifically focus on evidence in cSLE for diagnosis and treatment of all classes of LN using a systematic literature search. Unfortunately evidence in cSLE was limited and the need for new high-quality studies in this field is clear.

In conclusion, the SHARE project has resulted in evidence-based recommendations for diagnosis and treatment of LN, to support uniform and high quality care for all children with LN.

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