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15 **INTERNATIONAL CONSENSUS FOR THE DOSING OF CORTICOSTEROIDS IN**
16 **CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS WITH PROLIFERATIVE**
17 **LUPUS NEPHRITIS**

18 Running Head: Consensus on corticosteroid dosing in childhood-onset proliferative lupus
19 nephritis

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1 **ABSTRACT**

2 **Objective:** To develop a Standardized Steroid dosing Regimen (SSR) by physicians treating
3 childhood-onset systemic lupus erythematosus (cSLE) complicated by lupus nephritis (LN),
4 using consensus formation methodology.

5 **Methods:** Parameters influencing corticosteroid (CS) dosing were identified (Step-1). Data
6 from children with proliferative LN were used to generate Patient Profiles (PP) (Step-2).
7 Physicians rated change in activity of renal and extra-renal cSLE between two consecutive
8 visits and proposed CS dosing (Step-3). Using PP ratings, the SSR was developed (Step-4)
9 with refinements achieved in a physician focus group (Step-5). A second type of PP
10 describing cSLE course for ≥ 4 months since kidney biopsy were rated to validate the SSR-
11 recommended oral and intravenous CS-dosages (Step-6). PP adjudication was based on
12 majority ratings for both renal and extra-renal disease courses, and consensus level was set
13 at 80%.

14 **Results:** Degree of proteinuria, estimated glomerular filtration rate, change in renal and
15 extra-renal disease activity, and time since kidney biopsy influenced CS dosing (Steps-1/2).
16 Considering these parameters in 5,056 PP-ratings from 103 raters, and renal and extra-renal
17 course definitions, CS-dosing rules of the SSR were developed (Steps-3-5). Validation of the
18 SSR for up to 6 months post kidney biopsy was achieved with 1,838 PP-ratings from 60
19 raters who achieved consensus for oral and intravenous CS dosage as per the SSR (Step-
20 6).

21 **Conclusion:** The SSR represents an international consensus on CS dosing for use in
22 patients with cSLE and proliferative LN. The SSR is anticipated to be used for clinical care
23 and standardize CS-dosage during clinical trials.

24 **KEY WORDS:**

25 Childhood-onset systemic lupus erythematosus; lupus nephritis; corticosteroids; treatment.

26

1 **INTRODUCTION**

2 Corticosteroids (CS) remain one of the mainstays of therapy in childhood-onset systemic
3 lupus erythematosus (cSLE), especially with major organ involvement such as lupus
4 nephritis (LN). Due to lack of strong medical evidence, dosing of CS for cSLE treatment
5 remains mainly provider dependent (1). Delphi surveys and expert opinion were previously
6 employed to propose standards for CS use (2, 3), including for proliferative LN in children as
7 part of the Consensus Treatment Plans for pediatric LN (CTP_{LN}) (4). However, when tested
8 in real life settings, providers followed the CS dosing recommended by the CTP_{LN} in only
9 68% of patients by 3 months, and just 37% of patients by 6 months of induction therapy for
10 LN (5).

11 Objectives for this study were to use consensus formation methods in conjunction with
12 real-life patient data 1) to delineate determinants that influence CS dosage in cSLE with
13 proliferative LN, and 2) develop as well as 3) initially validate the Standardized Steroid
14 dosing Regimen (SSR).

15
16 **PATIENTS AND METHODS**

17 **Overview.** *Figure 1* sketches the experimental design (Steps 1-6). Building on the
18 experience from the CTP_{LN} (4), we focused on cSLE patients with biopsy proven, new-onset
19 LN class III or IV with/without class V overlap, as per the International Society for
20 Nephrology/Renal Pathology Society (ISN/RPS) (6). Consensus formation methodology was
21 combined with statistical modeling of Patient Profiles (PP) ratings that were derived from a
22 contemporary cSLE cohort. We invited an international group of physicians experienced in
23 the care of pediatric LN to participate in this research.

24 **Details of experimental design.** Step-1: A review of the literature was conducted and
25 revealed limited high-quality evidence regarding the dosing of CS in patients with cSLE (7).
26 In April 2018, after literature review, followed by a Delphi survey, consensus was achieved
27 around candidate determinants of oral-CS and IV-CS use (CS-determinants) at an in-person
28 meeting held in Denver, CO, using modified nominal group technique (8). Demographic,
29 laboratory and clinical parameters were identified as candidate CS-determinants.

1 Consensus meeting participants were 51 members of the Childhood Arthritis and
2 Rheumatology Research Alliance (CARRA) Lupus Nephritis Work Group.

3 Step-2: The medical records of 143 LN patients followed at eight pediatric tertiary
4 care centers were retrospectively reviewed for up to 24 months, starting from the time of
5 kidney biopsy that newly diagnosed the patient as having proliferative LN (6). **Table 1**
6 summarizes principal eligibility criteria of patients whose data were abstracted for PP
7 generation.

8 PP formats previously developed to judge the overall disease course of cSLE (9)
9 were adapted and piloted among 20 physicians. PP included information about patient
10 demographics (age, gender, race, ethnicity); organ involvement with SLE per the 1997
11 American College of Rheumatology (ACR) classification criteria (10); kidney biopsy results
12 (LN class (6), activity and chronicity scores (11, 12)); vitals (body surface area, height,
13 actual body weight, blood pressure); laboratory testing [complete blood count, erythrocyte
14 sedimentation rate (ESR), C3, C4, anti-dsDNA antibodies], and the response variables for
15 pediatric LN (LN-RVs) (4), namely proteinuria [spot urine protein/creatinine ratio (UPCR) or
16 24-hour timed proteinuria], renal function [estimated glomerular filtration rate (eGFR), serum
17 creatinine], and urine sediment [white blood cells (WBC)/high powered field (HPF), red blood
18 cells (RBC)/HPF and heme-granular or RBC casts]; scores of Systemic Lupus International
19 Collaborating Clinics/ACR Damage Index (SDI) (13) and SLE Disease Activity Index (version
20 SLEDAI-2K) (14); parent/patient global assessment of overall well-being; physician global
21 assessment of overall disease activity; usage of oral-CS and IV-CS (dose, route, frequency),
22 use of immunosuppressant (mycophenolate mofetil, cyclophosphamide with dose and
23 frequency) and angiotensin system blockers (Yes/No). Each PP provided this information for
24 two consecutive patient assessments [Visit-1, Visit-2] to describe the course of cSLE over a
25 4-week period.

26 Step-3: Of 2,215 PP generated, 460 PP, with complete patients' information, were
27 selected for rating by 142 physicians (PP-raters) who were members of the CARRA Lupus
28 Nephritis Work Group, the Pediatric Rheumatology European Society Lupus Working Party,
29 or the Pediatric Nephrology Research Consortium. PP selection for the development dataset

1 focused on capturing all permutations of combined renal and extra-renal disease courses
2 between Visit-1 and Visit-2. PP-raters judged the renal and extra-renal disease courses as
3 follows: active stable; active improved; active worsened; inactive; or not enough information.
4 PP-raters were also asked to suggest oral-CS and IV-CS dosages for the 30 days following
5 Visit-2, at stable, increasing, or tapering dosages. PP-raters were randomized to rate 66 PP
6 each (also see **supplemental figure S1**).

7 **Step-4:** Only PP for which consensus about the course of cSLE between visits was
8 achieved were included in the dataset that was used to develop the SSR. As done in the
9 past (9), adjudication of the renal and extra-renal course described in a given PP was based
10 on majority vote among PP-raters, i.e. $\geq 50\%$ of PP-raters agreed on one specific
11 combination of renal plus extra-renal disease course between Visit-1 and Visit-2. SSR-
12 recommended CS dosage was the median daily CS dose that achieved consensus by PP-
13 raters.

14 **Step-5:** Following statistical analysis (see below), an additional Delphi questionnaire
15 was sent to a randomly selected subset of PP-raters (n=70). This questionnaire was aimed
16 at clarifying maximum daily oral-CS dosages, use of divided daily oral-CS doses, IV-CS use
17 upon initiation of induction therapy, and IV-CS and/or oral-CS dosages prescribed with flares
18 (LN and/or extra-renal cSLE). This was followed by a focus group (KO, DML, SW, MKG) to
19 clarify CS use for children <40 kg and the importance of the type of immunosuppressant
20 prescribed (here: cyclophosphamide or mycophenolate mofetil) for the use of IV-CS. Step-5
21 information was utilized to refine the preliminary SSR (from Step-4) (4, 5).

22 **Step-6:** Among available patients with ≥ 4 months of follow-up, 66 patients (or PP)
23 were selected to serve as validation set. PP format used for Step-6 were similar to those of
24 Step-3. However, in addition to renal and extra-renal disease course information, the SSR-
25 recommended dosage of oral-CS and/or IV-CS for up to 6 months since kidney biopsy were
26 shown (see **supplemental figure S2**). These 66 PP were sent to 80 PP-raters randomly
27 selected from the pool of available PP-raters (Step-3); each PP-rater was asked to rate 33
28 PP. Specifically, PP-raters were asked whether the SSR-recommended CS dosage at each

1 time point was acceptable for treating the vast majority (>80%) of patients with similar
2 clinical presentations and comparable renal and extra-renal disease courses.

3

4 **Data management & statistical analysis.** Following PP-ratings (Step-3), the frequencies
5 and percent of agreement were calculated for each PP for the renal, extra-renal, and overall
6 (renal plus extra-renal) disease courses. As the analysis unit, each PP was reviewed and
7 rated by multiple pediatric rheumatologists and nephrologists, and their responses were
8 summarized and analyzed to evaluate the level of consensus for oral-CS and IV-CS dosage
9 as recommended by the SSR. Only PP with majority ratings ($\geq 50\%$) for a given disease
10 course were considered in these statistical analyses. Logistic regression analyses identified
11 CS-determinants relevant to renal, extra-renal and overall disease courses (Step-3).
12 Descriptive statistics (mean, standard deviation, median, Q1 and Q3) for the percent
13 agreement among PP-raters for oral-CS and IV-CS dosing were computed, followed by
14 distribution and probability plots (Step-4). CS dosing regimens for each disease course were
15 summarized and synthesized to build the preliminary SSR (Step-4). Step-5 considered
16 consensus among survey respondents. The validation of the SSR (Step-6) used statistics
17 similar to Step-4. Research Electronic Data Capture (REDCap) software
18 (<https://projectredcap.org/software>) was used for data capture, storage, surveys and PP-
19 ratings. Data were analyzed using SAS, version 9.4.

20 The study was approved by the ethics committees / institutional review boards of the
21 participating centers.

22

23 RESULTS

24 **Proposed determinants that influence CS use in cSLE with LN.** For Step-1, 25 of 51
25 physicians of the CARRA Lupus Nephritis Work Group responded to the Delphi
26 questionnaire (response rate: 49%) that aimed at confirming the LN-RVs and identifying
27 additional CS-determinants. There was consensus (>80%) that complement levels (C3 and
28 C4) and UPCR were important determinants of CS dosage. Structured discussions and
29 voting as part of a nominal group exercise at a subsequent face-to-face meeting provided

1 confirmation of these candidate CS-determinants. These included time since index kidney
2 biopsy, kidney histological features, status and change of the LN-RVs since prior
3 assessment, and extra-renal disease activity as measured by the scores from the respective
4 domains of the SLEDAI-2K, ESR, physician global assessment of disease activity, and
5 patient overall well-being. Case examples that were presented highlighted the extent of
6 variation of CS use among group members (n=15) when treating proliferative LN, hence
7 supporting the rationale for developing the SSR.

8

9 ***Determinants influencing PP-raters adjudication of status and changes in renal and***
10 ***extra-renal disease used in the SSR.*** In Step-3, 103 physicians (response rate
11 103/142=73%) reviewed 460 PP producing 5,080 PP-ratings. Out of the 5,080 PP-ratings,
12 24 were excluded due to data quality issues resulting in 5,056 PP-ratings that were
13 analyzed. These 460 PP represented 120 of the 143 LN patients with available data. **Table**
14 **2** summarizes the baseline characteristics of these 120 cSLE patients represented by the
15 PP. There were 352 PP (352/460=77%) that achieved majority ratings for the course of renal
16 plus extra-renal disease between Visit-1 and Visit-2, hence qualified for inclusion in the
17 subsequent steps of the SSR development.

18 Among the proposed CS-determinants included in Step-3, the renal course was best
19 predicted by the eGFR, UPCR, and urine RBCs. Pyuria was common (**Table 2**), however,
20 was not associated with LN course (active stable; active improved; active worsened;
21 inactive; odds-ratio (OR)=1.03, p-value=0.97). Course (active stable; active improved; active
22 worsened; inactive) of extra-renal disease from PP-ratings was closely associated with
23 change in extra-renal SLEDAI-2K score (OR=0.91, p-value=0.004). Thus, the following CS-
24 determinants were considered in the preliminary SSR: patient actual body weight, time from
25 index kidney biopsy, extra-renal SLEDAI-2K score, UPCR, urine RBCs, and eGFR. We used
26 a conservative estimate for normal eGFR at ≥ 95 ml/min/1.73m² (15, 16).

27

28 ***Summary and overarching principles of the SSR.*** In the SSR, the oral-CS of choice is
29 prednisone, and the IV-CS is methylprednisolone. It is understood that patients are treated

1 with an additional immunosuppressant during induction and maintenance therapy for LN.
2 Building on the CTP_{LN} (4), the SSR considers time from the index kidney biopsy for the oral-
3 CS and IV-CS use. The SSR assumes potential CS dose adjustments to occur every 4
4 weeks. More frequent adjustments may occur during the initial 4 weeks of induction therapy
5 and with severe renal or extra-renal flares. In the following sections, we assumed patients'
6 body weights ≥ 40 kg and a maximum daily oral-CS dosage at 60 mg; for cSLE patients with
7 body weight < 40 kg the equivalent maximum dose is 1.5 mg/kg/day (Step-5). Lower oral-CS
8 dosages (prednisone) for patients < 40 kg can be calculated as follows: daily SSR-dosage for
9 ≥ 40 kg patients \times body weight $\times 0.025$. We anticipate that the SSR can be used for the vast
10 majority ($> 80\%$) of children as indicated by the PP-raters' responses for oral-CS and IV-CS
11 dosing (in Step 6).

12

13 **Categorization of disease course between assessments.** The SSR categorizes changes
14 in extra-renal activity (a-d) between patient assessments as follows: a) active- much worse;
15 b) active-mild/moderate worse; c) active-stable or active-improved; and d) inactive. For
16 induction therapy, changes in renal activity between assessments are categorized (A-D) as
17 follows: A) active-worse; B) active-stable; C) active-improved or inactive prior to week 12;
18 and D) inactive starting week 12. Changes in renal activity categories (i-iv) used during
19 maintenance therapy are: i) LN flare after partial renal remission (PRR) or complete renal
20 remission (CRR); ii) worse after PRR or CRR; iii) PRR stable; and iv) CRR or PRR
21 improved. **Table 3** summarizes the definitions of the changes in renal and extra-renal
22 courses between visits that govern SSR-recommended CS dosages, with additional details
23 pertaining to the interpretation of the changes of the LN-RVs provided in **Figure 2 A-C**.
24 Logistic regression analysis identified variable thresholds that were used in the proposed
25 definitions to classify renal courses (A-D) and extra-renal courses (a-d). Using these
26 definitions allowed us to model renal and extra-renal courses (as per the PP-raters) with $>$
27 90% accuracy based on area under the curve from receiver operating characteristic curve
28 analysis (see **supplemental figure S3**).
29

1 **SSR-recommended CS dosage during the initial 4 weeks post index kidney biopsy.**
2 The SSR allows for up to 3 infusions of high dose methylprednisolone (30 mg/kg/dose; max
3 1 gram) upon diagnosis with proliferative LN. Maximum starting dosage of daily oral-CS is
4 60 mg, which may be given in divided doses. Depending on extra-renal disease activity and
5 response of LN to therapy, oral-CS dosage may be decreased weekly, resulting in a
6 minimum daily oral-CS dosage of 40 mg (maximum 60 mg) at week 4 of induction therapy.

7
8 **SSR-recommended CS dosage during induction therapy (weeks 5-26).** The SSR is
9 adjusted in at least monthly intervals during weeks 5-26 of induction therapy (minimum oral-
10 CS dosage at week 26: 10 mg). Considering the pathology of LN, even if all LN-RVs have
11 normalized, CS reduction is more conservative prior to week 12 than thereafter. Given the
12 known toxicity of CS, small decreases of oral-CS occur even with stable renal and/or extra-
13 renal activity. **Figure 3A** provides an example for SSR suggested adjustment of the CS
14 dosage for a patient who experiences major worsening of extra-renal disease activity, in the
15 setting of improving renal disease during the first 12 weeks post index kidney biopsy.

16
17 **SSR-recommended CS dosage during maintenance therapy (starting week 27).** PRR
18 and CRR determination occurs upon completion of induction therapy at week 26. Based on
19 focus group feedback, the SSR assumes that non-responders to induction therapy are likely
20 to undergo repeat kidney biopsy, with CS-dosage then chosen according to (repeat) biopsy
21 findings. For all other patients, CS dosage will depend on categories of both renal courses (i-
22 iv) and extra-renal activity (a-d). As during induction therapy, provided there is well-
23 controlled extra-renal disease, the SSR allows for CS tapering even in the setting of active
24 stable renal disease. Likewise, with moderate worsening of extra-renal disease in the setting
25 of improving renal disease, the CS dosage is kept stable. Patients who enter maintenance
26 therapy in CRR and on oral-CS of 10 mg will taper oral-CS by 1-2 mg monthly, provided
27 extra-renal disease is not worsening. An example of the SSR-recommended CS dosage for
28 a patient receiving oral-CS at 30 mg at the time of a LN flare during maintenance therapy is
29 shown in **Figure 3B**.

1
2 **Major worsening of extra-renal disease.** Exploratory analyses suggested that daily oral-
3 CS dosages at ≥ 40 mg are guided by the renal course, except in the setting of major extra-
4 renal flares with potential organ damage. Major increase in extra-renal disease activity will
5 prompt an increase of the oral-CS dosage in the SSR by 60-70% with stable renal courses,
6 by 30-40% with renal improvement or with the use of oral-CS doses of ≥ 40 mg at the time of
7 the extra-renal exacerbation. If extra-renal major deterioration fails to respond to increased
8 oral-CS within 10-14 days as judged by the physician, then the SSR recommends the
9 potential use of IV-CS.

10

11 **SSR validation.** The complete SSR is shown in *supplemental table S1*. In Step 6, a total
12 of 66 PP describing cSLE disease course for 4-6 months post index kidney biopsy were
13 rated by 60 PP-raters which provided a total of 1,838 PP-ratings (response rate: 60 of 80
14 PP-raters invited=75%). **Table 2** provides the baseline characteristics of the patients
15 represented by the PP used in Step-6. PP-raters achieved agreement (95%) on all SSR-
16 recommended oral-CS and/or IV-CS dosages. PP-raters stated that in >80% of their patients
17 with similar cSLE features, both with regard to renal plus extra-renal disease courses, the
18 SSR recommended oral-CS and/or IV-CS dosage was appropriate for clinical care.

19

20 DISCUSSION

21 In this study, an international group of pediatric rheumatologists and nephrologists
22 collaborated to develop the SSR, a novel algorithm that standardizes oral-CS and IV-CS
23 dosing decisions in cSLE patients with proliferative LN. As part of this research,
24 determinants that influence medical decisions pertaining to CS-dosage were identified. This
25 allowed us to model CS dosage, based on the renal and extra-renal disease courses with
26 high accuracy.

27 Practice patterns are strongly variable among physicians (1, 3, 17, 18) and indicate
28 that physician attributes may be more important than patient characteristics when
29 prescribing CS (1, 3). While crucial in the treatment of cSLE, CS use is associated with

1 damage accrual (19-21), and the severity of CS side effects make CS-dosage a constant
2 focus for the treating physician. This emphasizes the importance of the developed SSR as
3 an innovative tool to standardize CS dosage among physicians and centers treating cSLE
4 patients.

5 A review of the literature has confirmed the lack of strong medical evidence to guide
6 CS dosing in cSLE and LN (7). Our overall approach to this project was based on a stringent
7 methodological framework using consensus formation techniques that were successfully
8 used in previous pediatric rheumatology studies to develop the criteria for cSLE flare (9, 22),
9 cSLE inactive disease and remission (23), the previous CTP_{LN} (4), and classification criteria
10 for Macrophage Activation Syndrome (24, 25). Our methodology was aligned with the
11 recommendations of the Classification and Response Criteria Subcommittee of the ACR
12 Committee on Quality Measures (26).

13 A strength of the SSR is that it has been derived from real-life patient data and was
14 developed based on the consensus of a large number of experienced physicians who
15 regularly treat cSLE and LN. The preliminary SSR developed in Steps 4/5 was further
16 validated among a group of experts in the management of cSLE and LN using longitudinal
17 data for the initial six months of induction therapy (Step 6). Our study validation achieved
18 majority agreement (95%) among PP-raters for the use of the SSR-recommended oral-CS
19 and IV-CS dosages which they considered acceptable in the vast majority (>80%) of their
20 cSLE patients during induction therapy for LN. Although not specifically tested, we
21 hypothesize that the SSR dosing for maintenance therapy can also be used for cSLE
22 treatment that is not complicated by renal disease.

23 The SSR builds on the CTP_{LN} which offers guidance for CS use with active proliferative LN,
24 under the assumption of complete LN response at week 24 and CS use governed solely by
25 LN (4). Unfortunately, such cSLE disease courses are rare based on the results of a pilot
26 study testing the CTP_{LN} (5). Different from the development of the CTP_{LN} (4), the current
27 study used real-life data from patients to deduce common CS use with cSLE. Disease
28 courses considered in the SSR include variable courses of proliferative LN, extra-renal
29 involvement with cSLE over time, multiorgan involvement with cSLE, renal and extrarenal

1 flares, and inactive disease. Our validation exercise (Step-6) supports that the SSR is highly
2 acceptable among physicians treating cSLE, supporting its future relevance for clinical care
3 of and research in cSLE.

4 By design the SSR is expected to support CS dosing decisions in most patients with
5 cSLE. However, the limitations of this study are related to the known marked phenotypic
6 variation with cSLE which may prohibit SSR use in patients with extreme phenotypes, such
7 as children with life threatening acute manifestations of cSLE. Notably, cSLE patients
8 requiring renal replacement therapy were not reflected in our PP. Thus, additional validation
9 is needed to evaluate the usefulness of the SSR in such situations.

10 Chronic, especially high-dose use of CS is a major risk factor for infections, a leading
11 cause of death in SLE (7). Due to their CS-sparing properties, concurrent use of
12 immunosuppressive medications is recommended during induction therapy for LN, and was
13 considered in the development of the SSR. In exploratory analysis, use of mycophenolate
14 mofetil as opposed to cyclophosphamide did not influence CS dosing by the PP-raters.

15 A short-coming of the SSR assumes that patients are adherent to their medications,
16 including CS. Non-adherence to CS would be associated with lack of cSLE and LN
17 improvement, or even disease flares. Such uncontrolled cSLE courses would be reflected in
18 a lack of tapering of CS as per the SSR and likely prompt clinicians to consider patient's
19 difficulties with adherence to a treatment plan.

20 Personalized dosing of CS that take into account a cSLE patient's pharmacogenetic
21 and pharmacodynamic make-up are a highly active area of research (27, 28). We consider
22 the SSR a long-needed tool to advance such research in the association between CS use,
23 CS pharmacology, and control of inflammation or development of damage with cSLE.

24 We are cognizant that the development of the SSR is a dynamic process especially
25 with new progress in biomarker studies. This would require, in our opinion, validation in large
26 longitudinal datasets that capture the differential accrual of disease damage with specific CS
27 uses. Indeed, additional insights in the biological factors that modulate response to and
28 damage from CS should be used in future research to enhance the SSR. In this context, the
29 SSR provides a new template to which other CS dosing regimens can be compared.

1 Potentially, the use of biologic agents with marked steroid sparing effects may support more
2 rapid CS tapering. Such a steroid sparing effect could be quantified using the SSR and,
3 subsequently, may necessitate updates to the SSR for patients treated with such
4 medications.

5 In clinical trials, variability of CS dosing introduces bias and threatens the validity of
6 study results (17). By standardizing CS use, the SSR can counterbalance such bias, and
7 possibly increase the willingness of physicians to contribute patients to studies. The SSR
8 may also support CS use in clinical care, especially by health care providers with less
9 exposure to the treatment of cSLE and pediatric LN. We would like to note that, to enhance
10 the widespread use of the SSR, a web-based calculator is in development.

11

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FIGURE LEGENDS

25 **Figure 1. Development of the Standardized Steroid dosing Regimen (SSR) for**
26 **childhood-onset SLE.** The experimental design used can be summarized in Step-1 to
27 Step-6, and consists of various consensus formation methods, statistical analyses and the
28 use of real-life data from pediatric patients with LN in Patient Profile ratings.

1 Abbreviations used are: Oral-CS: oral corticosteroids; IV-CS: intravenous corticosteroids;
2 CARRA: Childhood Arthritis and Rheumatology Research Alliance; PP: patient profiles; LN:
3 lupus nephritis; REDCap is a browser-based, metadata-driven electronic data capture
4 software and workflow methodology for designing clinical and translational research
5 databases; for additional details please see: <https://projectredcap.org/software>

6

7 **Figure 2. Operational definitions for changes in the lupus nephritis response
8 variables for use in the SSR.**

9 A: Estimated glomerular filtration rate (eGFR) of ≥ 95 ml/min/1.73 m² was considered to be
10 normal, and abnormal for eGFR values < 95 ml/min/1.73 m², irrespective of patient age.

11

12 B: Values of the urine protein creatinine ratio (UPCR) from a random urine sample were
13 considered normal for values ≤ 0.2 mg/mg and abnormal for values >0.2 mg/mg. Changes of
14 the UPCR of ± 0.3 were deemed to represent stable proteinuria. Examples of changes of the
15 UPCR between Visit 1 and Visit 2 and assessment of UPCR status are as follows:
16 0.5→0.25 (decrease by 50%, but decrease is <0.3 , so UPCR is stable); 0.5→0.2 (UPCR
17 normal); 0.5→0.8 (increase by $>50\%$ and increase by 0.3, so UPCR is worse); 0.5→0.75
18 (increase by 50%, but increase is <0.3 , so UPCR is stable).

19

20 C: Only glomerular hematuria was considered when assessing urine microscopy, whereas
21 pyuria and cellular casts were omitted. Five categories of glomerular hematuria measures in
22 RBC/High Power Field (HPF) were defined as follows: normal: 0-5 RBC/HPF; mild: 6-10
23 RBC/HPF; moderate: 11-25 RBC/HPF; severe: 26-50 RBC/HPF; gross: >50 RBC/HPF.

24

25 **Figure 3. Examples of SSR suggested changes in prednisone (or equivalent dose of
26 another corticosteroid).**

27 A: Suggested prednisone dose adjustment of a cSLE patient (≥ 40 kg) whose kidney biopsy
28 showed proliferative lupus nephritis within the preceding 12 weeks. Upon re-assessment,
29 the patient was taking prednisone 30 mg daily, his renal course was “Active-improved” and

1 extra-renal disease course “Active-much worse”. The SSR recommends increasing daily
2 prednisone dose to 40 mg. If tolerated, tapering oral-CS during the subsequent 4 weeks post
3 assessment to 35 mg is proposed.

4

5 B: Suggested prednisone dose adjustment of a cSLE patient (≥ 40 kg) who completed
6 induction therapy for LN, and achieved at least partial renal remission at week 26. Upon re-
7 assessment, the patient was taking prednisone 30 mg daily and having a “LN flare after
8 PRR”. The SSR recommends increasing the daily prednisone dose to 60 mg, irrespective of
9 the extra-renal course. If renal response is improved with higher oral-CS doses, then oral-
10 CS tapering can be initiated at day 10. The minimum allowable daily prednisone dose at day
11 30 following LN flare is 40 mg. If the patient has not improved by day 10, then intravenous
12 pulse methylprednisolone (1-3 doses) should be considered.

1 TABLES

2 Table 1. Principal eligibility criteria for patients utilized for patient profile generation

Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none">1. Males and females fulfilling 1997 American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus2. Age \leq 18 years at the time of index kidney biopsy[#]3. Time of index kidney biopsy between January 2008 and June 20184. Index kidney biopsy consistent with new diagnosis of LN[¥] Class III, III/V, Class IV, or IV/V as per the ISN/RPST[†] Classification Criteria of LN5. Induction therapy with cyclophosphamide or mycophenolate mofetil	<ol style="list-style-type: none">1. Use of rituximab within six months of diagnosis with proliferative LN2. Chronic medical conditions, other than SLE, that necessitate chronic CS use3. Renal replacement therapy requirement within 6 months of index kidney biopsy4. History of kidney transplant5. Follow up for LN at the center for fewer than 6 months after index kidney biopsy6. Lack of biopsy report for index kidney biopsy in patient's medical record

3 [#] Patient could have had other renal biopsies indicating presence of other classes of LN

4

5 [¥] Lupus nephritis

6

7 [†] International Society for Nephrology/ Renal Pathology Society

Table 2: Baseline characteristics of patients used for patient profile development

Variables	Patients for Step-3 (N=120)	Patients for Step-6 (N=66)
	Mean +/- SD or (N) %	Mean +/- SD or (N) %
Age at LN onset (year)	13.47 ± 3.06	13.50 ± 2.89
Female	(96) 80%	(55) 83%
Race		
White	(59) 49%	(35) 53%
Black or African American	(45) 37.5%	(25) 38%
Other	(13) 11%	(5) 8%
Unknown	(3) 2.5%	(1) 1%
Ethnicity		
Hispanic	(35) 29%	(19) 29%
Non-Hispanic	(84) 70%	(47) 71%
Unknown	(1) 1%	(0) 0%
Laboratory testing		
UPCR (mg/mg) *	3.04 ± 3.85	2.77 ± 2.46
Serum Creatinine (mg/dL)	0.90 ± 0.70	0.98 ± 0.89
SDI Total Score at LN onset¹¹	0.19 ± 0.58	0.15 ± 0.47
SLEDAI-2K[†]; % with feature present		

Seizure	(2) 2%	(1) 2%
Organic Brain Syndrome	(3) 3%	(1) 2%
Visual Disturbances	(2) 2%	(0) 0%
Cranial Nerve Disorder	(1) 1%	(1) 2%
Lupus Headache	(1) 1%	(1) 2%
CVA#	(1) 1%	(0) 0%
Vasculitis	(10) 10%	(8) 14%
Arthritis	(45) 43%	(28) 49%
Myositis	(7) 7%	(5) 9%
Urinary Casts	(36) 35%	(17) 30%
Hematuria	(80) 77%	(47) 82 %
Proteinuria	(92) 88%	(53) 93%
Pyuria	(60) 58%	(36) 63%
Rash	(58) 56%	(34) 60%
Alopecia	(7) 7%	(4) 7%
Mucosal Ulcers	(13) 12.5%	(8) 14%
Pleurisy	(7) 7%	(1) 2%
Pericarditis	(12) 12%	(5) 9%
Low Complement	(96) 92 %	(53) 93%
Increased DNA Binding	(93) 89%	(53) 93%
Fever	(21) 20%	(12) 21%
Thrombocytopenia	(15) 14%	(9) 16%

	Leukopenia	(19) 18%	(12) 21%
SLEDAI-2K Total Score		19.88 ± 7.43	20.86 ± 6.78
Oral Prednisone			
(equivalent [‡]) (mg/day)			
<7.5		(11) 9%	(6) 9%
7.5, 16		(7) 6%	(1) 2%
16, 45		(51) 42.5%	(28) 42%
>45		(51) 42.5%	(31) 47%
Other medications at			
Visit-1; % present			
IV		(3) 2.5%	(1) 2%
Methylprednisolone			
Mycophenolate		(3) 2.5%	(1) 2%
mofetil			
Cyclophosphamide		(33) 27.5%	(26) 39%
Angiotensin system inhibitors		(51) 42.5%	(24) 36%

¥ Urine protein creatinine ratio (UPCR)

¶ Systemic Lupus International Collaborating Clinics/ACR Damage Index. For item definitions please see: Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis and rheumatism*. 1996;39(3):363-9.

† SLE disease activity index, version 2K. For item definitions please see: Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol*. 2002;29(2):288-91.

Cerebrovascular accident (CVA)

‡ Other corticosteroid dosages were converted to prednisone equivalent doses

Table 3. Categorization of renal and extra-renal disease courses between two consecutive assessments (Visit-1 and Visit-2) as used in the Standardized Steroid dosing Regimen (SSR)

Renal courses		Extra-renal course \$
<i>Induction therapy (weeks 1-26)</i>	<i>Maintenance therapy (after week 27)</i>	
<i>LN* - Active worse #:</i> Worsening of ≥ 1 LN-RV [†]	<i>LN flare after PRR or CRR</i> ¶: Worsening (persistent* & substantial) of ≥ 1 LN-RV	<i>Active - Much worse:</i> Δ SLEDAI score: $\geq +8$
<i>LN - Active stable:</i> <u>Neither Active Worse nor Active Improved</u>	<i>LN worse[#] after PRR or CRR:</i> Worsening of ≥ 1 LN-RV	<i>Active - Mild-moderate worse</i> Δ SLEDAI score: +4 to +7
<i>LN - Active improved:</i> Improvement of ≥ 1 LN-RV with the remaining LN-RV(s) not being worse	<i>PRR stable:</i> PRR with changes of LN-RVs not qualifying for being worse or improved	<i>Active - stable:</i> Δ SLEDAI score: ± 3
<i>PRR[‡]:</i> Clinically relevant improvement of ≥ 2 LN-RVs with the remaining LN-RV not being worse	<i>PRR improved:</i> PRR with improvement of ≥ 1 LN-RV with the remaining LN-RV(s) not being worse	<i>Active - Improved:</i> Δ SLEDAI score: ≤ -4
<i>LN - Inactive:</i> All LN-RVs are within normal range	<i>CRR:</i> All LN-RVs are within normal range	<i>Inactive:</i> Absolute SLEDAI score: ≤ 2

*Lupus Nephritis

All “worsening” is considered to be due to LN

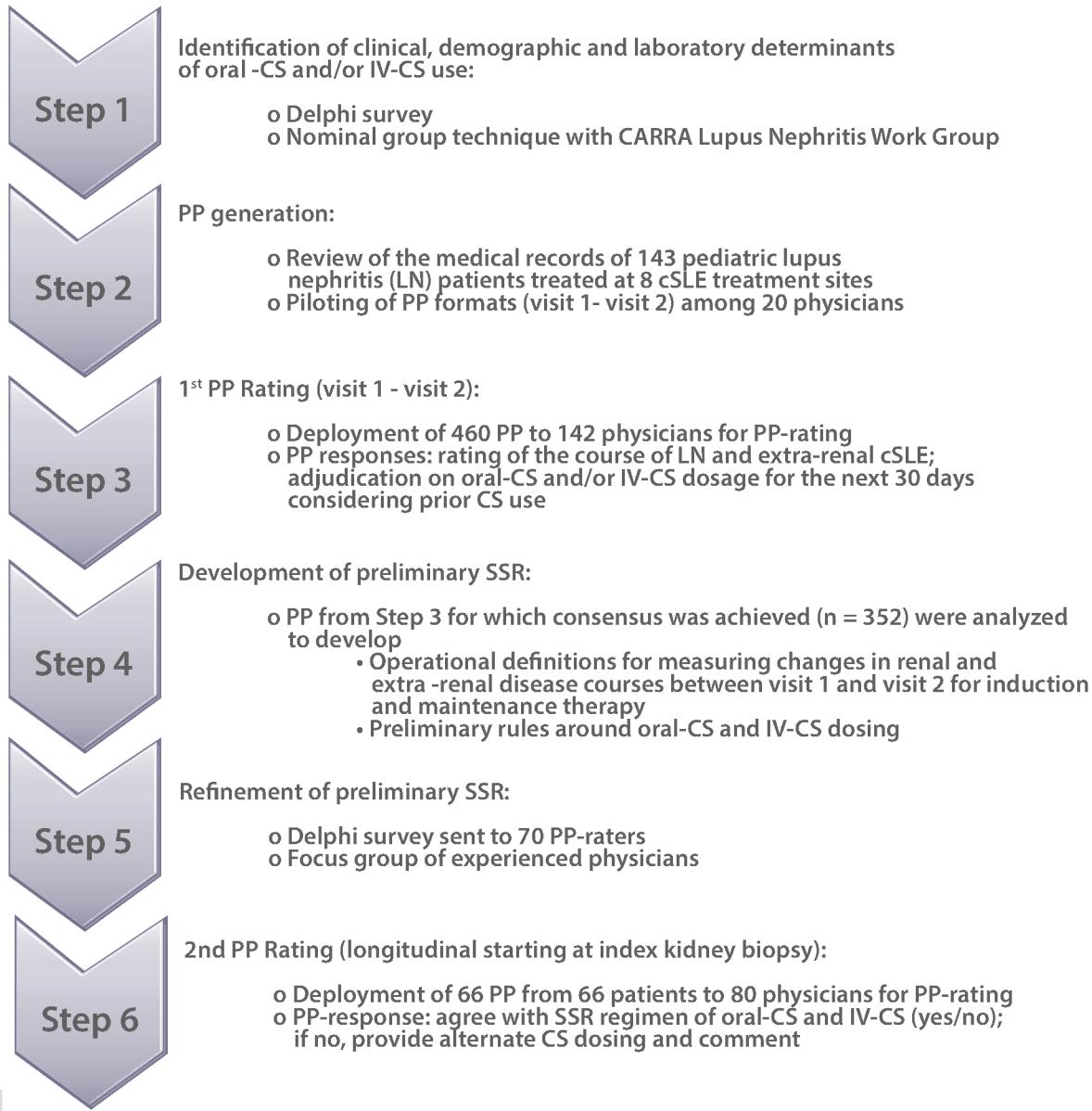
† Lupus nephritis response variables, i.e., Urine protein creatinine ratio (UPCR), hematuria, estimated glomerular filtration rate (eGFR). Normal values for the LN-RVs are always considered as "improved" for the purpose of the course definitions (for details please see Figure 2)

‡ Partial renal remission assesses the change between baseline and week 26 and can only be measured starting week 26 of induction therapy

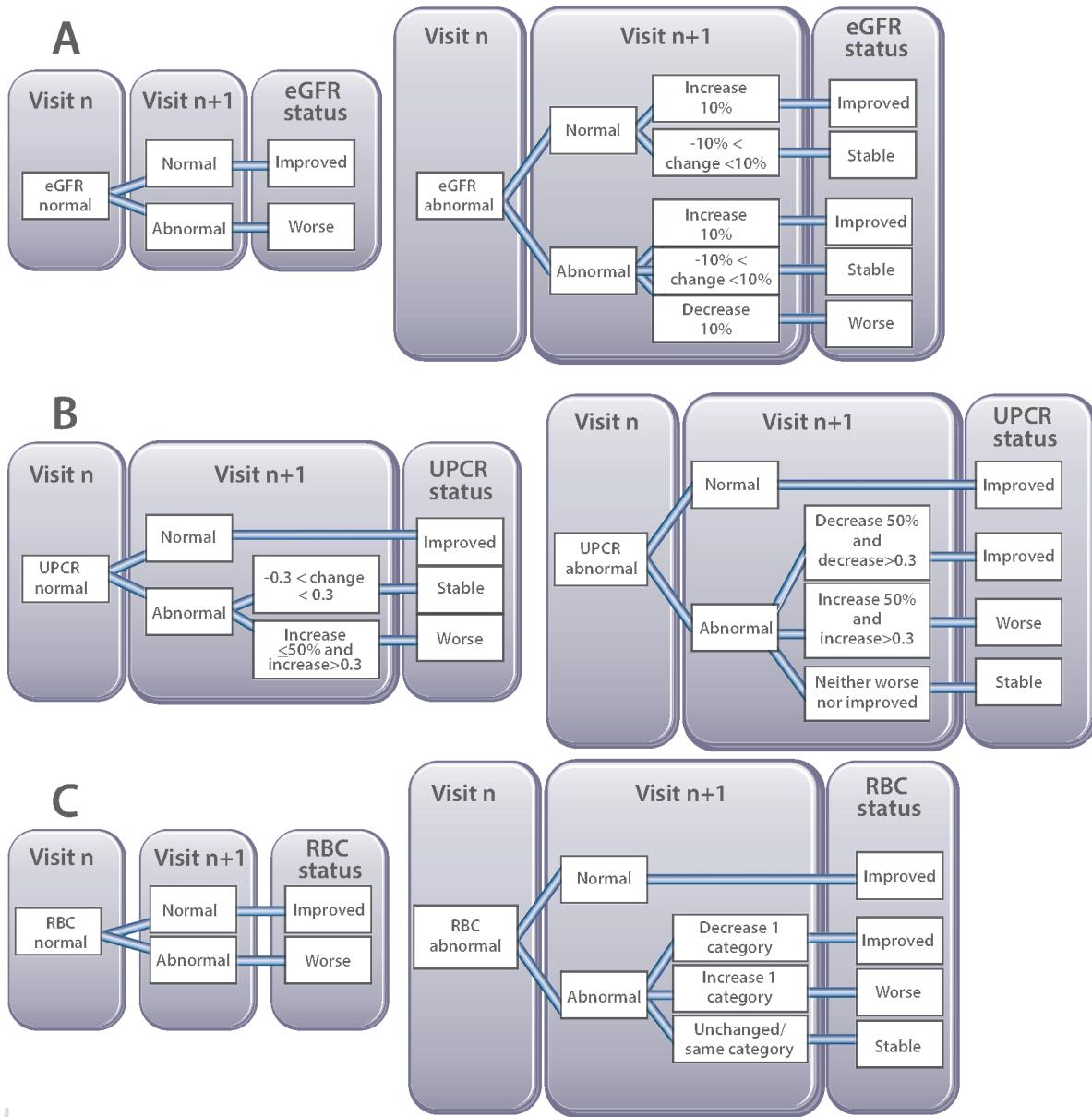
¶ Complete renal remission

¥ Worsening of 1 or more LN-RVs on >2 subsequent time points >1 week(s) apart as follows: Newly abnormal eGFR or abnormal eGFR that decreased by >10%; Persistent increase of UPCR to >0.5, after CRR; Persistent doubling of UPCR with values >1.0, after PRR; Newly active or worsening by 2 categories of urine RBCs.

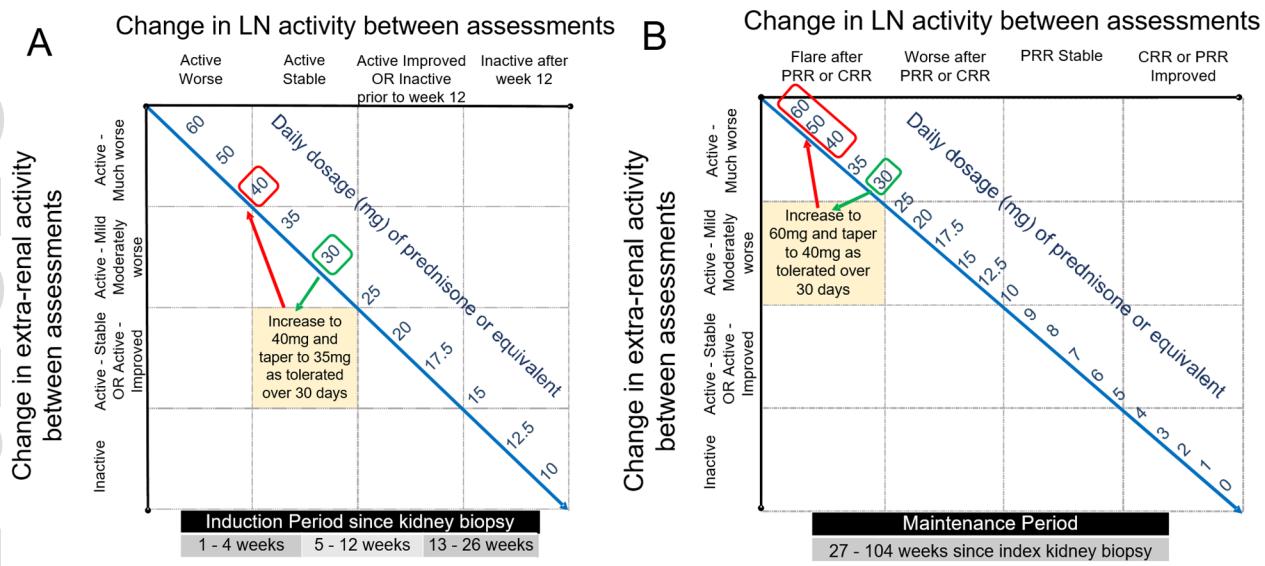
\$ Based on changes in the score of the SLE disease activity index, version 2K. For item definitions please see: Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol*. 2002;29(2):288-91.



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