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503 DEVELOPING A STANDARDIZED STEROID DOSING REGIMEN IN PEDIATRIC PROLIFERATIVE LUPUS NEPHRITIS

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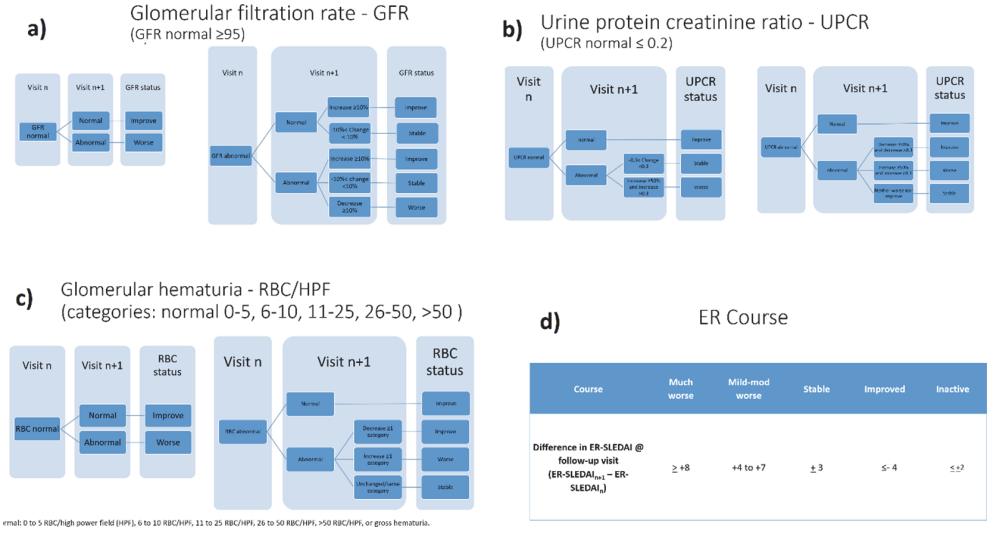
Background Corticosteroids (CS) remain the mainstay of therapy for childhood-onset systemic lupus erythematosus (cSLE) although there are no widely accepted dosing strategies of oral (PO CS) or intravenous CS (IV CS). We aimed to (1) develop a standardized CS dosing regimen (SSR) and (2) achieve consensus for this SSR among pediatric rheumatology and nephrology providers treating cSLE complicated by lupus nephritis (LN).

Methods Consensus formation techniques were used. A Delphi questionnaire pertaining to CS use in cSLE was completed to inform formats of the Patient Profiles (PP, Step 1). Using data from 147 children with proliferative LN at 8 major cSLE treatment sites in North America PP were generated providing information about the course of LN and extra-renal cSLE (ER) at 2 subsequent visits (Step 2). PP were sent to 142 physicians (PP-raters) experienced in cSLE to adjudicate the course of ER and LN and propose the PO/IV CS dosages (Step 3). Using data from PP for which consensus was achieved, the SSR was developed (Step 4) and refined based on responses from another questionnaire and a focus group of experienced physicians (Step 5). The SSR was tested using a second type of PP that described ER and LN courses for 6 months from the time of biopsy (Step 6). Consensus was defined as agreement of the majority of PP-raters (Step 3, Step 6).

Results For Step 1 and Step 3, 103 physicians answered Delphi questions and filled 353 PP (response rate: 73%). Step 6 activities were completed by 18 physicians (13.4 years of average experience) who were asked to review 33 PP each. This resulted in 564 completed PP ratings, of which 437 (77.5%) and 460 (81.6%) ratings yielded consensus on POSSR-and IV SSR dosing, respectively. PO CS and/or IV CS dosages as per the SSR (SSR-dose) depend on patient weight, the course of ER activity measured by the ER-SLE-DAI score (figure 1d), and the course of LN described by changes/status of 3 *LN response variables (LN-RVs*, figure 1a-c). The SSR mimics dosing customs agreed upon by the PP-raters. Table 1 summarizes the SSR with focus on 2 ER/LN settings (1:stable ER/various LN courses; 2:stable LN/various ER courses), with several permutation of the course of ER (much worse, mild-moderately worse, active stable/improved, inactive) and LN (flare, mild-moderately worse, active stable/improved/partial renal remission (PRR), complete renal remission (CRR)). Use of dosages of PO CS $\geq$ 40 mg are governed by the course of LN except in major ER flares with potential organ damage. The SSR adjusts PO CS dosages in at least monthly intervals. IV CS are used for worsening of ER or LN courses that fail to respond to increased oral CS of $\geq$ 40 mg up to 4 weeks. Small decreases of PO CS occur even with stable ER or stable LN activity. Achieving CRR leads to more pronounced reduction of PO CS (table 1). Beyond 6 months post kidney biopsy (maintenance therapy), the PO/IV CS dosage is informed by LN status (PRR, CRR), the course of LN and ER activity (table 1).



Abstract 503 Figure 1

Abstract 503 Table 1 Steroid use provided by the standardized steroid regimen (SSR)

INITIAL 4 WEEKS OF INDUCTION THERAPY		
	PO CS	**IV CS**
Patients ≥ 50 kg	Prednisone* 60 mg/day divided in up to 4 doses	Up to 3 doses (30 mg/kg; max 1 gram of methylprednisolone)
Patients < 50 kg	Prednisone 1.5 mg/kg/day	
Median – lowest PO CS dose at week 4**	40 mg/day - 30 mg/day	
WEEK 5 – 26 OF INDUCTION THERAPY (based on LN and ER trends since last visit)		
LN course *(assumption ER is stable)*	*Much worse*	Increase PO CS to 50-60mg/day; re-assess in 1-3 weeks; if response to increased PO CS is (a) *Satisfactory→ No IV CS; (b) non-satisfactory→ IV pulses + PO CS;* Possible change of immunosuppressive drug
	Mild – moderately worse	Increase PO CS by about 30% (if dose < 40 mg; max 60 mg)
	Active stable	Stable PO CS dose (if dose < 40 mg; else: slow decrease)
	Improved active or PRR[1]	Slow decrease of PO CS dose
	CRR[2]	More pronounced decrease of PO CS dose
ER course *(assumption LN is stable)*	*Much worse*	Increase PO CS dose; Re-assess in 1-3 weeks; if response to increased PO CS dose is (a) *Satisfactory→ No IV CS; (b) non-satisfactory→ IV pulses + PO CS dose;* Possible change of immunosuppressive drug
	Mild- moderately worse	Increase PO CS by 20% for doses < 40 mg; otherwise stable PO CS dose
	Active stable or improved active	Stable PO CS dose
	Inactive	Decrease PO CS dose
Median - Lowest PO CS dose possible at week 26	12.5 - 10 mg/day	
BEYOND 26 WEEKS POST KIDNEY BIOPSY - MAINTENANCE THERAPY		
LN course *(assumption ER is stable)*	Flare[3] after PRR/CRR	Prednisone ≥ 40 mg, irrespective of ER course Re-assess in 1-3 weeks; if response to increased PO CS is (a) *Satisfactory→ No IV CS; (b) non-satisfactory→ IV pulses + PO CS*
	Worse after PRR/CRR	Increase the PO CS dose FIRST
	PRR stable	Slow decrease of the SSR-dose
	Inactive/CRR or PRR improved	More pronounced decrease of the SSR dose
ER course *(assumption PRR parameters are stable)*	*Much worse*	Increase PO CS dose by 30-50% (max 60 mg) ; Re-assess in 1-3 weeks; if response to increased PO CS dose is (a) *Satisfactory→ No IV CS ; (b) non-satisfactory→ IV pulses + PO CS;* Possible change of immunosuppressive drug
	Mild- moderately worse	Increase PO CS dose by 25% for doses < 40 mg; otherwise stable PO CS dose
	Stable/Improved/Inactive	Decrease of the PO CS dose

** For patients ≥ 50 kg; * or corticosteroid equivalent dose.
[1]Partial renal remission (PRR): >50% improvement of ≥2 LN-RVs PLUS remaining LN-RV is NOT worse.
[2]Complete renal remission (CRR): All LN-RVs are NORMAL.
[3]LN flare defined by at least 1 of the LN-RV changes being persistently present on ≥2 subsequent time points ≥1week apart. LN-RV changes are defined as (a) newly abnormal GFR, (b) abnormal GFR that decreased by >10%, (c) persistent increase of UPCR to ≥0.5, after CRR, (d) persistent doubling of UPCR with values ≥1.0, after PRR, or (e) newly active or worsening glomerular hematuria.

Conclusions SSR for the treatment of cSLE complicated by LN has been developed which simulates PO/IV CS use among treating physicians. The proposed SSR may be useful for clinical care and to regulate background CS use during clinical trials of new medication for cSLE.

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504 SPECIFIC *IN SITU* INFLAMMATORY ARCHITECTURES PREDICT PROGRESSION TO RENAL FAILURE IN HUMAN LUPUS NEPHRITIS

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Background In human lupus nephritis (LN), tubulointerstitial inflammation (TII) on biopsy predicts refractory disease and progression to end stage renal disease (ESRD). However, while approximately half of patients with moderate or severe TII develop ESRD, half do not. Therefore, we hypothesized that TII is heterogeneous with distinct inflammatory states each associated with different renal outcomes.

Methods We interrogated renal biopsies from LN longitudinal (55 patients) and cross-sectional cohorts using both conventional and highly-multiplex (24 analytes) confocal microscopy. To accurately segment cells across whole biopsies, and to understand their spatial relationships, we trained and implemented a suite of computer vision tools, including multiple parallel Mask-R convolutional neural networks. This evolution of our previous analytic pipeline, Cell Distance Mapping (CDM)(*Nat Immunol*, 2019, 20:503), we refer to as CDM version 4.

Results Across biopsies, B cell densities were strongly associated with protection from ESRD ($p=2x10^{-8}$, Mann-Whitney). In contrast, CD4- T cell population densities, which included CD8, gd and double negative (CD4-CD8-, DN) T cells, predicted progression to ESRD ($p=5.7x10^{-16}$). Breath first search and other analyses revealed inflammation was