Systemic lupus erythematosus: pathogenesis, diagnosis, and treatment

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Lupus Nephritis Management Guidelines Compared

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Abstract

In the past years many (randomized) trials have been performed comparing the treatment strategies for lupus nephritis. In 2012 these data were incorporated in six different guidelines for treating lupus nephritis. These guidelines are European, American and internationally based, with one separate guideline for children. They offer information on different aspects of the management of lupus nephritis including induction and maintenance treatment of the different histologic classes, adjunctive treatment, monitoring of the patient, definitions of response and relapse, indications for (repeat) renal biopsy, and additional challenges such as the presence of vascular complications, the pregnant SLE patient, treatment in children and adolescents, and considerations about end-stage renal disease and transplantation. In this review we summarize the guidelines, determine the common ground between them, highlight the differences and discuss recent literature.

Introduction

Lupus nephritis (LN) is associated with poor survival[1 2] and considerable morbidity, particularly for patients who develop end-stage renal disease (ESRD) and require renal replacement therapy. The development of renal involvement within the course of disease ranges from ~20 to 60% of systemic lupus erythematosus (SLE) patients[3] with the highest risk of renal disease and renal failure in young black women.[4 5] Therapeutic possibilities have expanded from the solitary use of corticosteroids to the addition of a wide range of immunosuppressive drugs and other supportive treatment. Many trials have been conducted in the past 40 years leading to the publication of six guidelines in 2012 on the management of LN (Table 1).[6-11] These guidelines are American and European based, with separate guidelines from Spain and the Netherlands, with the addition of the KDIGO (Kidney Disease Improving Global Outcomes) guideline that is considered to be international. All guidelines were developed on the basis of extensive literature searches and (consensus)

Table 1. Guidelines that were compared

From	Date of publication	Geography	Population
EULAR/ERA-EDTA : European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association[6]	July 2012	Europe	Adults and children/adolescents
ACR: American College of Rheumatology[7]	June 2012	USA	Adults, particularly those receiving care in the USA Includes interventions available in the USA as of February 2012
KDIGO: Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group[8]	May 2012	International	Adults and children/adolescents
GEAS: Systemic auto-immune disease group of the Spanish Society of Internal Medicine and Spanish Society of Nephology[9]	March 2012	Spain	Not specified
DWP: Dutch Working Party on Systemic Lupus Erythematosus[10]	March 2012	The Netherlands	Not specified For proliferative LN only
CARRA: Childhood Arthritis and Rheumatology Research Alliance[11]	March 2012	North America	Children/adolescents For proliferative LN only Consensus treatment plan, not a guideline

LN, lupus nephritis; USA, United States of America

meetings. Furthermore, each guideline indicated the level of evidence or strength of a statement/recommendation, or both, for all topics (Supplemental Table 3). All guidelines were published in the same year and based on the same body of evidence and their main statements are congruent. However, there are also notable differences between them. The aim of this review is to compare the recent guidelines, outline a common view and highlight the differences, in particular in relation to indications for (repeat) renal biopsy, induction and maintenance treatment of the different classes, adjunctive treatment, monitoring of the patient, definitions of response and relapse, and additional circumstances such as the presence of vascular complications, the pregnant SLE patient, treatment in children and adolescents, and considerations about end-stage renal disease (ESRD) and transplantation (Tables 2 and 3, Supplemental Tables 1 and 2). We will also discuss recent literature and how to proceed further to increase the level of evidence based patient care.

Renal biopsy

All guidelines recommend a renal biopsy when there is a suspicion of renal involvement, because clinical and laboratory parameters cannot accurately predict the histologic class. Early diagnosis and treatment have been shown to improve outcomes.[12 13] The criteria for suspicion of renal involvement, however, differ. The common view is that an unexplained decrease in renal function, and proteinuria are indications for a renal biopsy. Also, an active urine sediment raises the level of suspicion of renal involvement and may be an additional argument for a renal biopsy. The GEAS (Spanish Society of Internal Medicine and Spanish Society of Nephrology) considers an active urine sediment alone a sufficient cause for biopsy. The required levels of proteinuria differ between the guidelines, but most use a urine protein-creatinine ratio of 50 mg/mmol (equivalent to ~0.5 g/24h) as a cutoff.

The biopsy is classified according to the system proposed by the International Society of Nephrology/ Renal Pathology Society (ISN/RPS) in 2003.[14] A minimum of 10 glomeruli is required in order to reasonably exclude focal disease and the biopsy should be examined by light microscopy, immunofluorescence and if possible, electron microscopy. Furthermore, data on activity and chronicity should be quantified (though activity and chronicity indices are not obligatory) and vascular and interstitial lesions described. The histologic class plays a fundamental role in the ensuing therapeutic decision process.

Although the evidence is sparse, in cases of worsening of disease, disease refractory to treatment or relapse, a repeat biopsy can be considered to determine activity and chronicity or detect other pathologies. Some also suggest taking a biopsy at the end of induction

Table 2. Guidelines compared; common views and differences

	Common view	Differences
Indication for renal biopsy	Inexplicable (persistent) decrease in renal function Reproducible proteinuria (required levels: different) Active sediment raises level of suspicion for LN and may be an additional argument for a renal biopsy	Proteinuria: – Most: isolated proteinuria ≥0.5 g/24 h – ACR: isolated proteinuria ≥1.0 g/24 h *or* ≥0.5 g/24 h and hematuria (5 RBCs/HPF) or cellular casts Active sediment: sufficient to warrant biopsy in GEAS, others consider a biopsy, sometimes when in combination with low levels of proteinuria
Biopsy evaluation	According to ISN/RPS 2003 classification system for LN Examine by light microscopy, immuno-fluorescence and if possible electron microscopy Quantify data on activity and chronicity and describe vascular and interstitial lesions	-
Indication for repeat biopsy	Consider in case of: – Worsening of disease or disease refractory to treatment – Relapse, in order to demonstrate change or progression in histological class, change in activity and chronicity (index) or other pathologies	-
Treatment class II	Treat proteinuria with RAAS (first)	ACR: no immunosuppressive treatment EULAR/ERA-EDTA: proteinuria >1 g/24 h, especially in the presence of glomerular hematuria; low to moderate doses oral glucocorticoids (0.25-0.5 mg/kg/day) alone or in combination with AZA (1-2 mg/kg/day), if necessary KDIGO: proteinuria <1 g/24 h: treat as dictated by extrarenal manifestations. Proteinuria >3 g/24 h: corticosteroids or CNI as described for MCD GEAS: significant proteinuria (>1-2 g/24 h) and/or deteriorated renal function that is not attributable to functional factors; steroids up to 0.5 mg/kg/day, possibly plus AZA or MMF for 6-12 months
Induction treatment class III/IV *without* crescents (and/or other adverse parameters)	Oral glucocorticoids with or without three iv pulses methylprednisolone (MP) at start induction + ivCYC or MMF	Dosage and preferences for different severities (see also next section) and ethnic groups: Glucocorticoids: – MP dose ranging from 250 to 1000 mg/day (or weight dependent in children) – MP not always recommended; dependent on combination with MMF or ivCYC, or on severity – Oral dose ranging from 0.5 to 1 mg/kg/day, sometimes depending on combination with MP, MMF or ivCYC

Table 2. Continued

	Common view	Differences
		– Tapering schedule: unclear MMF: – Ranging from 2 to 3 g total daily dose – Sometimes preferred over ivCYC in patients of African or Hispanic descent ivCYC: – Either high dose (NIH; 0.5-1 g/m^2 monthly for 6 months) or low dose (Eurolupus; 500 mg fortnightly for 3 months): low dose usually preserved for (European) Caucasians and sometimes only for relatively mild disease – In case of low dose ivCYC, combine pulses MP
Induction treatment class IV or IV/V *with* crescents (and/or other adverse parameters)	No consensus	KDIGO, DWP, CARRA: same as without crescents (and/or other adverse parameters) ACR: ivCYC or MMF + three iv pulses MP + oral glucocorticoids; MMF and oral glucocorticoids at highest doses (MMF 3 g total daily dose; oral glucocorticoids 1 mg/kg/day) EULAR/ERA-EDTA: high dose (see above) ivCYC can also be prescribed GEAS: three pulses MP (250-1000 mg/day) and include ivCYC in regimen
Induction treatment class V	If nephrotic range proteinuria (≥3 g/24 h): oral glucocorticoids (0.5 mg/kg/day) combined with other immunosuppressive medication (except in GEAS)	GEAS: also in patients with non-nephrotic range proteinuria; oral glucocorticoids up to 1 mg/kg/day (max 60 mg) combined with either ivCYC, MMF, AZA or CNIs Type of additional immunosuppressive medication: – EULAR/ERA-EDTA: preferably MMF (3 g total daily dose), alternatives; high dose ivCYC, CNIs or rituximab – ACR: MMF (2-3 g total daily dose) – KDIGO: ivCYC, CNIs, MMF or AZA
Treatment class VI	Suggestions from different guidelines: – Prepare for renal replacement therapy – Treat with immunosuppressives only as dictated by extrarenal disease – Maintain RAAS inhibition and monitor for complications	-
Maintenance treatment	Class III/IV: – AZA (1.5-2.5 mg/kg/day) or MMF (1-2 g/day) – Plus low dose oral glucocorticoids Class V: – As class III/IV – CNIs can be considered	Class III/IV: – EULAR/ERA-EDTA recommends MMF over AZA if there was a response to MMF during the induction phase – GEAS recommends MMF over AZA – Duration of treatment: at least 3 years (EULAR/ERA-EDTA) or at least 1 (KDIGO) or 2 (GEAS) years after (complete) remission

Table 2. Continued

	Common view	Differences
Adjunctive treatment	HCQ for all unless contraindicated; screening ophthalmologist for retinopathy at baseline and yearly after 5 years (recommended by most) RAAS inhibition for proteinuria and to control blood pressure (<130/80 mmHg) Treat hyperlipidemia with statins, target LDL <100 mg/dL or 2.6 mmol/L Other treatment suggestions supported by one or more guidelines: – Calcium and vitamin D supplements – Bisphosphonates depending on glucocorticoid dose, age and renal function – Low dose acetylsalicylic acid in patients with aPL – Consider anti-coagulant treatment in patients with nephrotic syndrome and albumin <20 g/L – Avoid vaccination with live or attenuated viruses during immune suppression – GnRH analogues in women over 35 years if cumulative CYC dose >10 g	Required level of proteinuria to start treatment with RAAS inhibition: ranging from 0.5 g/24h or uPCR >50 mg/mmol to 1.0 g/24 h, if specified at all
Treatment for refractory disease	Switch from ivCYC to MMF or vice versa with or without three accompanying iv pulses MP Alternative treatments: rituximab (as add-on or monotherapy), CNIs or intravenous immunoglobulins	-
Pregnancy	Continue HCQ Allowed: glucocorticoids (non-fluorinated), AZA, CNIs, methyldopa, labetalol or nifedipine *Not*-allowed: MMF, ivCYC, RAAS inhibitor Consider low dose acetylsalicylic acid to reduce risk of pre-eclampsia and fetal loss Monitor closely, preferably by a multi-disciplinary team Do not taper glucocorticoids or AZA during pregnancy or within 3 months thereafter (KDIGO)	Plan pregnancy when: – EULAR/ERA-EDTA: stable (uPCR <50 mg/mmol, GFR preferably over 50 mL/min) for 6 months – GEAS: (partial) remission for 6 months – KDIGO: preferably delay until complete remission – ACR: not specified
Vascular complications	No consensus	EULAR/ERA-EDTA: ASPN; consider HCQ and/or antiplatelet/anticoagulant treatment. In case of definite APS, start anticoagulant treatment ACR: treat TMA with plasma exchange therapy KDIGO/GEAS: ASPN; anticoagulant treatment (INR 2-3) KDIGO: treatment for TTP is plasma exchange as in patients without lupus

Table 2. Continued

	Common view	Differences
Monitoring	Determine at each visit: body weight, BP, sCr, proteinuria, urinary sediment, C3/C4, anti-dsDNA (and serum albumin and complete blood count) Schedule visits: – Active nephritis: approximately monthly, or more frequently – No active nephritis: every 3-6 months	ACR: – Some parameters can be determined at larger intervals than others; BP and urinalysis most often, anti-dsDNA least often – Separate schedule for pregnancy; in short, if active LN, once a month, and if LN in history but none currently, BP and urinalysis once a month and uPCR, sCr, C3/C4 and anti-dsDNA every 3 months
Management of ESRD	Renal replacement therapy: – Increased risk of infection in patients still on immunosuppressives (EULAR/ERA-EDTA) – Increased risk of vascular access thrombosis in patients with aPL (EULAR/ERA-EDTA) – If lupus is inactive offer peritoneal dialysis; if lupus is active offer hemodialysis (GEAS) Transplantation: – Determine aPL; associated with increased risk of vascular events in the transplant	Transplantation: – If lupus activity absent or low for 3-6 (EULAR/ERA-EDTA) or 6-12 (GEAS) months

uPCR 100 mg/mmol ≡ 1000 mg/g ≡ 1(g/g) ≈ 1 g/24 h.[55] ACR, American College of Rheumatology; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; APSN, antiphospholipid-associated nephropathy; AZA, azathioprine; BP, blood pressure; CARRA, Childhood Arthritis and Rheumatology Research Alliance; CNI, calcineurin inhibitor; anti-dsDNA, antibodies to double stranded DNA; DWP, Dutch Working Party on Systemic Lupus Erythematosus; ESRD, end-stage renal disease; EULAR/ERA-EDTA, European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association; GEAS, Systemic auto-immune disease group of the Spanish Society of Internal Medicine and Spanish Society of Nephology; GFR, glomerular filtration rate; HCQ, hydroxychloroquine; HPF, high power field; ISN/RPS, International Society of Nephrology/Renal Pathology Society; ivCYC, intravenous cyclophosphamide; KDIGO, Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group; LN, lupus nephritis; MCD, minimal change disease; MMF, mycophenolate mofetil; MP, methylprednisolone; NIH, National Institute of Health; RAAS, renin-angiotensin-aldosterone system; RBC, red blood cell; sCr, serum creatinine; uPCR, urine protein-creatinine ratio.

treatment in order to determine the histologic response, as clinical parameters may underestimate (histologic) response.[15 16] However, this strategy has not been officially tested in a controlled study but repeat renal biopsy has been shown to have prognostic value.[17-20]

Treatment class II

There is little agreement among the guidelines on treatment of class II LN due to lack of evidence. Proteinuria should primarily be managed with renin-angiotensin-aldosterone

system (RAAS) inhibitors. The role of immunosuppression, however, is less clear. The ACR (American College of Rheumatology) guideline states that class II LN generally does not require immunosuppressive treatment. The EULAR/ERA-EDTA (European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association), however, recommends low to moderate doses of oral glucocorticoids (0.25-0.5 mg/kg/day) alone or in combination with azathioprine (AZA, 1-2 mg/kg/day), if necessary as a steroid sparing agent, in cases of proteinuria over 1 g/24 h, especially in the presence of glomerular hematuria. In the GEAS guideline steroids up to 0.5 mg/kg/day, if necessary with AZA or mycophenolate mofetil (MMF), for 6-12 months are suggested for class II nephritis with proteinuria (>1-2 g/24 h) and/or a deteriorated renal function that are not attributable to functional factors. The suggestions in the KDIGO guideline for the use of immunosuppressive therapy focuses on the presence/co-existence of podocytopathy [*i.e.*, minimal change disease (MCD)] in a subset of patients with class II LN, [21 22] and KDIGO suggests treating such patients with nephrotic range proteinuria (>3 g/24 h) with corticosteroids or calcineurin inhibitors (CNIs) as for MCD, but this presentation was not discussed in the ACR guidelines.

Induction and maintenance treatment class III/IV

Over the past decade several randomized controlled trials (RCTs) have been conducted for class III and IV LN, both in the induction and in the maintenance phase. Consequently, the guidelines are uniform in their recommendations for induction treatment: intravenous cyclophosphamide (ivCYC) or MMF (2-3 g total daily dose) in combination with oral glucocorticoids with or without three pulses of intravenous methylprednisolone (MP) at start of induction treatment. Although in general the use of both oral and intravenous glucocorticoids has been proven effective, evidence is scarce concerning dose and duration, and recommendations are mainly based on expert opinion. In the guidelines, the initial dose of oral glucocorticoids varies from 0.5 to 1.0 mg/kg/day. Only one small RCT compared high (1 mg/kg) and low (0.5 mg/kg) dose oral glucocorticoids (in a background of enteric coated mycophenolic acid). This study demonstrated an equal percentage (~20%) of complete responses at 24 weeks, although non-inferiority was not proven. It did, however, show a decrease in infections in favour of the low dose group.[23] Furthermore, advice for tapering of glucocorticoids is usually fairly general, except for the guideline from the Dutch Working Party on SLE (DWP), which devised a schedule for tapering (Supplemental Table 1). The use of pulse MP at induction is not always recommended and is reserved by some of the

guidelines for more severe cases. However, there is some indication that the use of pulse MP combined with medium dose oral glucocorticoids may be as effective as high dose oral glucocorticoids in inducing remission, but with less toxicity.[24] MMF and ivCYC have similar efficacy and adverse event rates when used with glucocorticoids for remission induction, but MMF avoids adverse effects on fertility. For ivCYC, both the low dose Eurolupus regimen (500 mg fortnightly for 3 months) and the higher dose NIH regimen (0.5-1 g/m^2 monthly for 6 months) can be used. However, the low dose is usually preferred for (European) Caucasians and sometimes only for milder cases because the original trials were mostly in this group of patients.[25 26] The ACCESS trial, communicated after publication of the guidelines, showed no benefit of abatacept as add-on to induction therapy. However, in a predominantly non-Caucasian study population comparable response rates to low dose ivCYC were observed to those previously reported, suggesting that low dose ivCYC may be as effective in non-Caucasians as in Caucasians,[27] although further evidence will be required. Finally, MMF is sometimes preferred over ivCYC in patients from African or Hispanic descent, based on a 'post-hoc' subgroup analysis of the ALMS trial.[28] Some of the guidelines advise more aggressive therapy in patients with crescents in the biopsy specimen, as detailed in Table 2. The EULAR/ERA-EDTA and KDIGO guidelines also state that patients should have active lesions (class III/IV_A or class III/$IV_{A/C}$) in order to be treated and should not have merely chronic lesions (class III/IV_C).

For severe LN, although not adequately defined, there is less evidence as these patients are often excluded from RCTs. However, a subgroup analysis of the ALMS trial in patients with a baseline estimated glomerular filtration rate (eGFR) <30 mL/min did not reveal a difference between ivCYC and MMF [29]. Unfortunately, numbers were small (32 in total) and there was no follow-up beyond the induction phase. Recently, Rovin *et al*. performed a systematic review using results extracted from clinical trials and drawn from expert opinion. Severe LN was arbitrarily defined by renal histology, resistance to therapy, or GFR at presentation. They showed that ivCYC and MMF are equally effective in inducing remission. For long-term follow-up (5 years), however, results from retrospective and observational studies suggest there may be a better preservation of renal function and fewer relapses with ivCYC.[30] Long-term follow-up data from RCTs, however, are lacking.

In the maintenance phase of treatment, MMF (1-2 g/day) or AZA (1.5-2.5 mg/kg/day) is recommended by all guidelines, supported by low dose oral glucocorticoids. The EULAR/ERA-EDTA recommends MMF over AZA if there was a response to MMF at induction based

on the combined results from the ALMS [31] and MAINTAIN trials.[32] The GEAS advises MMF over AZA, based on the results from the ALMS trial, although long-term effects of MMF are still lacking. Also, a recent meta-analysis of four trials (including MAINTAIN and ALMS) showed that there is no difference between MMF and AZA with respect to preventing relapse, progression to end-stage renal failure, death and doubling of serum creatinine.[33] Finally, with respect to duration of treatment, the guidelines differ: at least 3 years (EULAR/ERA-EDTA) or at least 1 (KDIGO) or 2 (GEAS) years after (complete) remission. Due to the length of completed studies, there is no advice on the optimal duration of therapy beyond 3 years.

Induction and maintenance treatment class V

Evidence in support of immunosuppressive therapy in patients with pure class V LN is less robust. Most of the guidelines suggest initiating immunosuppressive treatment if there is nephrotic range proteinuria (>3 g/24 h). If proteinuria is subnephrotic, management with RAAS inhibitors is recommended to reduce the levels of protein excretion. The GEAS, on the other hand, advises immunosuppression irrespective of the level of proteinuria. There is also no consensus on which immunosuppressive therapy to initiate, although there is agreement that glucocorticoids should be included in the regimen. The EULAR/ERA-EDTA and ACR guidelines prefer the addition of MMF over other immunosuppressives (ivCYC, CNIs, AZA or rituximab), in contrast to the GEAS and KDIGO that do not state a preference for any of the aforementioned possibilities. The preference for MMF is mainly based on a combined retrospective analysis of class V LN patients of two RCTs, demonstrating that MMF 2-3 g total daily dose plus daily prednisone for 6 months and ivCYC (0.5-1.0 mg/kg monthly) plus prednisone for 6 months resulted in similar improvement.[34] Unfortunately, due to the short follow-up of this study, the long-term efficacy remains unknown. Another RCT compared prednisone (40 mg/m^2 orally, tapered after 8 weeks to reach 10 mg/m^2 by 12 months) alone on alternate days with the addition of either ivCYC (500-1000 mg/m^2 every 2 months for six doses) or ciclosporin (5 mg/kg for 11 months). Results showed that the combination of prednisone with ivCYC or ciclosporin led to higher remission rates than prednisone alone, but relapse of nephrotic syndrome occurred significantly more often after completion of ciclosporin than after ivCYC.[35] As evidence is lacking on maintenance therapy in class V LN, it is suggested to treat according to maintenance regimens for class III/IV LN. The efficacy in idiopathic membranous glomerulopathy of tacrolimus, ciclosporin and rituximab also supports a therapeutic role for these agents in lupus membranous nephropathy.[36-38]

Monitoring

The guidelines differ in their approach but agree that patients with active nephritis should have a visit scheduled at least every month, particularly at induction, relapse and withdrawal of treatment. If there is no active nephritis every 3 to 6 months should suffice, although vigilance is required for prompt identification of disease relapse. At each visit body weight, blood pressure, serum creatinine (sCr), proteinuria, urinary sediment, complement levels, anti-dsDNA titres and according to some serum albumin and complete blood count, should be determined. The ACR states that some of the aforementioned can be determined at larger intervals than others (blood pressure and urinalysis frequent; anti-dsDNA less frequent) and drafted a separate monitoring schedule for pregnancy (Table 2 and Supplemental Table 1). Recommendations in this area are all based on expert opinion. Nevertheless, they can still serve as a guideline for the practicing physician. Also, a recommendation from the EULAR for monitoring patients with SLE was previously published.[39]

Adjunctive treatment/treatment for comorbidities

All guidelines recommend blood pressure control (target <130/80 mmHg), treatment of hyperlipidemia with statins (target LDL < 100 mg/dL or 2.6 mmol/L) and treatment of proteinuria with RAAS inhibition. The guidelines agree that all SLE patients should have a background of hydroxychloroquine (HCQ) unless contraindicated, since this is associated with less damage accrual.[40] There is a paucity of randomized evidence for the efficacy of HCQ on nephritis with only two retrospective studies supporting its use.[41 42] Patients receiving HCQ have a risk of developing retinopathy and should therefore be screened by the ophthalmologist at baseline and yearly after 5 years. Patients with severe renal or hepatic disease are at higher risk for developing retinopathy, due to less clearance of the drug. In those patients reducing the dose should be considered to avoid toxicity. Other recommendations made by one or more of the guidelines are listed in Table 2 and involve treatment for side effects of drugs, prevention of clotting events and osteoporosis. There are no clear recommendations from the guidelines on infective prophylaxis, such as for pneumocystis jirovecii pneumonia, or surveillance for other pathogens.

Definitions of response and relapse

When communicating about patients, either in trials or in clinical practice, it is essential that definitions for disease parameters such as partial and complete response and relapse or flare are the same. Previously, a very stringent European consensus statement was published on the terminology used in the management of lupus nephritis.[43] However, the choice

Table 3. Definitions of response to treatment and flares; common views and differences

	Common view	Differences
Complete response	Proteinuria: uPCR <50 mg/mmol or <500 mg/g, or <0.5 g/24 h (except CARRA) Plus (near) normal renal function	Proteinuria: uPCR <200 mg/g or age appropriate (CARRA) Renal function: ranging from normalization to baseline to baseline plus 25%. Or sCr <1.2 mg/dL (106 µmol/L) (GEAS) Plus inactive urinary sediment (<5 red blood cells/HPF, <5 leukocytes/HPF, no casts) (GEAS/CARRA) Plus serum albumin >30 g/dL (GEAS)
Partial response	≥50% decrease in proteinuria, to at least sub-nephrotic levels (except CARRA) Plus stabilization or improvement of sCr	GEAS: if proteinuria >3.5 g/24 h, partial response if proteinuria <3.5 g/24 h Renal function: – EULAR/ERA-EDTA: (near) normal – KDIGO/GEAS: stabilization (±25%) or improvement of sCr – DWP: sCr within 125% of baseline CARRA: different approach, for details, see Supplemental Table 2
Flare	Increase or recurrence of active urinary sediment (hematuria from <5 RBC/HPF to >15 RBC/HPF Or an increase in sCr (exact criteria different in the different guidelines, for details, see Supplemental Table 2) Or an increase in proteinuria: – If proteinuria <500 mg/g (complete response), an increase to ≥1000 mg/g is required – If proteinuria >500 mg/g (partial response), a doubling of uPCR to ≥2000 mg/g is required (EULAR/ERA-EDTA, KDIGO, GEAS) Depending on which of the above-mentioned criteria are met, the flare can be designated at either nephrotic or nephritic.	With respect to proteinuria the bar is raised in the DWP guideline and lowered in the CARRA guideline: – DWP: development of nephrotic syndrome if lowest proteinuria was <2 g/24 h, or proteinuria of ≥1.5 g/24 h in previously non-proteinuric patient – CARRA: after a complete response an increase to >500 mg/g is required and after a partial response a doubling of sCr to >1000 mg/g
Refractory disease	There is no consensus between guidelines and some guidelines state that a consensus was not reached	For details, see Supplemental Table 2

uPCR 100 mg/mmol ≡ 1000 mg/g ≡ 1(g/g) ≈ 1 g/24 h.55 ACR, American College of Rheumatology; CARRA, Childhood Arthritis and Rheumatology Research Alliance; DWP, Dutch Working Party on Systemic Lupus Erythematosus; EULAR/ERA-EDTA, European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association; GEAS, Systemic auto-immune disease group of the Spanish Society of Internal Medicine and Spanish Society of Nephrology; HPF, high power field; KDIGO, Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group; RBC, red blood cell; sCr, serum creatinine; uPCR, urine protein-creatinine ratio.

of primary endpoint in clinical trials can also substantially influence the ability to detect therapeutic benefit, as demonstrated by Wofsy *et al.*.[44] The common ground and differences for the definitions of complete and partial response, relapse or flare, and refractory disease are outlined in Table 3 and Supplemental Table 2.

Treatment for refractory disease

Although the definition for refractory disease is stated differently by the various guidelines and there is no clinical trial evidence for these approaches, there is agreement on the treatment. It is generally advised to switch from MMF to ivCYC or vice versa if induction treatment fails. Some guidelines also state that again three pulses of intravenous MP should be administered. If this approach fails, the guidelines recommend other options: rituximab, as add-on or monotherapy, CNIs (also as add-on or monotherapy) or intravenous immunoglobulins. Of these, the main focus in literature has been on the use of rituximab, although with the LUNAR trial of rituximab as add-on to a steroid-MMF combination failing to meet its endpoint, it has not yet been proven effective in an RCT. Putative explanations for this failure include the possible overtreatment of relatively mild disease, short follow-up and underpowered study for the detection of an effect mainly consisting of partial responses.[45] Recently, a summary of the literature on the use of rituximab in refractory LN was published,[46] which suggests that rituximab can induce a response in patients who did not achieve remission on standard therapy. Also, Jónsdóttir and colleagues recently showed in a group of 25 patients that add-on of rituximab to ivCYC and glucocorticoids resulted in both clinical and histologic improvements in the majority of patients.[47] A recent, non-randomized, prospective study found promising results for a steroid sparing induction regimen [48] consisting of two doses of rituximab (1 g) and MP (500 mg) on day 1 and 15, and maintenance with MMF without oral steroids. A phase 3 open label multicentre investigator led RCT (RITUXILUP, NCT01773616) will start in 2015 comparing this regimen with a 'standard' oral glucocorticoid/MMF regimen.

Although RCTs are lacking, there is a growing body of evidence that CNIs may be useful in refractory disease, but one should be aware of the nephrotoxic effects, especially in patients with decreased renal function. These nephrotoxic effects (reviewed by Naesens *et al*.[49]) seem to be less for tacrolimus than for ciclosporin. Although not studied in refractory disease, in a recent Chinese randomized trial the combination of MMF (1.0 g/day) with tacrolimus (4 mg/day) was proven superior to ivCYC (0.5-1 g/m^2 every 4 weeks for six doses) in achieving complete remission in patients with class IV, class V and class IV + V LN.[50] This

could be due to a faster anti-proteinuric effect of tacrolimus and longer follow-up data are needed to determine the comparable efficacy of the two regimens.

Pregnancy

Pregnancy should not be planned until remission is reached and maintained for 6 months (EULAR/ERA-EDTA and GEAS). HCQ should be continued as multiple studies (reviewed by Ruiz-Irastorza *et al*.[40]) have demonstrated its safety in pregnancy. RAAS inhibitors, MMF and cyclophosphamide are prohibited during pregnancy. As alternatives AZA, CNIs, methyldopa, labetalol or nifedipine can be prescribed, despite the classification of AZA (the same as MMF and ivCYC) as category D by the Food and Drug Administration ("positive evidence of human fetal risk based on adverse reaction data, potential benefits may warrant use of the drug in pregnant women despite the potential risk"). AZA is considered safe during pregnancy as there is no evidence that AZA increases the risk of congenital abnormalities (in contrast to MMF and CYC) and AZA cannot be metabolized to the active metabolite 6-mercaptopurine by the fetal liver.[51 52] Low dose oral glucocorticoids (non-fluorinated) are acceptable. It is advised by the KDIGO not to taper glucocorticoids or AZA during pregnancy or for 3 months thereafter. Furthermore, low dose acetylsalicylic acid should be considered to reduce the risk of pre-eclampsia. Finally, all patients should be monitored closely, preferably by a multidisciplinary team that is used to managing such patients and is aware of the need to distinguish between a flare and pre-eclampsia, which may also co-exist.

Vascular complications

Anti-phospholipid syndrome-associated nephropathy (APSN) is a vascular nephropathy that can occur in SLE patients and may be associated with the presence of anti-phospholipid (aPL) antibodies. The EULAR/ERA-EDTA guideline takes the use of HCQ and/or antiplatelet or anticoagulant treatment into consideration, while the KDIGO and GEAS merely suggest treatment with anticoagulants (INR 2-3). The ACR suggests treating thrombotic microangiopathy (TMA) primarily with plasma exchange. This area is further complicated by the inconsistent terminology used. TMA is a histologic lesion, which is part of the APSN spectrum, but also has a clinical counterpart with systemic manifestations such as the presence of schistocytes in peripheral blood. Thrombotic thrombocytopenia (TTP) is a clinical syndrome associated with TMA in the renal biopsy, recommended to be treated promptly with plasma exchange by KDIGO (and other guidelines for idiopathic TTP, as TTP especially in SLE has a high mortality). In summary, recommendations differ because of inconsistent

terminology and lack of evidence. Until this is solved, we recommend viewing TMA in the renal biopsy in the clinical context when determining treatment. If APSN is considered to be a small vessel manifestation of APS and laboratory criteria for the diagnosis of APS are met, it may be wise to treat it as such (with antiplatelet or anticoagulation therapy), at least until new evidence becomes available.

Management of ESRD and transplantation

The modality of dialysis should be determined by patient choice. However, the risk of infection in increased with the use of immunosuppressive drugs. Hence, the GEAS suggests peritoneal dialysis should only be offered to patients with inactive disease on minimal immunosuppression. Hemodialysis is suitable for patients with active disease/more immune suppression.

It is advised to determine the presence of aPL antibodies because this can increase the risk of vascular access thrombosis during dialysis and of vascular events in the transplant. Lupus activity should be absent or low for a period of 3-6 months (EULAR/ERA-EDTA) or 6-12 months (GEAS) to be eligible for transplantation. Although ESRD is often associated with remission of lupus activity, this is not universal and extra-renal lupus flares can still occur, patients should be managed accordingly.

Children and adolescents

The rate of developing LN during the course of disease is higher in children than in adults.[53] However, large trials comparing different treatment strategies in juvenile LN are lacking. The guidelines generally advise the same treatment strategies as for adults, except for the CARRA guideline, which is specifically aimed at children and adolescents. For dosages of the immunosuppressive drugs in children, we refer to this guideline. In 2012, the first results from an RCT, a subgroup analysis of the ALMS trial, were published.[54] This subgroup analysis included adolescents aged 12 to 18 years. Although the numbers were small (24 patients in the induction phase and 16 in the maintenance phase) and therefore not sufficient to yield statistically significant results, it was noted that in general there was similar efficacy in adolescents and adults. Due to the small numbers the effect of ethnicity could not be determined.

Conclusion

Although a substantial part of the management of LN is evidence-based, a significant part still rests on uncontrolled trials and expert opinion. Despite an increase in clinical trial activity during the last decade, there are areas where evidence is lacking, such as for the treatment of severe and refractory LN and of children. Furthermore, although the most important outcome is the long-term follow-up beyond 10 years due to the risk of end-stage renal failure at this time despite initial improvement in disease parameters, these data are scarce. Finally, it must be kept in mind that all guidelines are meant to assist physicians in the management of LN, but they can never replace the insight of the experienced clinician in reaching a therapeutic strategy tailored to the individual patient.

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Conflict of interest statement

I.M.B. is a consultant for Roche; L.L.: Roche are providing drugs free of charge for the Rituxilup trial; honoraria /advisory boards/lecturing—GSK, Anthera Pharmaceuticals, MedIm- mune, Merck, Aspreva/Vifor Pharma, Biogen-Idec, UCB; C.G. is a consultant on clinical trial design and has received 465 honoraria for consultancy, participation in scientific advisory boards and lecturing for UCB, GSK and Bristol-Myers Squibb, and has received honoraria from Aspreva/Vifor Pharma, Med- Immune, Genentech, Roche and Merck Serono. D.J.: Roche/ Genentech is providing drugs for the RITAZAREM trial; 470 honoraria/advisory boards/lecturing—GSK, Medimmune, Merck, Biogen-Idec and UCB; V.T.: Lecturing for GSK and Roche.

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Supplemental Table 1. Guidelines compared; overview of all guidelines

	EULAR/ERA-EDTA	ACR	KDIGO	GEAS	DWP	CARRA
From	European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association	American College of Rheumatology	Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group	Systemic auto-immune disease group of the Spanish Society of Internal Medicine and Spanish Society of Nephology	Dutch Working Party on Systemic Lupus Erythematosus	Childhood Arthritis and Rheumatology Research Alliance
Indication for renal biopsy	• Reproducible proteinuria ≥0.5 g/24h, especially with glomerular hematuria and/or cellular casts (2C) • Consider: – Persisting isolated glomerular hematuria – Isolated leucocyturia (other causes excluded) – Unexplained renal insufficiency with normal urinary findings	• Increasing serum creatinine without compelling alternative causes (such as sepsis, hypovolemia, or medication) (C) • Confirmed proteinuria of ≥1g/24h (C) • Combinations of the following (confirmed in 2 tests in short period of time and in absence of alternative causes) (C) – Proteinuria ≥0.5 g/24h AND hematuria (≥5 RBCs/HPF) – Proteinuria ≥0.5 g/24h AND cellular casts	Not provided	• Confirmed proteinuria: ≥0.5 g/24h urine samples or protein/creatinine ratio in first morning samples ≥0.5, or a ratio ≥0.5 ratio calculated in 24h urine sample, or active urinary sediment (microhematuria/ leucocyturia/casts) • Inexplicable decrease in renal function (NG)	• >0.5 g/24h proteinuria, independent of presence of hematuria or elevated serum creatinine (C) • ≤0.5 g/24h proteinuria: – Normal creatinine and microscopic hematuria → consider biopsy – Elevated creatinine without microscopic hematuria → consider biopsy when either: ○ Persistent elevation of serum creatinine of >30% ○ Other causes of renal impairment are excluded ○ Positive antiphospholipid antibodies ○ Extrarenal involvement/presence of anti-dsDNA	Not provided

Supplemental Table 1. Continued

	EULAR/ERA-EDTA	ACR	KDIGO	GEAS	DWP	CARRA
					antibodies/hypo-complementemia (C)	
Biopsy evaluation	• At least 8 glomeruli • Score according to ISN/RPS (2C) with assessment of active and chronic glomerular (1A) and tubulo-interstitial changes (2B) and of vascular lesions associated with aPL/APS (3C) • Examine with HE, PAS, Ag, trichrome, IF and if possible EM	Not provided	Not provided	• Classify according to ISN/RPS (NG) • Optimal optical microscope and IF techniques and EM recommended (NG) • Quantified data on activity and chronicity and a description of vascular and interstitial lesions should be provided (NG)	Not provided	According to ISN/RPS classification system
Indication for repeat biopsy	In selected cases: – Worsening or refractory to treatment (failure to decrease proteinuria ≥50%, persistent proteinuria beyond 1 year and/or worsening of GFR) – At relapse, to demonstrate change or progression in histological class, change in activity	Not provided	Consider if: – No complete remission after 1 year (NG) – During relapse if there is suspicion that the histologic class has changed or there is uncertainty whether a rise in sCr or proteinuria represents	Only if findings can lead to a change in treatment or prognosis (NG): – Increase or reappearance of proteinuria, nephrotic syndrome, or active urinary sediment, especially if the first biopsy revealed a non-proliferative form – Increased sCr or inexplicable evolution towards renal failure – Refractory to immunosuppressives	Only if therapeutic consequences (C): – Persistence proteinuria after partial response (despite optimal supportive treatment): active or chronic disease or progression to FSGS – Failure to respond at 12 months, in order to differentiate between chronic and active	No consensus reached

Supplemental Table 1. Continued

	EULAR/ERA-EDTA	ACR	KDIGO	GEAS	DWP	CARRA
	and chronicity index, to provide prognostic information and to detect other pathologies (3C)		disease activity or chronicity (NG) – In patients with worsening sCr and/or proteinuria after completing one of the initial treatment regimens in order to distinguish active LN from scarring (NG)	– Uncertainty with regard to activity/chronicity of renal lesions (deciding upon treatment) – Suspicion of non-lupus related nephropathy		
Treatment class II	Proteinuria >1 g/24h despite RAAS inhibition, especially in the presence of glomerular hematuria; low to moderate doses oral glucocorticoids (0.25-0.5 mg/kg/day) alone or in combination with AZA (1-2 mg/kg/day)	No immunosuppressive treatment (C)	• Proteinuria <1 g/24h: treat as dictated by extrarenal manifestations (2D) • Proteinuria >3 g/24h: corticosteroids or CNI as described for MCD (2D)	Significant proteinuria (>1-2 g/24h despite renal protective treatment) and/or deteriorated renal function that is not attributable to functional factors; steroids up to 0.5 mg/kg/day, possibly plus AZA or MMF for 6-12 months (2D)	Not provided	Not provided
Induction treatment class III/IV *without* crescents (and/or other adverse parameters)	• For A or A/C classes (ISN/RPS 2003) • Regimens: – Glucocorticoids: 3 iv pulses MP; 500-750 mg/day (3C) + oral; 0.5	• Regimens: – Glucocorticoids: 3 iv pulses MP; 500-1000 mg/day + oral; 0.5-1 mg/kg/day and taper (C) – MMF (2-3 g total	• Regimens: – Glucocorticoids: 3 iv pulses MP (widely used for more severe disease, no dose provided) + oral; (1A) up to 1	• Regimens: – Glucocorticoids: 3 iv pulses MP (250-1000 mg/day) in presence of extracapillary proliferation or acute deterioration of renal function (2C) + oral; start	• Regimens: – MMF to 3 g total daily dose in 3 weeks + oral glucocorticoids; 1 mg/kg/day, max 60 mg (A) and taper: after 4 weeks 10 mg every 4 weeks to 20	• Regimens: – Glucocorticoids: 3 iv pulses MP (30 mg/kg/dose up to 1000 mg/dose)

Supplemental Table 1. Continued

	EULAR/ERA-EDTA	ACR	KDIGO	GEAS	DWP	CARRA
	mg/kg/day for 4 weeks, reducing to ≤10 mg/day by 4-6 months (C) – MMF (3 g total daily dose) for 6 months (seems preferable) (1A) or low dose ivCYC (1B) (in Caucasians) • African descent: MMF might be better but further confirmation needed • Mild cases: AZA (2 mg/kg/day) can be considered (2B)	daily dose; Asian 2 g considered) or ivCYC (white European high or low dose (B); rest high dose) • African Americans and Hispanics: favor MMF • MMF over ivCYC if child bearing concerns • Keep up for 6 months unless worsening at 3 months	mg/kg/day and taper according to clinical response over 6-12 months – MMF (1B) or ivCYC (1B); low dose ivCYC effective in Caucasians with not too severe disease, unclear if also case for other ethnicities and severe disease • MMF equivalent to high dose ivCYC in short term, not clear for long-term • If worsening LN (rising sCr, worsening proteinuria) in first 3 months → change to alternative initial (induction) therapy or repeat kidney biopsy (2D) • Race: further information required	up to 1 mg/kg/day (max 60 mg), 0.5 mg/kg/day can be used with concomitant pulses of MP (2C) and if possible taper to 5 mg/day – MMF 2-2.5 g/day (1B) or ivCYC; either monthly 750 mg/m^2 for 6 months (NIH), or fortnightly 500 mg for 3 months (Eurolupus) with 3 MP pulses (750 mg/day), followed by oral prednisone 0.5 mg/kg/day (1B)	mg, followed by 5 mg every 4 weeks to 10 mg – Low dose ivCYC + 3 iv pulses MP + oral glucocorticoids 0.5-1 mg/kg/day (A) and taper: after 4 weeks every 2 weeks with 2.5 mg to 5-7.5 mg at 30 months • Race: MMF may be better in Blacks	and/or oral glucocorticoids depending on which of the 3 scheme's (primarily oral, primarily iv or mixed oral/iv) is chosen – ivCYC; 6 monthly doses, initial dose 500 mg/m^2, subsequent doses higher but not more than 1500 mg (C) (most often used in practice), or MMF; 600 mg/m^2/day twice daily with a max of 1500 mg twice a day (C)

Supplemental Table 1. Continued

	EULAR/ERA-EDTA	ACR	KDIGO	GEAS	DWP	CARRA
Induction treatment class IV or IV/V *with* crescents (and/or other adverse parameters)	With adverse prognostic profile (acute deterioration renal function, substantial cellular crescents and/or fibrinoid necrosis): – Same regimen (MMF (2B); low dose ivCYC (4C)) – CYC can also be prescribed monthly iv at higher doses (0.75-1 g/m^2) for 6 months (1A) or orally (2-2.5 mg/kg/day) for 3 months (3B)	Either CYC or MMF(3 g total daily dose, instead of 2-3 g) (C) + 3 pulses MP and oral glucocorticoids at 1 mg/kg/day, instead of 0.5-1 mg/kg/day	Not different from without crescents (and/or other adverse parameters)	• 3 pulses MP (250-1000 mg/day) in presence of extracapillary proliferation or acute deterioration of renal function (2C) • Include ivCYC if severe decrease in renal function (sCr >3 mg/dL) or cellular crescents or fibrinoid necrosis (2C)	Not different from without crescents (and/or other adverse parameters)	Not different from without crescents (and/or other adverse parameters)
Induction treatment class V	• If nephrotic range proteinuria (≥3 g/24h): prednisone (0.5 mg/kg/day) and MMF 3 g total daily dose for 6 months(2B) • Alternatives: high dose ivCYC (2A), CNIs (ciclosporin (2A); tacrolimus (3B)) or rituximab (4C)	If nephrotic range proteinuria (≥3 g/24h): prednisone (0.5 mg/kg/day) and MMF 2-3 g total daily dose (A)	• If normal kidney function, non-nephrotic range proteinuria → no immunosuppressives unless dictated by extrarenal disease (2D) • Persistent nephrotic range proteinuria: corticosteroids plus immunosuppres	• Oral steroids up to 1 mg/kg/day (max 60 mg) initially and taper • Plus one of: – ivCYC (1B), dose as in class III/IV – CNIs (ciclosporin, dose 2-5 mg/kg/day (1B); tacrolimus, dose 0.15-0.2 mg/kg/day (2C)) – MMF (1B), dose as III/IV – AZA (1C), dose 1.5-2 mg/kg/day	Not provided	Not provided

Supplemental Table 1. Continued

	EULAR/ERA-EDTA	ACR	KDIGO	GEAS	DWP	CARRA
			sive (ivCYC (2C), CNI (2C), MMF (2D) or AZA (2D))			
Treatment class VI	Not provided	Prepare for renal replacement therapy	Treat with corticosteroids and immunosuppressives only as dictated by extrarenal disease (2D)	• Maintain RAAS inhibition and monitor for complications (2C) • Slowly decrease immune suppression until it can be discontinued (unless dictated by extrarenal disease) (1B)	Not provided	Not provided
Maintenance treatment	• Class III/IV: – AZA (2 mg/kg/day) or MMF (2 g/kg/day) (1A) for at least 3 years (3C) – If response to MMF at induction, stay on MMF (C) – Plus low dose oral glucocorticoids (5-7.5 mg/day) • Pure class V: – As class III/IV – CNIs can be considered (4C)	• Class III/IV: – AZA or MMF (A) – Plus low dose oral glucocorticoids	• Class III/IV: – AZA (1.5-2.5 mg/kg/day) or MMF (1-2g/day) (1B) – Plus low dose oral glucocorticoids (≤10 mg/day prednisone equivalent) – CNIs if intolerant to MMF or AZA (2D) – After complete remission, continue maintenance for at least 1 year (2D) – No complete remission after 1 year → consider	• Class III/IV: – MMF (1.5-2 g/day) (over AZA (1.5-2 mg/kg/day)) (2A) – Plus low dose oral glucocorticoids – Duration of treatment: at least 2 years after remission has been reached (2C) • Pure Class V: – Low dose steroids and MMF, CNIs or AZA (2B) – Dosage and duration as in class III and IV	• Class III/IV: – MMF over AZA (A) – Plus low dose oral glucocorticoids	Not provided

Supplemental Table 1. Continued

	EULAR/ERA-EDTA	ACR	KDIGO	GEAS	DWP	CARRA
			repeat biopsy (NG) – If during tapering renal function deteriorates and/or proteinuria worsens, increase to previous level (2D)			
Adjunctive treatment	• HCQ for all (3C); screening ophthalmologist for retinopathy (baseline and yearly after 5 years) • RAAS inhibition for patients with proteinuria (uPCR >50 mg/mmol) or hypertension (target <130/80) (2B) • Statins (target LDL <100 mg/dL = 2.58 mmol/L)) (C) • Acetylsalicylic acid in patient with aPL (C), calcium and vitamin D supplementation (C), and	• Background HCQ unless contraindicated (C) • Proteinuria ≥0.5 g/24h → RAAS inhibition (A) • Control hypertension, target ≤130/80 (A) • LDL >100 mg/dL → statins (C)	• HCQ for all unless contraindicated (2C); screening ophthalmologist for retinopathy (baseline and yearly after 5 years) • Leuprolide/testosterone should be offered to protect fertility • In general in glomerular disease: – Blood pressure control – Treatment of hyperlipidemia – RAAS inhibition in managing	• HCQ for all unless contraindicated (1B); screening ophthalmologist for retinopathy (baseline and yearly thereafter) (1C) • RAAS inhibition in patients with hypertension and/or proteinuria (1B) • Weight loss against proteinuria (1C) if obese • Reduce cardiovascular risks (1B) (lifestyle, BP <130/80, statins) • Calcium and vitamin D (1A) for patients on oral glucocorticoids; bisphosphonates if older than 50 years (1A) • Drugs for gastric protection if history of gastrointestinal	• Background HCQ (B); screening by ophthalmologist for retinopathy (baseline and yearly after 5 years) • Proteinuria ≥1 g/24h → RAAS inhibition (A) • Hypertension control, target <130/80 (A; if proteinuria >1 g/24h) • Treatment hyperlipidemia (C); target 2.6 mmol/L • Calcium and vitamin D (osteoporosis) for patients on oral glucocorticoids; bisphosphonates if >15 mg oral glucocorticoids daily or if >70 years old and 7.5-15 mg oral	Not provided

Supplemental Table 1. Continued

	EULAR/ERA-EDTA	ACR	KDIGO	GEAS	DWP	CARRA
	immunization with non-live vaccines (C) may reduce treatment or disease related comorbidities and should be considered • Consider anti-coagulant treatment in nephrotic syndrome with albumin <20 g/L, especially if also aPL (C)		proteinuria – Manage hypercoagulability	hemorrhage or peptic ulcer disease, or with combination of corticosteroids and NSAIDs (1B) • Avoid vaccines containing live or attenuated viruses during immune suppression (1B) • GnRH analogues in women over 35 y if cumulative CYC dose >10 g (1C)	glucocorticoids daily unless clearance <60mL/min or pregnancy wish • Low dose acetylsalicylic acid if aPL positive • Coumarines considered if nephrotic syndrome with albumin <20g/L (C) • Lifestyle	
Treatment for refractory disease	• Switch from ivCYC to MMF or vice versa (4C), or rituximab (4C) • Other options: CNIs, ivIg, plasma exchange for rapid progressive glomerulonephritis, or immunoadsorption	• Switch from ivCYC to MMF or vice versa accompanied by 3 pulses MP (C) • In some cases rituximab can be used • No consensus on CNI	• In patients with worsening sCr and/or proteinuria after completing one of the initial treatment regimens, consider performing a repeat biopsy to distinguish active LN from scarring (NG) → if active LN, treat with alternative induction therapy (NG) • Responders who	• Switch from CYC to MMF or vice versa (1A) • Alternative treatments (if above fails): rituximab (2B), CNIs (2B), ivIg (2C) or combining drugs (2B) • Change treatment scheme if there are no sign of response before completing the sixth month of induction (1B) • Rule out presence of other diseases and ensure compliance (NG) • If nothing works, consider a new biopsy	• Switch from ivCYC to MMF or vice versa accompanied by 3 pulses MP (C) • Consider: rituximab, tacrolimus, NIH ivCYC	Not provided

Supplemental Table 1. Continued

	EULAR/ERA-EDTA	ACR	KDIGO	GEAS	DWP	CARRA
			have failed more than one induction may be treated with rituximab, ivlg or CNIs (2D)			
Pregnancy	• If stable (uPCR <50 mg/mmol, GFR preferably over 50 mL/min) for 6 months (2B) • Acceptable medications: HCQ (3B), low dose prednisone (4C), azathioprine (4C) or CNIs (4C) • Intensity of treatment should not be reduced in anticipation of pregnancy (C) • Consider acetylsalicylic acid to reduce risk of pre-eclampsia (3C) • Assess at least every 4 weeks (C)	• Prior LN but no current systemic or renal activity: no nephritis medication • Mild systemic activity: HCQ (200-400 mg daily) • Clinically active nephritis or substantial extrarenal disease: oral glucocorticoids, if necessary AZA (max 2 mg/kg) (C)	• Preferably delay pregnancy until in complete remission (2D) • Don't use CYC, MMF, ACE-I and ARBs during pregnancy (1A) • Continue HCQ (2B) • If pregnant while on MMF, switch to AZA (1B) • Relapse: corticosteroids possibly with AZA (1B) • Don't taper corticosteroids or AZA during pregnancy or within the 3 months after (2D) • Low dose aspirin to decrease risk of fetal loss (2C)	• Plan after at least 6 months of (partial) remission (1B) • Monitor closely by multi-disciplinary team (NG) • For blood pressure control suspend RAAS inhibitors and use methyldopa, labetalol or nifedipine (1B) • Avoid teratogenic drugs (CYC, MMF, MTX); AZA safe • Continue HCQ during pregnancy • Aspirin at low doses (100 mg/day) before week 12 to reduce risk of pre-eclampsia and fetal loss (1A)	Not provided	Not provided
Vascular	• In patients with	Treat TMA with plasma	• APS involving	• Maintain indefinite	Not provided	Not provided

Supplemental Table 1. Continued

	EULAR/ERA-EDTA	ACR	KDIGO	GEAS	DWP	CARRA
complications	APSN; consider HCQ (C) and/or antiplatelet/ anticoagulant treatment (C) • Definite APS → anticoagulant treatment	exchange therapy	the kidney (APSN) with or without LN → anticoagulation INR 2-3 (2D) • If TTP → plasma exchange as in patients without lupus (2D)	anticoagulant treatment in patients with ASPN (2C) • Treat thrombosis of major renal vessels with prolonged anticoagulation (1B), as in non-APS associated thrombosis		
Monitoring	• Active LN should be regularly monitored by determining at each visit body weight, BP, sCr and eGFR, serum albumin, proteinuria, urinary sediment (microscopic evaluation), serum C3 and C4, serum anti-dsDNA and complete blood cell count • Anti-phospholipid antibodies and lipid profile should be measured at baseline and monitored intermittently • Visits should be scheduled every 2-4 weeks for the	• Active nephritis at onset of treatment: BP 1, urine 1, uPCR 1, sCr 1, C3/C4 2, anti-DNA 3 (monthly intervals) • Previous active nephritis, none currently: BP 3, urine 3, uPCR 3, sCr 3, C3/C4 3, anti-DNA 6 (monthly intervals) • Pregnant with active GN at onset of treatment: BP 1, urine 1, uPCR 1, sCr 1, C3/C4 1, anti-DNA 1 (monthly intervals) • Pregnant with previous nephritis, none currently: BP 1, urine 1, uPCR 3, sCr 3, C3/C4 3, anti-DNA 3	Not provided.	• Every 3 months by determining creatinine proteinuria, anti-dsDNA, C3 and C4 (NG) • Proteinuria should be measured in 24-hour urine, follow-up may only include protein/creatinine ratio in first morning urine (NG) • At baseline more lab tests particularly those relevant for assessing cardiovascular risks (see detailed scheme in table 8 (in original article))	Not provided	Not provided

ivCYC high dose (NIH regimen) = 0.5-1 g/m2 monthly for 6 months; ivCYC low dose (Eurolupus regimen) = 500 mg every 2 weeks for 3 months. A, active; (A)/(B)/(2A), level of evidence (for criteria see table S3); Ag, silver staining; aPL, anti-phospholipid antibodies; APS, antiphospholipid syndrome; APSN, anti-phospholipid syndrome-associated nephropathy; AZA, azathioprine; BP, blood pressure; C, chronic; CNI, calcineurin inhibitor; (e)GFR, (estimated) glomerular filtration rate; EM, electron microscopy; FSGS, focal segmental glomerulosclerosis; GnRH, gonadotrophin-releasing hormone; HCQ, hydroxychloroquine; HD,

Supplemental Table 1. Continued

	EULAR/ERA-EDTA	ACR	KDIGO	GEAS	DWP	CARRA
	first 2-4 months after diagnosis or flare (C) and every 3-6 months for life (C)	(monthly intervals) • No prior or current nephritis: BP 3, urine 6, uPCR 6, sCr 6, C3/C4 6, anti-DNA 6 (monthly intervals) (C)				
Management of ESRD	• Renal replacement therapy: possible increased risk of infection in patients still on immunosuppressives (2B) and of vascular access thrombosis in patients with aPL (3C) • Transplantation: – If lupus activity absent or low for at least 3-6 months (3C) – Determine aPL; associated with increased risk of vascular events in the transplant (2B)	Not provided	Not provided	• ESRD: – If reached during flare, induction treatment should be continued for 4-6 months after beginning dialysis, until lack of recovery is observed (NG) – Decrease immunosuppressives to levels required for extrarenal lupus (1B) • Renal replacement therapy: – Inactive lupus → offer PD; active lupus → offer HD (2C) – Increase prophylaxis against infections for PD and HD • Transplantation: – If lupus activity absent or low for 6-12 months (NG) – Determine aPL; associated with increased risk of vascular events in the transplant (NG)	Not provided	Not provided

haemodialysis; HE, haematoxylin and eosin staining; IF, immunofluorescence; ISN/RPS, International Society of Nephrology/Renal Pathology Society; ivCYC, intravenous cyclophosphamide; ivIg, intravenous immunoglobulins; LN, lupus nephritis; MCD, minimal change disease; MMF, mycophenolate mofetil; MP, methylprednisolone; NG, not graded (level of evidence); NSAID, non-steroidal anti-inflammatory drug; PAS, periodic acid Schiff staining; PD, peritoneal dialysis; RBC, red blood cell; sCr, serum creatinine; TMA: thrombotic microangiopathy; TTP, thrombocytopenic purpura; uPCR, urine protein-creatinine ratio.

Supplemental Table 2. Definitions of response to treatment and flares

	EULAR	KDIGO	GEAS	DWP	CARRA
Complete response	• uPCR <50 mg/mmol [approx. <0.5 g/24h] • Plus (near) normal (within 10% of normal GFR) renal function	• A decline in the uPCR to <500mg/g • Plus return of sCr to previous baseline	• Proteinuria ≤0.5 g/24h • Plus sCr <1.2 mg/dL (or decrease to initial values or ±15% of baseline value in patients with sCr ≥1.2 mg/dL [106 µmol/L]) • Plus inactive urinary sediment (≤5 RBCs/HPF (debatable), ≤5 WBCs/HPF, 0 RBC casts) • Plus serum albumin >3g/dL	• Proteinuria <0.5 g/24h • And/or sCr within 125% of the baseline value at 6 to 12 months after the start of induction therapy	• uPCR <200 mg/g or age appropriate • Plus normalization of renal function • Plus inactive urine sediment (<5 WBCs/HPF, <5 RBCs/HPF, and no casts)
Partial response	• ≥50% reduction in proteinuria to subnephrotic levels • Plus (near) normal renal function • It should be achieved preferably by 6 months but no later than 12 months following treatment initiation	• ≥50% decrease in uPCR • If there was nephrotic-range proteinuria (uPCR ≥3000mg/g), improvement requires a ≥50% reduction in uPCR, and a uPCR <3000 mg/g • Plus stabilization (±25%), or improvement of sCr, but not to normal	• In patients with baseline proteinuria <3.5g/24h, >50% reduction in proteinuria compared to initial values • In patients with ≥3.5 g/24h, decreased proteinuria <3.5 g/24h • Plus stabilization (±25%) or improvement in serum creatinine with regard to initial values	• Reduction of proteinuria of >50% (and at least <3 g/24h) • Plus sCr within 125% of the baseline value at 6 to 12 months after the start of the induction therapy	Moderate response • At least 50% improvement in 2 core renal parameters (with max uPCR ≤1000 mg/g) without clinically relevant worsening of the remaining renal core parameter Mild response • 30–50% improvement in 2 core renal parameters without clinically relevant worsening of the remaining renal core parameter *Renal core parameters:* proteinuria (uPCR), renal function (creatinine clearance or sCr) and urine sediment (WBCs, RBCs, and casts)
Flare	Nephritic flare • Reproducible	Mild kidney relapse • ↑ glomerular hematuria	Mild recurrence • ↑ RBCs in sediment from <5	• An increase in disease activity that requires intensification of the	Nephritic renal flare • Increase or recurrence of

Supplemental Table 2. Continued

	EULAR	KDIGO	GEAS	DWP	CARRA
	increase of serum creatinine by ≥30% (or, decrease in GFR by ≥10%) • Plus active urine sediment with increase in glomerular hematuria by ≥10 RBCs/HPF • Irrespective of changes in proteinuria Proteinuric flare • Reproducible doubling of uPCR to >100 mg/mmol after complete response • Or reproducible doubling of uPCR to >200 mg/mmol after partial response	from <5 to >15 RBC/hpf, with ≥ 2 acanthocytes/HPF • And/or recurrence of ≥1 RBC cast, WBC cast (no infection), or both Moderate kidney relapse • If baseline sCr is: – <2 mg/dL [<177 mmol/L]; increase of 0.2–1.0 mg/dL [17.7–88.4 mmol/L] – ≥2 mg/dL [≥177 mmol/L]; increase of 0.4–1.5 mg/dL [35.4–132.6 mmol/L] • And/or if baseline uPCR is: – <500 mg/g; increase to ≥1000 mg/g – 500–1000 mg/g; increase to ≥2000 mg/g, but less than absolute increase of <5000 mg/g – >1000 mg/g; increase of ≥2-fold with absolute uPCR <5000 mg/g Severe kidney relapse • If baseline sCr is: – <2 mg/dL [<177 mmol/L]; increase of >1.0 mg/dL [>88.4 mmol/L] – ≥2 mg/dL [≥177 mmol/L]; increase of >1.5 mg/dL [>132.6 mmol/L] – *and/or* an absolute increase of uPCR >5000 mg/g	to >15/HPF with ≥2 dimorphic RBCs/HPF • And/or ≥1 cast, leukocyte count (in the absence of urinary infection), or both Moderate recurrence • If baseline sCr is: – <2 mg/dL, ↑ by 0.2-1 mg/dL – >2 mg/dL, ↑ by 0.4-1.5 mg/dL • And/or if the uPCR is: – <500 mg/g , ↑ by ≥1000 mg/g – 500-1000 mg/g, ↑ by ≥2000 mg/g – But with an absolute increase < 5000 mg/g Severe recurrence • If baseline sCr is: – <2 mg/dL, ↑ by >1 mg/dL – ≥2 mg/dL, ↑ by >1.5 mg/dL • And/or a uPCR >5000 mg/g **NB:** in case of relapse rule out non-compliance.	therapy, defined as: – An increase of ≥25% in the lowest sCr measured during the period of induction therapy – And/or the development of either a nephrotic syndrome (proteinuria >3.5 g/24h and serum albumin <30 g/L), while the lowest protein excretion so far has been ≤2.0 g/24h repeatedly, or proteinuria >1.5 g/24h in a previous non-proteinuric patient	active urinary sediment (increased hematuria with or without reappearance of cellular casts) • With or without a concomitant increase in proteinuria Proteinuric/nephrotic renal flare • A persistent increase in uPCR >500 mg/g after achieving complete response • Or a doubling of proteinuria with uPCR >1000 mg/g, after achieving a partial response

Supplemental Table 2. Continued

	EULAR	KDIGO	GEAS	DWP CARRA
Refractory disease	• Failing to improve within 3–4 months • No partial response after 6–12 months of treatment • No complete response after 2 years of treatment	No consensus definition	Resistance to treatment is defined as an absence of complete or partial response after completing the induction therapy phase. But there is no consensus on how to define the minimum time for the induction therapy phase or the minimum cumulative dose of immunosuppressive drugs needed to consider the disease resistant to treatment	**DWP**: Persistent or worsening renal disease activity as manifested by progressive deterioration of renal function and/or proteinuria despite optimal immunosuppressive therapy and supportive treatment, and involving at least one of the following conditions: I) failure of the initial induction treatment at three months, for which a switch to another induction therapy regime has already been carried out; II) intolerance for CYC and MMF; III) exceeding a cumulative dose of 15 gram of cyclophosphamide, IV) a second relapse within two years after start of the initial induction therapy, and V) a relative contraindication for high-dose oral or intravenous (iv) prednisone, such as avascular osteonecrosis, previous psychosis on corticosteroids, osteoporosis and/or severe obesity (BMI ≥35 kg/m^2)

ACR: "Definitions of response, degree of response, flare, severity of flare, and remission vary significantly in the literature and depend on the starting point in each individual patient; therefore, an exact definition of these terms was not included in the scenarios. Identification of response, flare, and failure to respond were based on the experienced clinician's opinion, and it is intended that the treating clinician make similar judgments in employment of the recommendations outlined here"

uPCR 100 mg/mmol ≡ 1000 mg/g ≡ 1(g/g) ≈ 1 g/24 h.55 ACR, American College of Rheumatology; CARRA, Childhood Arthritis and Rheumatology Research Alliance; DWP, Dutch Working Party on Systemic Lupus Erythematosus; EULAR/ERA-EDTA, European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association; GEAS, Systemic auto-immune disease group of the Spanish Society of Internal Medicine and Spanish Society of Nephrology; GFR, glomerular filtration rate; HPF, high power field; KDIGO, Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group; RBC, red blood cell; sCr, serum creatinine; uPCR, urine protein-creatinine ratio.

Supplemental Table 3. Quality of evidence and strength of recommendations as applied by the different guidelines

EULAR/ERA-EDTA: European League Against Rheumatism and European Renal Association- European Dialysis and Transplant Association			
Level of evidence	Diagnosis/Monitoring/Prognosis	Treatment	
1	The available evidence is *strong* and includes consistent results from well-designed, well–conducted studies	Meta-analysis of randomized controlled trial (RCT) or >1 RCTs	
2	The available evidence is *sufficient* to determine effects, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies, inconsistency of findings across individual studies, limited generalizability of findings	Single RCT; long-term follow-up study of primary/secondary outcomes or post-hoc analysis based on the original randomization allocation	
3	The available evidence is *weak* due to the limited number or size of studies, important flaws in study design or methods, inconsistency of findings across individual studies, gaps in the chain of evidence, lack of information on important outcomes	Non-randomized controlled study (prospective or retrospective)	
4	-	Uncontrolled studies (case series)	
Strength of statements			
A	Based on level 1 evidence	Based on level 1 or 2 evidence without concerns for the validity of the evidence	
B	Based on level 2 evidence; or extrapolated recommendations from category 1 evidence	Based on level 1 or 2 evidence but with concerns about the validity of the evidence; or level 3 evidence without major concerns about the validity of the evidence	
C	Based on category 3; or extrapolated recommendations from category 2 evidence; or no data (expert opinion); or extrapolation from non-SLE literature	Based on level 3 evidence with concerns about the validity of the evidence; or level 4 evidence; or no data (expert opinion); or extrapolation from non-SLE literature	
ACR/DWP: American College of Rheumatology/Dutch Working Party on SLE			
A	Evidence represents data derived from multiple randomized controlled trials (RCTs) or meta-analysis		
B	Evidence from a single RCT or non-randomized study		
C	Evidence from consensus, expert opinion or case series		
KDIGO: Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group			
Strength of recommendation	Patients	Clinicians	Policy
1 (recommend)	Most people in your situation would want the recommended course of action and only a small proportion would not	Most patients should receive the recommended course of action	The commendation can be evaluated as a candidate for developing a policy or performance measure

Supplemental Table 3. Continued

2 (suggest)	The majority of people in your situation would want the recommended course of action, but many would not	Different choices will be appropriate for different patients; each patient needs help to arrive at a management decision consistent with her or his values and preferences	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	The true effect may be substantially different from the estimate of the effect
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth
GEAS: Systemic auto-immune disease group of the Spanish Society of Internal Medicine and the Spanish Society of Nephrology		
Quality level of evidence		
A	High	
B	Moderate	
C	Low	
D	Very low	
Recommendations grade		
1	Strong	
2	Weak	
NG	Not graded	
CARRA: Childhood Arthritis and Rheumatology Research Alliance		
A	Supported by randomized clinical trials (RCTs)	
B	Supported by non-randomized controlled studies or extrapolations from RCTs	
C	Supported by uncontrolled studies, extrapolations from non-randomized controlled studies, or marked extrapolation from RCTs (e.g. adults to pediatrics)	
D	Based on expert opinion