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Original article

Consensus of the Brazilian Society of Rheumatology for the diagnosis, management and treatment of lupus nephritis

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ABSTRACT

Objective: To develop recommendations for the diagnosis, management and treatment of lupus nephritis in Brazil.

Method: Extensive literature review with a selection of papers based on the strength of scientific evidence and opinion of the Commission on Systemic Lupus Erythematosus members, Brazilian Society of Rheumatology.

Results and conclusions: (1) Renal biopsy should be performed whenever possible and if this procedure is indicated; and, when the procedure is not possible, the treatment should be guided with the inference of histologic class. (2) Ideally, measures and precautions should be implemented before starting treatment, with emphasis on attention to the risk of infection. (3) Risks and benefits of treatment should be shared with the patient and his/her family. (4) The use of hydroxychloroquine (preferably) or chloroquine diphosphate is recommended for all patients (unless contraindicated) during induction and maintenance phases. (5) The evaluation of the effectiveness of treatment should be made with objective criteria of response (complete remission/partial remission/refractoriness). (6) Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers are recommended as antiproteinuric agents

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for all patients (unless contraindicated). (7) The identification of clinical and/or laboratory signs suggestive of proliferative or membranous glomerulonephritis should indicate an immediate implementation of specific therapy, including corticosteroids and an immunosuppressive agent, even though histological confirmation is not possible. (8) Immunosuppressives must be used during at least 36 months, but these medications can be kept for longer periods. Its discontinuation should only be done when the patient could achieve and maintain a sustained and complete remission. (9) Lupus nephritis should be considered as refractory when a full or partial remission is not achieved after 12 months of an appropriate treatment, when a new renal biopsy should be considered to assist in identifying the cause of refractoriness and in the therapeutic decision.

Consenso da Sociedade Brasileira de Reumatologia para o diagnóstico, manejo e tratamento da nefrite lúpica

Palavras-chave:
Lúpus eritematoso sistêmico
Nefrite lúpica
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RESUMO

Objetivo: Elaborar recomendações para o diagnóstico, manejo e tratamento da nefrite lúpica no Brasil.

Método: Revisão extensa da literatura com seleção dos artigos com base na força de evidência científica e opinião dos membros da Comissão de Lúpus Eritematoso Sistêmico da Sociedade Brasileira de Reumatologia.

Resultados e conclusões: 1) A biópsia renal deve ser feita sempre que possível e houver indicação e quando não for possível, o tratamento deve ser orientado com base na inferência da classe histológica. 2) Devem ser implementados medidas e cuidados idealmente antes do início do tratamento, com ênfase na atenção ao risco de infecção. 3) Devem-se compartilhar riscos e benefícios do tratamento com os pacientes e familiares. 4) O uso da hidroxicloroquina (preferencialmente) ou difosfato de cloroquina é recomendado para todos os pacientes (exceto contraindicação) durante as fases de indução e manutenção. 5) A avaliação da eficácia do tratamento deve ser feita com critérios objetivos de resposta (remissão completa/remissão parcial/refratariedade). 6) Os inibidores da enzima conversora da angiotensina ou bloqueadores dos receptores da angiotensina são recomendados como antiproteinúricos para todos os pacientes (exceto contraindicação). 7) A identificação de sinais clínicos e/ou laboratoriais sugestivos de GN proliferativa ou membranosa deve indicar início imediato de terapia específica incluindo corticosteroides e agente imunossupressor, mesmo que não seja possível comprovação histológica. 8) O tempo de uso dos imunossupressores deve ser no mínimo de 36 meses, mas eles podem ser mantidos por períodos mais longos. A sua suspensão só deve ser feita quando o paciente atingir e mantiver remissão completa sustentada. 9) Deve-se considerar NL refratária quando a remissão completa ou parcial não for alcançada após 12 meses de tratamento adequado, quando uma nova biópsia renal deve ser considerada para auxiliar na identificação da causa da refratariedade e decisão terapêutica.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease which ethiopathogenesis involves multiple genes and hormonal and environmental factors. SLE is a pleomorphic disease with wide phenotypic variability of presentation, severity and clinical course, usually progressing with periods of activity and remission. Most patients exhibit a relatively benign course, but overall survival is lower, when compared to the general population, with a standardized mortality ratio from 2.4 to 6.4.[1] The main causes of death are infection, disease activity, cardiovascular disease, kidney damage and cancer **(A)**.[1–3] The morbidity and mortality are particularly high in patients with renal impairment **(C)**.[2–9] Glomerulonephritis (GN) is the most frequent cause for the use of high doses of corticosteroids (CS) and immunosuppressants, being also the condition that requires more hospitalizations and the main factor related to increased mortality. Progression to end stage renal disease, or more recently, established renal failure (ERF), defined by a glomerular filtration rate (GFR) $\leq$15 mL/min, requiring renal replacement therapy, occurs in 10–30% of patients, especially those with proliferative glomerulonephritis (PGN).[10,11] At the same time, in SLE patients on dialysis, the 5-year survival is lower than that of individuals on dialysis without SLE.[9]

The renal involvement in SLE occurs clinically in about 60% of patients and can determine tubular, interstitial, vascular and glomerular changes; but is the involvement of the latter compartment that determines most of the signs and symptoms of lupus nephritis (LN) **(B)**.[12] Similarly to the demonstrations in other systems, LN also shows different degrees of severity, with periods of activity and remission, which determine the choice of therapeutic agents to be used **(B)**.[13] In clinical practice, it is not always possible to perform a kidney biopsy, although this is a relatively simple procedure when performed by experienced professionals.[14] The biopsy allows the recognition of diagnostic and prognostic markers that may influence the therapeutic choice. For patients not undergoing a kidney biopsy and for all patients in the course of evolution, clinical and laboratory markers that help characterize the severity and activity of GN are used **(B)**,[15] guiding the use of immunomodulatory and/or immunosuppressant agents.

The main goal of the treatment is to achieve a complete remission (CR), which is associated with a good long-term prognosis.[11,16] However, despite current therapeutic regimens, less than 50% of patients with LN achieve CR after the first 6 months of treatment **(B)**.[17–19]

This consensus aims to present the main recommendations for the clinical management of LN, involving diagnosis, prognosis, treatment (induction and maintenance), care during the use of pharmacological agents, immunosuppression-adjuvant therapy, refractory case approaches and identification of associated comorbidities, all contextualized to the reality of our country.

Materials and methods

This consensus was developed after a systematic review of the literature, in association with the opinion of 13 rheumatologists with clinical experience in LN, 11 of them being members of the SLE Commission of SBR, besides two guests (CAAS and EMNA). The systematic review of the literature, including the prior selection of a number of issues previously identified by the working group and the voting of recommendations, was performed according to a modified Delphi method. The databases included MEDLINE, SciELO, PubMed and EMBASE until November 2013. After consideration of the data obtained in the literature, the participants expressed their opinion on each topic in discussions *via* Internet, and voted on recommendations confidentially. Voting occurred in face-to-face meetings held in May and July 2014 in a hierarchical manner, according to the following alternatives: (a) I completely agree; (b) I agree with some reservation; (c) I agree with many reservations; (d) I reject with reservations; (e) I completely reject. In cases of non-agreement of at least 70% of the participants (for options a, b or c), new discussions were held, followed by adjustments for the recommendation and a new round of voting, until this minimum percentage was reached. For each recommendation, the percentages of agreement among the participants were informed. When possible, the levels of evidence were expressed according to the Oxford classification:

A –Experimental or observational studies of greater consistency.
B – Experimental or observational studies of lower consistency.
C – Case reports (non-controlled studies).
D – Opinion without critical evaluation, based on consensuses, physiological studies or animal models.

Renal biopsy

Recently, the ACR (American College of Rheumatology)[20] and the EULAR (European League Against Rheumatism), in combination with two European groups of Nephrology (European Renal Association – European Dialysis and Transplant Association)[21] published recommendations for the management of SLE patients with renal involvement, based on histological findings.

A renal biopsy should be performed whenever possible,[20,21] considering that clinical, immunological and laboratory parameters are not predictors of the histological findings.[20–22] This procedure may better guide the treatment and prognosis, and should always be performed by experienced and qualified professionals.[23]

EULAR recommends obtaining a renal biopsy whenever there is any sign of renal involvement, especially proteinuria ≥0.5 g/24 h accompanied by glomerular dysmorphic hematuria and/or cellular casts **(C)**.[21] ACR recommends a biopsy (unless strongly contraindicated) whenever there are signs of renal involvement with an elevated serum creatinine with no apparent cause (not related to SLE), proteinuria ≥1.0 g/24 h or an isolated proteinuria ≥0.5 g/24 h associated with hematuria and/or cellular casts **(C)**.[20] When GFR <30 mL/min, the decision to obtain a biopsy should take into consideration the normal kidney size (>9 cm) and/or evidence of active renal disease.[21]

The histological pattern of LN should follow the new definitions, revised by international societies of nephrology and pathology,[24,25] known as the classification of lupus nephritis of the International Society of Nephrology/Renal Pathology Society 2003 (ISN/RPS 2003) **(C)** (Table 1). According to these guidelines, glomeruli and the tubulointerstitial region should be evaluated, with descriptions of activity and chronicity, besides the vascular component that is usually associated with antiphospholipid antibody syndrome (APS) **(C)**.[20,21,24,25] A sample is considered adequate if it has more than 8 glomeruli, and immunofluorescence or immunohistochemistry is recommended to identify complement and immunoglobulin deposits. If possible, electron microscopy should also be performed, because this examination facilitates the evaluation of proliferative and membranous lesions **(C)**.[21,24,25]

Usually there is no need for a repeat biopsy in the case of new outbreaks of renal activity[26,27] because this procedure does not provide additional information about renal outcomes in the long term.[28] However, in patients without adequate response to treatment, repeat biopsy may help in the identification of the cause of refractoriness[20,21,29] and assist in therapeutic decision.[21,29]

In this consensus, we recommend obtaining a renal biopsy whenever the patient exhibits an elevated serum creatinine with no apparent cause, and when this finding is potentially associated with SLE, with isolated proteinuria ≥1.0 g/24 h or

Table 1 – Classification of the International Society of Nephrology/Renal Pathology Society 2003 for lupus nephritis.

Class I – minimal mesangial LN Normal glomeruli under light microscopy (LM), but with immune deposits under immunofluorescence (IF).
Class II – proliferative mesangial LN Pure mesangial hypercellularity of any degree or mesangial matrix expansion under MO with immune deposits in the mesangium. There may be few and isolated subepithelial or subendothelial deposits visible under IF or electron microscopy (EM), but not under OM.
Class III – focal LN Active or inactive, focal, segmental or global, endo- and extracapillary glomerulonephritis (GN) involving <50% of all glomeruli, typically with subendothelial immune deposits, with or without mesangial alterations. It is further classified into: A, active; A/C, active/chronic; C, inactive chronic.
Class IV – diffuse LN Active or inactive, segmental or global, endo and extracapillary glomerulonephritis (GN) involving ≥50% of all glomeruli, typically with subendothelial immune deposits, with or without mesangial alterations. It is divided into segmental diffuse (IV-S), in which ≥50% of glomeruli involved present segmental lesions (involving less than half of the tuft) and into global diffuse (IV-G), in which ≥50% of glomeruli involved have global lesions (involving more than half of the tuft). This class includes cases with diffuse wire-loop deposits with little or no glomerular proliferation. It is further classified into: A, active; A/C, active/chronic; C, inactive chronic.
Class V – membranous LN Global and segmental subepithelial immune deposits or its morphological sequelae under OM and IF or EM, with or without mesangial changes. May occur in combination with class III or IV.
Class VI – advanced sclerosis Global glomerular sclerosis in ≥90%, with no residual activity.

Adapted from Weening et al., 2004.[24,25]

AB, antibody; GN, glomerulonephritis; IF, immunofluorescence; EM, electron microscopy; OM, optical microscopy; LN, lupus nephritis.

proteinuria ≥0.5 g/24 h associated with glomerular dysmorphic hematuria and/or the presence of cellular casts. These changes must be confirmed in a second biopsy (Table 2).

Evaluation of LN without renal biopsy: inference of histological class for a therapeutic decision and progression assessment

In most cases of NL, clinical, serologic and laboratory tests cannot accurately predict the histological findings, nor could they differentiate other possible causes of renal disease.[20–22] However, this dataset can be very useful in the clinical monitoring of nephritis and, in particular, assisting in the diagnosis of renal disease activity.[30]

The active urinary sediment, defined by the presence of hematuria (with a dysmorphic glomerular pattern), leukocyturia and presence of cellular casts, is admittedly one of the most important parameters for characterization of an active glomerulonephritis. Proteinuria, measured in 24 h or inferred by the relationship proteinuria/creatininuria (R P/C) in a random spot urine sample, may also indicate inflammatory activity.[30,31] The positivity or increase in titers of anti-dsDNA antibodies and low blood levels of complement, especially with low levels of C3, are also considered as an evidence of renal involvement, but these indicators should not be used in isolation to define this condition.[30] The reduction in glomerular filtration, nephrotic proteinuria and the presence of hypertension (HBP) suggest greater severity and a worse prognosis.[32,33]

In patients with APS associated with SLE, the presence of HBP and renal dysfunction should be considered as an alert to the possibility of a vasculopathy associated with antiphospholipid antibodies (aPl), especially when there are no signs of GN detected in urinary sediment.[34]

In recent years, several new noninvasive urinary biomarkers were described, including lidocalin-type prostaglandin D synthase (L-PGDS), α(1)-acid glycoprotein (AAG), transferrin (TF), ceruloplasmin (CP), neutrophil gelatinase-associated lipocalin (NGAL) and monocyte chemotactic protein 1 (MCP-1).[35] The combination of these biomarkers with laboratory parameters of renal function is promising to histologic class inference and to quantify activity and chronicity **(B)**.[35] The anti-ribosomal P antibody, in the absence of anti-dsDNA, has also been described as possibly associated with membranous nephritis in SLE patients, and with a predictive value of better renal prognosis **(B)**.[36,37]

The determination of histological class based only on clinical and laboratory parameters is limited. However, the sum of some elements may suggest one or another particular class – a necessary inference in daily clinical practice. Patients exhibiting an elevated creatinine (with no other apparent cause), associated with proteinuria >0.5 g/24 h or R P/C >0.5 and recent HBP and/or an active urinary sediment (dysmorphic hematuria and/or cellular casts), and hypertension, particularly if accompanied by low blood levels of complement and anti-dsDNA, probably present PGN (class III or IV). On the other hand, it is more likely that patients with proteinuria >2 g/24 h or R P/C >2, with no urinary sediment activity or hypertension, especially without anti-dsDNA and with normal complement levels, are suffering from membranous GN (class V). However, we cannot exclude an early-stage proliferative lesion, or even its association, in these patients. In exclusively mesangial lesions (Class I or II), proteinuria is generally <1 g/24 h or R P/C <1, serum creatinine levels are normal and patients usually are not hypertensive. However, in patients with these changes, we cannot exclude the possibility of early-phase proliferative or membranous GN. Except in these typical forms, class inferences have very little accuracy, and this is also valid for the possibility of class overlapping (Table 2).

Table 2 – SBR recommendations for lupus nephritis management.

Recommendations	Agreement
Indications for renal biopsy	
Perform a renal biopsy whenever possible and when indicated.	a) 1.0
Elevation of serum creatinine with no apparent cause and potentially associated with SLE.	a) 1.0
Isolated proteinuria >1.0 g/24 h (or R P/C >1.0).	a) 1.0
Proteinuria ≥ 0.5 g/24 h associated with glomerular dysmorphic hematuria and/or cellular casts.	a) 1.0
Note: changes must be confirmed with a second test.	a) 1.0
Inference of histological class	
Possibility to make some inference based on clinical and laboratory criteria.	a) 0.54; b) 0.46
Creatinine elevation (with no other cause) associated with proteinuria >0.5 g/24 h or R P/C >0.5 and recent HBP and/or active urinary sediment: consider as proliferative GN (class III or IV), especially if accompanied by low blood levels of complement and anti-ds-DNA AB.	a) 0.9; b) 0.1
Proteinuria >2 g/h or R P/C >2, with no activity in urinary sediment or hypertension, and mostly without anti-ds-DNA AB and normal complement levels, suggestive of membranous GN (class V). However, we cannot exclude proliferative lesion.	a) 0.9; b) 0.1
Proteinuria <1 g/24 h or R P/C <1 with normal creatinine and without HBP suggests mesangial GN (class II). However, we cannot exclude initial-stage proliferative or membranous GN.	a) 1.0
Also consider the possibility of other causes of renal injury at all stages of evolution of LN (APSN, renal vein thrombosis, TIN, ATN, diabetic nephropathy, hypertensive nephropathy and/or nephropathy secondary to infection).	
Care for immunosuppressed patients	
Vaccine update.	a) 1.0
Avoid live virus vaccines.	a) 1.0
Tuberculosis (latent or disease) screening.	a) 1.0
Continuous evaluation for infections throughout the period of immunosuppression.	a) 1.0
Share risks and benefits of treatment with patient and his/her family.	a) 1.0
Guidance on contraception (avoiding estrogens), and risks of pregnancy during treatment.	a) 1.0
Empirical antiparasitic treatment.	a) 1.0
Consider prophylaxis for *Pneumocystis jirovecii* in cases of previous infection or in patients with lymphopenia <500 mm^3.	a) 1.0
Prescribe hydroxychloroquine for patients, unless contraindicated.	a) 1.0
Obtain an informed and free consent form (IFCF).	a) 1.0
Response criteria	
The treatment efficacy evaluation should be made with objective criteria of response.	a) 1.0
Complete remission: proteinuria <0.5 g/24 h or R P/C <0.5 and normal GFR; or reduction ≤10% of previous value for the patient or ULN of method (if the first is not available) and a normal urinalysis.	a) 1.0
Partial remission: reduction >50% of initial proteinuria with a value <3.0 g/24 h or R P/C <3.0, normal GFR or reduction ≤10% of the previous value of the patient, or ULN of method (if the first is not available) and a normal urinalysis.	a) 0.9; b) 0.1

Agreement: the numbers in each recommendation express the percentages of agreement among the members, according to the classification used.
AB, antibody; GN, glomerulonephritis; HBP, systemic arterial hypertension; ULN, upper limit of normal; APSN, nephropathy of antiphospholipid syndrome; ATN, acute tubular necrosis; TIN, tubulointerstitial nephritis; R P/C, ratio proteinuria/creatininuria in a random urine sample; GFR, glomerular filtration rate.

For the purpose of analyzing the response to treatment, we established criteria that are similar to those adopted by EULAR[21] and ACR.[38] Complete remission (CR) was defined as a proteinuria <0.5 g/24 h or R P/C <0.5, and normal or reduced GFR <10% of the previous value of the patient or of the upper limit of normal (ULN) for the method (if the first option is not available) and a normal urinalysis. Partial remission (PR) was defined as a reduction of >50% of the initial proteinuria, with a value <3.0 g/24 h or R P/C <3.0, and a normal GFR or a reduction of <10% of the previous value or of ULN for the method (if the first option is not available) and a normal urinalysis (Table 2).

Care for immunosuppressed patients

The immunosuppression caused by disease and/or its treatment increases the risk of infection, including the opportunistics,[39] and often the differential diagnosis with disease activity is a challenging task in clinical practice.[40] Infections are associated with increased morbidity and mortality in SLE[2,3] and, therefore, prevention strategies, such as vaccination, use of antimicrobials and antiparasitic drugs, preferably before the start of immunosuppressive therapy, should be implemented. Moreover, tuberculosis can also be a factor of disease activation.[41] Risk factors for major infections

are: leukopenia/lymphopenia, low blood levels of complement, hypogammaglobulinemia, splenectomy, and the use of CS and immunosuppressants,[42] usual conditions during the whole treatment of LN, so that a continuous assessment must be made for the presence of infection throughout the period of immunosuppression.

On the other hand, it was demonstrated that the use of hydroxychloroquine (HCLQ) is associated with a lower frequency of infections in patients with SLE.[43] Due to the morbidity and mortality related to infections, the sharing of risks and benefits of treatment with the patient and his/her family is strongly sugested, as well as providing specific clarification on the medications used, including signing of an Informed Consent Form.

All patients should also be counseled about contraception and pregnancy risks during treatment (Table 2).

Vaccination

An update of the vaccination card should always be performed, preferably with the disease in an inactive period and before the implementation of any synthetic or biological immunosuppressive therapy.[44,45] Vaccines without living organism – (influenza IM); pneumococcal; tetanus; diphtheria; pertussis; Haemophilus type B; viral hepatitis A and B, poliomyelitis (inactivated – IPV); meningococcal; HPV; typhoid fever (IM); and rabies – are safe at any stage of treatment and often determine an adequate immunogenicity.[46,47] In this context, the most important vaccines are:

(a) Pneumococcal (23-valent polysaccharide): must be administered every five years[48] as recommended by the *Programa Nacional de Imunizações* (PNI) (National Immunization Program) of Brazil. However, the *Sociedade Brasileira de Imunização* (SBIM) (Brazilian Society of Immunization) in agreement with the Centers for Disease Control of the United States, has recommended that the vaccine used in immunosuppressed individuals must be the pneumococcal conjugate vaccine, followed by polysaccharide vaccine after 8 weeks (CDC, 2011);
(b) Influenza: the vaccine must be administered annually[49];
(c) Diphtheria and tetanus (dT): follow PNI guidelines.

The live virus vaccines (MMR, herpes zoster and yellow fever) should be avoided and used only in special cases, after a joint evaluation with an infectologist (Table 2).[42]

Antimicrobial prophylaxis

(a) Tuberculosis: the treatment of latent tuberculosis, especially in the case of positive epidemiological data, should be considered in cases with tuberculin test – PPD ≥5 mm (if the patient is using CS) or with a chest radiograph suggestive of prior untreated tuberculosis.[50]
(b) *Pneumocystis jirovecii*: indication of prophylaxis before the onset of immunosuppression in cases of previous infection by this organism and in patients with lymphopenia <500 mm^3, especially if associated with a genetic or acquired hypocomplementemia.[51]
(c) Antiparasitic agents: before immunosuppression, an empiric treatment with broad spectrum anthelmintics (*e.g.*, albendazole or ivermectin) is recommended, especially in patients with positive epidemiological data – an almost universal condition in our country (Table 2).

Mesangial glomerulonephritis (classes I and II) – induction and maintenance therapy

For most patients with mesangial GN, the treatment is offered only with CS and HCLQ. However, for those patients who experience persistent proteinuria >1.0 g/24 h (or R P/C >1.0), one must consider the combination of azathioprine (AZA) or mycophenolate mofetil (MMF) (Table 3).

Proliferative glomerulonephritis – remission induction therapy

Better-quality randomized controlled studies evaluating different treatment regimens in LN had as inclusion criteria the confirmation and classification of nephritis according to renal biopsy. This approach has the advantage of avoiding an aggressive treatment for mild cases, with no indicative factors of severity, as well as the implementation of ineffective treatments in patients with chronic and irreversible changes. It is recognized that the treatment is urgent and it must be intensive in proliferative forms of LN (classes III and IV, with or without association with class V), in which the risk of progression to renal failure is high.[21] The target to be achieved in six months (induction period) is CR.

Since studies published in the 80s, the superiority of cyclophosphamide (CY) has been acknowledged, as compared to the isolated use of CS in the treatment of PGN.[52] The use of CY for prolonged periods was more effective for the prevention of relapse and for maintaining renal function[53]; however, this drug is associated with multiple side effects, particularly gonadal insufficiency.[54]

In a controlled, randomized, multicentre study on LN (class III/IV and V[16%]), the effectiveness of MMF was not inferior to intravenous (IV) CY in a conventional scheme,[55] confirming earlier studies.[56,57] Meta-analyses also showed that CY and MMF have comparable efficacy **(A)**.[58–60]

Cyclophosphamide may be used in low doses (Scheme Euro Lupus Trial – ET), consisting of the administration of 500 mg IV every 2 weeks for 3 months (total dose of 3 g), followed by maintenance with AZA[61]; or at high doses (classical scheme – "NIH") of 0.5–1.0 g/m^2 of body surface area (BSA) IV at monthly intervals for 6 months, followed by applications at quarterly intervals for another 18 months.[52] In a study comparing high-dose (for 12 months) *versus* low dose (for three months) of CY, both followed by AZA, the authors observed after 10 years no difference in the doubling of creatinine value, evolution to ERF and mortality.[7] It should be emphasized that these results were obtained in studies with European patients, whose severity of nephritis tends to be lower than that observed in African descendants.[10,61] A systematic review

Table 3 – SBR recommendations for the treatment of lupus nephritis including proliferative and mesangial types.

Recommendations	Agreement
Adjuvant measures for all histologic classes	
The use of hydroxychloroquine (preferably) or chloroquine is recommended for all patients (unless contraindicated) during induction and maintenance phases.	a) 1.0
ACE inhibitors and/or ARBs are recommended as antiproteinuric agents for all patients (unless contraindicated).	a) 1.0
Prevent and treat risk factors for cardiovascular disease: physical inactivity, dyslipidemia (LDL <100 mg/dL), diabetes, obesity, HBP (BP <130 × 80 mmHg) and smoking.	a) 1.0
Encourage a diet rich in calcium and consider supplementation, when necessary.	a) 1.0
Consider supplementation of vitamin D (25 (OH) (if vitamin D serum levels >30 ng/mL).	a) 1.0
Avoid nephrotoxic drugs, especially non-steroidal anti-inflammatory agents.	a) 1.0
Protocol for induction and maintenance in mesangial GN (classes I and II)	
For patients with persistent proteinuria ≥1.0 g/24 h or R P/C ≥1.0: induction and maintenance of remission, consider AZA or MMF.	a) 1.0
Protocol for induction in proliferative GN (classes III and IV)	
Target to be achieved in six months is RC.	a) 1.0
The identification of clinical and/or laboratory signs suggestive of proliferative GN should indicate an immediate specific therapy, including CS and an immunosuppressant agent, even in cases when histological confirmation is not possible.	a) 1.0
The treatment should begin with MP pulse therapy [0.5–1.0 g IV (or 10–30 mg/kg/day in PSLE patients) for 3 days]. Doses of prednisone between 0.5 and 1.0 mg/kg/day for 3–4 weeks, with subsequent reduction and with the goal of achieving a dose of 5–10 mg/day for 6 months.	a) 0.9; b) 0.1
In conjunction with CS, include CY IV 0.5–1.0 g/m^2 BSA monthly for 6 months, or CY IV 0.5 g every 15 days for 3 months, or MMF (2–3 g/day).	a) 0.9; b) 0.1
In patients with severity criteria, consider CY as a first option, taking into account its availability, absorption and tolerance to medication and treatment adherence.	a) 0.9; b) 0.1
Lack of response or worsening of renal disease after 3 months of an appropriate therapy suggests the need to consider an early change of the induction protocol.	a) 1.0
After 6 months of treatment at this stage, if CR or PR were not achieved, the patient should be considered as refractory to induction; in this case, a new therapy with MP and replacement of CY by MMF, or of MMF by CY, are recommended.	a) 1.0
Protocol for maintaining proliferative GN (classes III and IV)	
AZA or MMF are indicated for patients who have achieved CR or PR in the induction phase.	a) 1.0
These medications must be used for at least 36 months, but they can be kept for longer periods. Their suspension should only be performed after achieving and maintaining a complete and continuous remission.	a) 1.0
The doses of corticosteroids should be reduced progressively and, if possible, discontinued, ideally after achieving and maintaining a complete and sustained remission.	a) 0.9; b) 0.1

Agreement: the numbers in each recommendation express the percentages of agreement among the members, according to the classification used.
AZA, azathioprine; ARB, angiotensin receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; CY, cyclophosphamide; CS, corticosteroids; GN, glomerulonephritis; HBP, systemic arterial hypertension; MMF, mycophenolate mofetil; MP, methylprednisolone; CR, complete remission; PR, partial remission; R P/C, proteinuria/creatininuria ratio in a random urine sample; BSA, body surface area; GFR, glomerular filtration rate.

of ten randomized controlled trials found that low doses of CY, when compared to higher doses, had similar efficacy in reducing relapses, but with lower infection rates **(A)**.[62]

The use of CY PO was evaluated retrospectively in a series of patients with LN (class III, IV and V). The dose of 1.0–1.5 mg/kg/day for an average use of 4 months was effective in controlling LN, with frequency of side effects and the need for discontinuation of the medicament occurring in less than 10% of the patients, without difference in response between Euro- and African descendants.[63] Previous studies have shown efficacy of CY PO in Chinese patients, comparable to CY IV **(C)**.[64,65]

In a subgroup exploratory analysis of ALMS study, it was observed that although CY and MMF IV have presented similar efficacy, race, ethnicity, and geographic region factors seem to have influenced the response to treatment of LN. Groups of African American and Hispanic patients appear to have had a better response to MMF *versus* CY, and Asian patients had more side effects to MMF. But, as this was a subgroup analysis, these results cannot be considered conclusive **(C)**.[66]

In another *post hoc* analysis evaluating only 32 patients with severe renal impairment (creatinine clearance <30 mL/min) it was observed that the reduction of proteinuria and serum creatinine was comparable in patients using MMF and CY, with no significant difference in the frequency of side effects **(C)**.[67]

There is only one randomized controlled trial specifically designed to include cases of severe NL (GFR 25–80 mL/min or with crescent cells/necrosis in more than 25% of the glomeruli), in which high doses of CY IV associated with pulsed methylprednisolone (MP) were effective **(C)**.[68] Thus,

there are virtually no studies designed to evaluate the efficacy of MMF in these patients with severely impaired renal function.

The use of AZA as induction therapy in PGN is not recommended, because studies showed less effectiveness *versus* CY in this phase of treatment.[52,69] One study with repeated renal biopsy also showed that AZA was less effective in preventing the evolution to glomerular fibrosis.[69] However, AZA may be a therapeutic option in LN for Euro-descendants without predictors of severity and who do not tolerate CY or MMF, despite the higher risk of nephritis reactivation when comparing this agent to CY **(C)**.[69]

In women with LN who still wish to become pregnant, it is recommended preferably the use of MMF, as CY is associated with an increased risk of infertility, particularly in those women over 30 years and that had a prolonged use of this agent (approximate risk: 60%). However, MMF is formally contraindicated during pregnancy because its teratogenicity; and it must be emphasized the need for an effective contraception during its use. The use of CY for shorter periods (6 months) in young women, even at high doses, is associated with lower rates of infertility (4.3–10%),[7,54] a percentage similar to the Eurotrial scheme (4.5%).[7] Given the greater number of side effects with MMF use in Asians, doses ≤2 g/day are recommended in these patients. Given that some studies showed a worse response of CY in African-descendant and Hispanic patients, it may be advantageous the use of MMF in these cases. However, we should point out that a study specifically targeted to the Brazilian population with the use of this agent has not yet been published (Table 3).

Corticosteroids

Although in most studies CS were administered PO at doses of 0.5–1 mg/kg/day with gradual reduction, pulse therapy IV with MP for three days at the beginning of treatment could allow the subsequent use of lower doses of CS PO, as shown by Houssiau.[70] In order to reduce the side effects of high doses of CS, and also to allow a more rapid control of the inflammatory process, the use of MP at a dose of 0.5–1.0 g/day IV (or 10–30 mg/kg/day for pediatric patients) for 3 days is recommended, keeping the prednisone dose in 0.5–1.0 mg/kg/day for 3–4 weeks, followed by a progressive reduction, aiming to achieve doses of 5–10 mg/day after six months. Some extrarenal manifestations may require maintaining higher doses for longer periods, but due to the high frequency of adverse effects of CS, every effort should be made for reducing the daily dose. Patients with worse prognosis factors, *e.g.*, presence of cellular crescents and of necrosis, as well as those with higher creatinine levels, should receive higher doses of prednisone (1.0 mg/kg/day).[20]

In the case of achieving only PR after 6 months of an appropriate treatment, the induction phase may be extended from 7 to 9 months, according to clinical judgment.

After six months of induction treatment, if CR or PR has not been achieved, the patient is considered with refractory LN and a new induction therapy with MP and replacement of CY by MMF or MMF by CY is recommended (Table 3).

Proliferative glomerulonephritis – maintenance treatment

Although there is no evidence to establish the duration of the induction phase, most authors and international consensuses consider the period of six months.[20,71] At the same time, changing the therapeutic regimen for that of maintenance phase depends on CR or PR achievement. In some instances, even after the first six months of induction, a second scheme will be required until CR or PR is reached. Controlled studies that have addressed the duration of this phase are also lacking, but most authors agree that it should last 24–48 months. For patients with PGN, there are two major acknowledged alternatives for patient maintenance: AZA or MMF, both associated with low-dose prednisone (5–10 mg/day). The maintenance with CY IV every 3–4 months has not been used anymore, due to its side effects and also because the available options (AZA or MMF) have proven reasonably safe, with few side effects in the long term.

These two immunosuppressive agents were compared in two studies, MAINTAIN[72] and Aspreva Lupus Management Study – ALMS.[71] The designs of these studies were different and did not show the same outcomes. The MAINTAIN study included European Caucasian patients and did not show significant differences between drugs. On the other hand, the ALMS study, which selected only patients who had achieved good responses in the induction phase with CY IV or MMF for six months and that occurred in little more than 50% of those patients included, showed superiority of MMF *versus* AZA in preventing new episodes of renal activity.

EULAR recommends that patients with good responses to induction therapy for LN should use MMF (2 g/day) or AZA (2 mg/kg/day) for at least three years, while other authors recommend at least five years, with discontinuation of the drug in a very gradual manner and under monitoring.[73,74] The discontinuation of this medication should be gradual and initiated always by CS.[21]

ACR also recommends that patients who responded to induction therapy have a maintenance treatment with AZA 2 mg/kg/day or MMF 2 g/day, combined with low doses of CS. According to ACR, the existing data are insufficient to recommend the time to dose reduction or discontinuation of medication **(A)**.[20]

In summary, in the maintenance therapy of patients with PGN with complete or partial response in the induction phase, they should be treated with AZA or MMF, and the choice should be evaluated case by case. Mycophenolate sodium may also be an option to mycophenolate mofetil, if there is intolerance to this latter drug.

Facing the possibility of pregnancy, it is preferable to administer AZA, considering the teratogenicity of MMF. Due to the high cost of MMF and the favorable results for those milder forms of LN, patients without markers of severity of LN and who have had a complete response can be treated with AZA as first choice in their maintenance phase.

Results of some studies and, especially, the opinion of some authors suggest that AZA could be administered preferably in Euro-descendants,[75] and MMF in African descendants (Table 3).[66]

Membranous glomerulonephritis – induction treatment

Membranous GN (MGN) is present in 10–20% of cases undergoing biopsy. This disease can occur alone or in association with other histological classes.[76] The usual expression of MGN is the presence of proteinuria and edema without concomitant systemic manifestations, complement consumption or presence of anti-ds-DNA **(D)**.[77] the classic features of GN, as hematuria (dysmorphic), cellular casts, HBP and early elevation of serum creatinine, are infrequent. As with other classes, MGN can also progress from a "silent" type, including a slightly elevated proteinuria.[78] On the other hand, nephrotic syndrome (NS) occurs in up to 75% of patients,[79] representing a greater risk of venous thrombosis (3–22%), including renal veins (a still greater risk in patients with aPl),[80,81] coronary artery disease (RR = 2.8) and acute myocardial infarction (RR = 5.5).[82] The association of MGN with proliferative forms determines a worse prognosis and, even in isolated forms, 7–53% of patients progress to ERF in 10 years **(C)**.[80,82] Thus, it is understood that despite MGN not being the most aggressive histological class in LN patients, we should not consider it as a mild form of renal involvement.

Nonetheless, there are few studies available in the literature, and most of them evaluating small series, with short periods of observation and varied treatment regimens with respect to doses of CS, concomitant use of MP, use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) and especially with heterogeneity of response criteria (reduction in proteinuria *versus* CR/PR rates).

AZA is one of the more often used immunosuppressants in the treatment of SLE patients and, by having a better safety profile than other agents, this drug has been long used as a CS-sparing agent and even in the treatment of milder GNs. However, few prospective studies with this drug were published. In an open-label, prospective, multicenter study with 38 Asian patients on AZA associated with prednisone (without pulse therapy with MP, or ACE inhibitors or ARBs), the results were analyzed at 12 months with respect to CR (whose criterion was: stable or improved serum creatinine and proteinuria <1.0 g/24 h) or PR (reduction in proteinuria of at least 50% with sub-nephrotic level) rates. CR was achieved in 67% and PR in 22% of patients (refractoriness in 11%). The authors concluded that the results with AZA were similar to, or better than, those obtained with other regimens.[83]

Evidence of response to cyclosporine (CsA) was obtained in a few studies, each with a small number of patients. One open-label study followed 10 patients treated with CsA associated with prednisone for 24 months. The only response criterion was the intensity of proteinuria decrease, but in some patients, an increase in creatinine, secondary to this agent, was observed. Thus, CsA does not seem to be a suitable option, except for refractory cases, with its use as an alternative therapy.[84]

In some studies, CY has been used for induction in cases of MGN. One of these studies prospectively followed 20 patients with MGN and NS; the induction was done with oral CY (2.0–2.5 mg/kg/day) for 6 months in combination with prednisone, with sequential reduction and maintenance with AZA (without adjuvant therapy with ACEI and/or ARB or pulse therapy with MP). The response was based on the achievement of CR (proteinuria <0.3 g/24 h, stable serum creatinine and a normal urinalysis) or PR (proteinuria >0.3 and <3.0 g/day, a stable creatinine). In 12 months, CR and PR were achieved in 55% and 35% of patients, respectively.[79]

Cyclophosphamide was also evaluated in a randomized controlled study comparing this drug with CsA and with prednisone alone for induction of remission in GNM patients with NS. CY IV was administered every two months for one year (0.5–1.0 g/m^2 BSA) and CsA daily (5 mg/kg/day) for 11 months; both medications were associated with prednisone and ACE inhibitors, as decided by the assistant physician. CR and PR rates obtained in 12 months with CY were 40% and 20%, respectively, compared with 50% for CR and 30% for PR obtained for CsA and 13% for CR and 23% for PR with prednisone alone. Both immunosuppressants were superior to CS used alone ($p = 0.002$); however, throughout the observation period (12 months), there were more relapses with CsA *versus* CY ($p = 0.02$) **(B)**.[85]

MMF was used for induction of remission in GNM, although in a few studies with a small number of cases, most of them with no more than 20 patients. In 2010, a study gathered data from two multicentric randomized controlled trials, with similar protocols previously published which evaluated responses of the induction of remission in 6 months with regimens including CY or MMF in patients suffering only MGN ($n = 84$). Patients were treated with CY IV (0.5–1.0 g/m^2 BSA monthly); MMF was administered at a dose of 2–3 g/day, both for 6 months. No pulse therapy with MP was used. The majority of patients were treated with ACE inhibitors. There was no difference between groups regarding the percentage change in proteinuria and serum creatinine, and CR was achieved by only 1 (2.5%) patient, while PR was achieved by 60% of patients in both groups. The analysis was limited to patients who completed treatment (analysis per protocol); furthermore, 23% of cases were lost to follow up during the observation period after six months (induction); nevertheless, the authors assumed that the induction treatment for GNM with MMF have been as effective as with CY,[86] although in both groups (CY and MMF) the rates of complete/partial remission were low **(B)**.

MMF was also used for induction of remission in patients with MGN as compared to tacrolimus (TAC). Yap et al. studied 16 patients with GNM and NS whose treatment was done with MMF (7 cases) or TAC (9 cases), both associated with prednisone, whose initial dose was 0.8 mg/kg/day (without association of ACEI or ARB). In both groups an improvement in proteinuria was observed, but remission rates were only determined at 24 months (CR for MMF and TAC, 57% and 11%, respectively, and PR for MMF and TAC, 11% and 44%, respectively). The authors demonstrated that the time to reach a (complete) response to treatment was 15.3 months for MMF and 21.7 months for TAC.[6]

It is also likely that, in cases of MGN, the concomitant use of hydroxychloroquine (HCLQ) during induction treatment is valid, as suggested by evaluation data from a prospective cohort that included 29 patients with a recent diagnosis of this histologic class (34.5%) or in combination with PGN (65.5%). Immunosuppressive treatment was done with MMF;

Table 4 – SBR recommendations for the treatment of membranous nephritis.

Recommendations	Agreement
Protocol for induction in membranous GN (class V)	
CR or PR are the targets to be achieved in six months.	a) 1.0
Immunosuppressants are recommended for all patients, because they are more effective than CS as monotherapy.	a) 1.0
Attention should be given to the exclusion of thromboses, including into renal veins, which are frequently present with positivity for aPl.	a) 1.0
The treatment should begin with MP pulse therapy [0.5–1.0 g IV (or 10–30 mg/kg/day in PSLE patients) for 3 days] followed by prednisone (0.5–1.0 mg/kg/day) for 3–4 weeks, with subsequent reduction and with the goal to achieve a dose of 5–10 mg/day within six months.	a) 1.0
In conjunction with CS, CY IV 0.5–1.0 g/m^2 BSA monthly for 6 months, or CY IV 0.5 g every 15 days for 3 months, or MMF (2–3 g/day) and AZA (2 mg/day) should be included.	a) 0.9; b) 0.1
Lack of response after 3 months of an appropriate therapy indicates the need to consider an early change of induction protocol.	a) 0.9; b) 0.1
After 6 months of induction treatment, if CR or PR have not been achieved, LN is considered refractory, and a new induction therapy with MP and an exchange of the immunosuppressive agent (CY, MMF or AZA) are recommended.	a) 1.0
Protocol for maintenance in membranous GN (class V)	
The modification of the treatment regimen for that of the maintenance phase depends on achieving CR or PR.	a) 1.0
AZA or MMF are indicated for patients who have achieved CR or PR in the induction phase.	a) 1.0
For patients who have not achieved a favorable response with AZA or MMF, switching to one another, or the substitution by a calcineurin inhibitor or rituximab, should be considered.	a) 1.0
These medications must be used for at least 36 months, but they can be kept for longer periods. Their suspension should only be performed after achieving and maintaining a complete and continuous remission.	a) 1.0
The doses of corticosteroids should be reduced progressively and, if possible, discontinued, ideally after achieving and maintaining a complete and sustained remission.	a) 0.9; b) 0.1

Agreement: the numbers in each recommendation express the percentages of agreement among the members, according to the classification used.
aPl, antiphospholipid antibodies; AZA, azathioprine; CY, cyclophosphamide; CS, corticosteroids; GN, glomerulonephritis; MMF, mycophenolate mofetil; MP, methylprednisolone; LN, lupus nephritis; CR, complete remission; PR, partial remission; BSA, body surface area.

and among the 11 patients (38%) achieving complete renal remission in 12 months, seven had been treated with HCLQ compared with four patients without HCLQ ($p = 0.036$) **(C)**.[87]

In summary, we can admit that, in relation to MGN, there exists little scientific evidence to guide our clinical decisions, but it is likely that we should not regard them as mild forms of LN (Table 4).

Membranous glomerulonephritis – maintenance treatment

Just as in PGN, the maintenance treatment in cases of MGN also includes an immunosuppressive agent such as AZA or MMF, in combination with prednisone at progressively lower doses. Except for the ALMS study, there are no other randomized controlled trials examining AZA in the maintenance of remission in patients with MGN. Nevertheless, this agent has been widely used in most centers and Mok, in 2009, published the results of an open-label study with an observation period of 12 ± 6 years, in which all patients received induction with AZA and prednisolone. At the end of this long observation period, 35% had suffered relapses, and despite the need for the use of other immunosuppressants and for increasing doses of CS, 79% of patients had reached proteinuria values lower than 1.0 g/24 h with preservation of renal function, and 21% had a proteinuria higher than 1.0 g/24 h, although still in a subnephrotic level. The doubling of serum creatinine was observed in 8% and no patient progressed to ERF.[80] The study design was not ideal and, furthermore, only included Chinese patients; however, longer observation period and the favorable results allow us to admit that AZA has potential for use in the maintenance period **(C)**.

In the ALMS study,[71] which evaluated the maintenance phase with MMF or AZA, only patients who had achieved a favorable response in the induction phase were included. Most patients presented PGN, but about 15% exhibited pure MGN (18 cases in MMF group and 17 in AZA group), and for these patients, there are no specific response data.

The recommendations of EULAR and ACR suggest the use of either of the two medications **(D)**.[20,21] However, there is no publication or consensus establishing the maximum time of therapy, as well as how fast should be the reduction of the selected medication.

CsA has been evaluated in a randomized controlled study of induction and maintenance in the short-term (12 months) and, when compared to the isolated use of prednisone, the drug was more effective as regards the achievement of CR **(B)**.[85] However, the period of one year does not allow us to generalize the long-term response to this agent, especially if

one considers the high frequency of relapses during follow-up.

Some case series suggest the use of TAC, with less nephrotoxic potential in the patient's maintenance.[73,86] TAC could be used in special cases, such as in patients with normal renal function, negativity for aPl and persistently elevated proteinuria **(D)**.

Although the results with CY for the maintenance phase are not favorable compared with AZA or MMF, this medication can also be considered as an alternative of exception for maintenance in patients with known poor adherence to treatment **(D)**.[54,88]

Although the existing data in the literature are inconsistent, we understand that, for the maintenance phase, in addition to low doses of prednisone (ideally less than 10 mg/day), the most suitable agents are AZA (2 mg/kg/day) or MMF (2–3 g/day) in combination with HCLQ and an adjuvant therapy, as discussed below. In cases of MGN refractoriness, one can consider the use of calcineurin inhibitors, especially TAC and even RTX (Table 4).[21]

Renal involvement in the antiphospholipid antibody syndrome – diagnosis and treatment

Renal involvement can occur in primary or secondary APS, but the impact on prognosis in NL patients is still controversial.[89] aPl (anti-cardiolipins, anti-β2-glycoprotein I and lupus anticoagulant) may trigger intrarenal vascular lesions, determining the development of an APS associated nephropathy (APSN).[90]

The clinical picture is characterized by HBP, non-dysmorphic hematuria, proteinuria and worsening of renal function, which may be acute, with rapid progression to dialysis; or chronic, with slow and progressive evolution.[34,91–93] Acute renal artery thrombosis evolves mainly with an acute, severe, difficult-to-control hypertension, with or without low back pain, hematuria and acute renal failure.[90] On the other hand, renal vein thrombosis evolves mainly with proteinuria, which can reach nephrotic levels and, if it occurs in a complete and acute form, may be associated with a sudden low back pain and loss of renal function.[90]

Histopathological findings of APSN occur in 4–40% of SLE patients, being more frequent in patients with a previous diagnosis of APS.[34,89,91–94] Thrombotic microangiopathy is the most important acute injury; it is characterized by the presence of fibrin thrombi in glomerular capillaries and arterioles.[95] However, this injury is hardly found alone in patients with SLE, given the frequent overlapping with the histopathological changes of lupus nephritis.[34] The following chronic injuries are frequently found, although they have less specificity for the diagnosis of APSN: fibrous intimal hyperplasia and the presence of organized thrombi with or without recanalization, fibrous or fibrocellular occlusion of arteries and arterioles, tubular tireoidization characterized by atrophy of tubules with eosinophilic casts, and focal cortical atrophy with or without depression in the contour of the renal capsule.[95] The association of at least one acute or chronic histopathological finding with the presence of aPl defines APSN.[95,96]

The main differential diagnoses involve clinical conditions associated with clotting disorder or endothelial injury, such as thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, malignant hypertension, diabetes, scleroderma renal crisis, pre-eclampsia (PE), drug toxicity (CsA and chemotherapics) and renal transplant rejection.[34,91–96]

APSN was associated with lupus anticoagulant, ACL IgG and beta 2 GPI, and even more often when two or more of these aPl are present. However, during the vasoocclusive event these antibodies may be temporarily absent.[89,94,96]

Echography with color Doppler, scintigraphy with 99m Tc-DMSA and renal-vessel angiography assist in the identification of vascular involvement,[97] but the histopathological changes necessary for the diagnosis of APSN are identified by renal biopsy.[90]

All patients with SLE and aPl must control the risk factors for thrombosis: obesity, HBP, smoking, diabetes and dyslipidemia. Furthermore, these patients should avoid using estrogen contraceptives and hormone replacement therapy **(D)**.[98] In cases of venous thrombosis, anticoagulation is indicated indefinitely with an INR between 2.0 and 3.0 **(B)**.[99] In cases of arterial thrombosis, although with this same recommendation, some authors advocate the combination of anticoagulation with an antiplatelet agent or maintaining an INR above 3.0 in recurrent cases **(C)**.[98] The use of statins could also play an adjuvant role in the treatment of patients with APS **(C)**[98] and in patients with APSN, one should take into account the use of HCLQ and an antiplatelet agent, or anticoagulation **(B)**.[21,100]

Adjuvant therapy in lupus nephritis

In addition to the judicious use of immunosuppressive agents, both in induction of remission as in the maintenance phase, several other measures can also contribute positively, not only to obtain a better control of the inflammatory process, but also for the preservation of renal function in the long term. These measures consist of non-pharmacological and pharmacological recommendations listed below:

(a) Provide dietary counseling for the prevention and control of dyslipidemia, diabetes, obesity, HBP and osteoporosis. Encourage a balanced diet with proteins, lipids and carbohydrates, with low levels of salt **(D)**.[101]
(b) Consider vitamin D supplementation for all patients, with doses 800–4000 IU/day, with sequential adjustments; the serum levels of 25 (OH) vitamin D should remain above 30 ng/mL, although the clinical benefits are still negligible **(B)**.[102,103] Encourage a calcium-rich diet and consider its supplementation in cases where there is a need, especially in patients treated with CS and in postmenopausal women **(C)**.[101]
(c) Avoid the use of nephrotoxic drugs, particularly nonsteroid anti-inflammatory drugs (NSAIDs) **(C)**.[104]
(d) Strongly encourage smoking cessation **(C)**.[101]
(e) Establish a strict control of blood pressure, targeting levels at or below 130/80 mmHg, in which there is a greater chance of preservation of renal function **(A)**.[105] There is a preference for the use of ACEI or ARB, whose efficacies

are already well established for chronic kidney disease from other etiologies, (a)[106] and by their renoprotector and antiproteinuric effects. For that reason, these agents should be used even in patients with normal blood pressure levels. These drugs should be used with caution in cases of renal failure, since they can both cause hyperkalemia, but can also reduce the filtration pressure, with a subsequent decline in glomerular filtration rates **(A)**.[107–110] The association of these classes of antihypertensive drugs appears to have an even greater antiproteinuric effect; however, their impact on renal function in the long term has not yet defined.[110] The dose should be adequate for a maximum antihypertensive and antiproteinuric effect, with monitoring of potassium levels and renal function.[21]

(f) HCLQ is associated with higher rates of response to treatment, lower frequency of relapses, less severe kidney damage, reduction of thromboembolic events and increased survival; for all that, this medication is indicated for all patients with LN, both in their induction and in maintenance phases, unless contraindicated **(B)**.[20,21,87,111–114] An ophthalmologic evaluation should be performed before starting the treatment and should be repeated annually after five years of continuous use, except in cases with increased risk for development of retinal toxicity: elderly patients; renal or hepatic dysfunction; HCLQ >400 mg/day (>6.5 mg/kg/day); cumulative dose of HCLQ >1000 g; or presence of prior retinal disease or maculopathy. In these cases, it is recommended an interval of one year after starting the treatment with HCLQ.[115]

(g) Contraceptives containing estrogens should be avoided, especially during the active phase of the disease, or if the patient has a prior history of cardiovascular event or of increased risk of occurrence of thromboembolic events **(B)**.[116] The use of hormone replacement therapy also should be avoided **(B)**.[117]

(h) The treatment of dyslipidemia with statins should be recommended for patients with LDL cholesterol >100 mg/dL,[20] despite the small number of studies involving patients with SLE **(C)**.[118,119]

Refractory lupus nephritis

Despite the significant improvement in survival and in the preservation of renal function in most patients with LN, about 10–29% progress to ERF.[16,120] This progression can occur silently,[78] or may be evident through the evolution, being more common in patients who develop proliferative forms. In most studies, at the end of the induction period, less than 50% of the individuals achieve CR[74]; in clinical practice, a more realistic goal seems to be the achievement of PR or CR in a period from 6 to 12 months. Cases that do not achieve CR or PR after this time with an appropriate treatment could be classified as refractory to the regimen instituted.

There are various clinical and/or laboratory aspects related to refractoriness, and among these, the most common are: LN appearance in adolescence, male gender, low blood levels of complement, thrombocytopenia, elevated serum creatinine and massive proteinuria at diagnosis of LN.[11,121] Some factors are directly related to the aggressiveness of glomerular inflammatory events, such as new episodes of renal reactivation, particularly in the first 18 months of the disease, massive presence of crescents and/or vascular necrosis, histological transformation, or overlapping of lesions secondary to APS.[122–128] On the other hand, the refractoriness to LN may be related to other variables, such as delaying the start of an effective treatment, besides an impossibility of compliance with the treatment protocol, either by infection and/or temporary suspension of medicines, or by poor adherence to treatment.[29,129–131]

Patients with treatment-refractory lupus nephritis (RLN) should be further evaluated for the presence of other possible causes of persistent proteinuria or renal function loss, for example, use of nephrotoxic drugs, thrombosis of renal veins/arteries, infections, and decompensated hypertension or diabetes mellitus.[20,21,29] Another condition that deserves to be investigated is the overlapping of injury secondary to tubulointerstitial nephritis (TIN) related, in most cases, to the use of antimicrobial agents, too common in phases of increased immunosuppression. The most suggestive findings are hyperuricemia, hypokalemia, isosthenuria and renal tubular acidosis, as well as findings in the urinary sediment, which may be the presence of a greater quantity of kidney tubule cells in association with absence of findings indicative of active GN.

In isolated cases, other causes of proteinuria (glomerulopathy secondary to diabetes, syphilis, or to HIV or HCV infection) can also co-exist, or may arise during the evolution, giving the impression of refractoriness. In the case of RLN, a new renal biopsy may be indicated, because this procedure may allow the identification of lesions (like some of those above) or the characterization of the presence of exclusively chronic lesions – or characterization of the presence of pure chronic lesions – and in the latter case, further immunosuppression would not benefit the patient **(A)**.[131,132]

After identifying a non-treatment responsive, persistent inflammatory activity, RTX, an anti-CD20 monoclonal antibody, has been considered as therapeutic option. Published studies of case series involving patients classified as refractory to treatment have shown good response in 47–89% of cases.[132,133] In a prospective controlled trial with RTX (LUNAR), which included patients with LN, no superiority of RTX was demonstrated, when this drug was used in combination with MMF and CS *versus* placebo. But it is likely that these negative results were more due to the study design than the lack of efficacy of the drug.[134] Despite the lack of controlled studies demonstrating efficacy of RTX for treatment of LN, this drug has been used with good results in most reference centers, and currently its use is recommended in the consensuses of EULAR and ACR for patients considered refractory, both in cases of PGN and MGN.[20,21] The administration regimen and doses used are similar to the recommendations for rheumatoid arthritis (two doses of 1000 mg, with an interval of 15 days) **(C)**.

Calcineurin inhibitors, including CsA, TAC and sirolimus, are targeted to T cells. Among these agents, TAC in particular has been used alone or in combination with MMF in the treatment of patients with RLN, mainly in small series with patients of Asian origin. The results show a reduction in proteinuria and benefits in relation to extra-renal manifestations, in addition to the possibility of its use during

Table 5 – SBR recommendations for the treatment of refractory lupus nephritis, APSN, LN in pregnancy, pediatric LN and management in ERF.

Recommendations	Agreement
Refractory LN	
LN should be considered refractory when CR or PR is not achieved after 12 months of an appropriate treatment.	a) 1.0
Consider a new kidney biopsy to assist in identifying the cause of refractoriness and in therapeutic decision.	a) 0.9; b) 0.1
Rituximab is indicated, including cases with renal insufficiency.	a) 1.0
Tacrolimus (alone or in combination with MMF) may be used as an alternative.	a) 1.0
APSN associated to LN	
Search aPl in patients with LN, due to the possibility of an association with APSN.	a) 1.0
Maintain control of risk factors associated with vasoocclusive events in patients with aPl.	a) 1.0
In patients with APSN, maintain INR close to 3 and consider the concomitant use of antiplatelet agents.	a) 1.0
LN and pregnancy	
SLE female patients should be advised not to become pregnant until disease remission for at least six months and with a normal renal function.	a) 1.0
Pregnancy should be planned, including discontinuation of teratogenic medications (ARB, CY, coumarin, ACE inhibitors, leflunomide, MMF and MTX).	a) 0.75; b) 0.25
Monitoring should be done by a multidisciplinary team throughout pregnancy and puerperium.	a) 0.9; b) 0.1
HCLQ should be used throughout pregnancy.	a) 1.0
CS and AZA can be used during pregnancy.	a) 1.0
LN in PSLE patients	
The treatment of nephritis in PSLE patients is similar to that of adults, with dose adjustment of drugs (AZA = 2.0–3.0 mg/kg/day, MP = 20–30; MMF = 30 mg/kg/day or 600 mg/m^2 BSA/day); reinforce adherence at every visit.	a) 1.0
LN and ERF	
Maintain the treatment by a rheumatologist even after RRT, including the use of HCLQ with adjustment of its doses.	a) 1.0
Extrarenal recurrences can be treated with CS, AZA and MMF (with adjusted doses).	a) 1.0
Consider renal transplantation in patients with ERF (living or cadaver donor).	a) 1.0
Special consideration should be given to patients with aPl, because of the risk of thrombosis in arteriovenous fistula and vasoocclusive lesions with potential graft loss.	a) 1.0

Agreement: the numbers in each recommendation express the percentages of agreement among the members, according to the classification used.
aPl, antiphospholipid antibodies; AZA, azathioprine; ARB, angiotensin receptor blockers; CY, cyclophosphamide; CS, corticosteroids; ERF, established chronic kidney disease; ACEI, angiotensin-converting enzyme inhibitors; SLE, systemic lupus erythematosus; PSLE, pediatric SLE; MMF, mycophenolate mofetil; MP, methylprednisolone; MTX, methotrexate; LN, lupus nephritis; APSN, nephropathy of APS; CR, complete remission; PR, partial remission; INR, international normalized ratio; RRT, renal replacement therapy.

pregnancy (class C). However, its known diabetogenic effect should be taken into account, especially in patients with metabolic syndrome, in addition to the thrombotic risk in aPl positive patients **(C)**.[135–138] Belimumab, an anti-Blys antibody, was not specifically evaluated in patients with LN, but in the two main studies with this agent approximately 10% of patients had GN with proteinuria of up to 6 g/day. In the analysis of this subgroup, the drug was effective in reducing the levels of proteinuria[139,140]; however, more studies are needed to determine the efficacy of belimumab in this condition (Table 5).[141]

Nephritis in pediatric systemic lupus erythematosus (PSLE)

In about 10–20% of patients with SLE, the onset of the disease occurs before reaching the age of 18, when the condition is classified as PSLE,[142,143] characteristically showing greater activity, cumulative damage and disease severity compared to the adults. Additionally, these patients show high frequency of nephritis (in up to 80% of patients), neurological and hematological involvement and pulmonary hemorrhage.[143–147]

The treatment of nephritis in patients with PSLE is similar to the treatment of adults, but the severity and poor adherence determine a higher annual cost.[148] For this reason, in most centers of reference the current concept is that one should emphasize adherence across all visits, particularly in the case of adolescents.[147] A consensus document published in 2012 for induction therapy of lupus PGN in children and adolescents suggested three regimens with CS: oral, MP pulse therapy, or a combination of these two. However, studies are lacking to determine which of these schemes with CS is the most suitable for LN in the pediatric age group.[149] Prolonged exposure to corticosteroids should always be avoided, reducing doses of prednisone to $\leq$10 mg/day

between 4 and 6 months[21] and discontinuation of this drug, whenever possible. As is recommended for adult patients, HCLQ (5.0–6.0 mg/kg/day) is indicated in all cases of PSLE nephritis.[21] NL class I or II is generally controlled by CS and HCLQ. For class III or IV, induction therapy is indicated with a combination of HCLQ, CS and an immunosuppressive agent: CY IV (0.5–1.0 g/m^2 BSA/month for 6 months) or MMF (30 mg/kg/day or 600 mg/m^2 BSA/day). Maintenance therapy is suggested with AZA (2.0–3.0 mg/kg/day) or MMF.[150] A controlled study of LN in patients with PSLE suggests a therapeutic response similar to that obtained in studies of adults with CY or MMF.[151] CY seems to have a better risk-benefit profile in children and adolescents compared with adults,[150] with rare occurrences of primary ovarian failure (early menopause),[152] besides facilitating adherence.[149] The scheme with low doses of CY (ET) has not been evaluated in the pediatric population.[21] In cases of LN class V, drugs to reduce proteinuria – HCLQ, CS and immunosuppressants (CY, MMF or AZA) – are indicated,[153] despite the absence of adequate prospective studies evaluating these agents in pediatric populations.

Therapy with RTX (375 mg/m^2 BSA/week for 4 doses) has been used in refractory nephritis in PSLE patients,[154] but this scheme still requires studies with a larger number of patients. To date, there is still no study of belimumab in children and adolescents with lupus (Table 5).

Established chronic kidney disease in lupus nephritis

Currently, about 10–29% of patients with NL develop ERF, requiring renal replacement therapy (RRT).[16] Data from the United States Renal Data System (USRDS) show an increased prevalence of LN as a cause of ERF, from 1.13 to 3.2% in the age group 20–44 years, possibly related to an earlier definition of diagnosis (USRDS 2011). As with in other countries, in Brazil the mean age of patients with SLE at the onset of RRT is 38 years, much lower than that of patients with HBP (70 years), diabetes mellitus type 1 (51 years) and DM type 2 (64 years) (SBR 2014 census) **(A)**.

Complication rates of ERF in SLE patients are similar to other etiologies, but with higher frequency of fistula loss.[155] There is also the possibility of renal function recovery, which may occur after the implementation of dialysis in up to 28% of patients, usually in the first 6 months of dialysis.[156–158]

Most patients remain in remission, but outbreaks of activity may occur.[159–163] In fact, many symptoms of ERF may be confused with manifestations of SLE, such as fever, arthralgia, arthritis, alopecia, retinal changes, headache, serositis, hematological changes and reduced levels of complement fractions. In this sense, non-renal SLEDAI score (SLEDAInr) which is derived from SLEDAI, was validated as a useful instrument for assessing activity in patients on RRT[160,163,164]; this tool can be used in approaching those patients **(B)**. The survival of patients with SLE in RRT at 5 years ranges from 50 to 89% and the mortality is typically multifactorial.[157,158,162,164–172] Recently, a prospective study showed an independent association of disease activity at the start of RRT (with SLEDAInr >8) with increased mortality at 5 years **(B)**.[9]

Both CS and HCLQ can be employed for RRT, but myelotoxic drugs such as methotrexate and CY should be avoided. Other drugs such as AZA and MMF should be evaluated individually. Doses of immunomodulatory medications should not be corrected and do not require an additional dose after dialysis of the drugs already mentioned. There is no evidence on the safety of the use of immunobiologicals in SLE patients on dialysis, but it is likely that in the event of such drugs are used, there is no need of dosage readjustment, for these are high molecular weight compounds not removable by dialysis membranes **(D)**. All things considered, all SLE patients in RRT should be monitored by the rheumatologist.

Renal transplantation (TxR) from cadaveric source has proved a successful option since the 1950s, but its use in patients with LN was questioned by the potential risk of recurrence in the transplanted kidney. However, since 1975 it has been demonstrated that patients with SLE have a behavior similar to other patients (Advisory Committee, 1975); and since that time, TxR procedures have been performed with a very low frequency of recurrence.[173–175] Factors such as an association with APS or high aPl titles[176,177] and donor type[178] contribute to worse results, but these are not hindering factors to this procedure in these patients **(C)** (Table 5).

Lupus nephritis and pregnancy

The fertility rate in patients with SLE is considered normal; however, severe renal failure and high doses of CS can cause menstrual irregularities and amenorrhea.[179] At the same time, some immunosuppressants such as CY can induce ovarian failure, and this complication depends on the patient's age at onset of medication, duration of treatment and, additionally, the accumulated dose **(D)**.[180]

Pregnancy in patients with SLE should be considered as being a high-risk event; a multidisciplinary approach up to puerperium is recommended. Studies report a two to threefold increase in the frequency of disease activity during pregnancy **(C)**[181,182] and the occurrence of complications, especially in women with moderate to severe disease **(C)**.[183]

Women with SLE should be advised to avoid pregnancy until the disease is in remission for at least six months **(D)**[184–186] and that GFR >50 mL/min.[21] **(D)** Furthermore, the use of improper medication for the period is avoided.[187]

The risk of obstetric and neonatal complication is higher in women with SLE compared to the general population **(A)**.[188,189] However, in the last decades there has been a reduction from 43% (between 1965 and 1969) to 17% (between 2000 and 2003) in fetal loss **(D)**.[190] The frequency of miscarriage is increased and intrauterine fetal death is five times greater. Pre-eclampsia (PE) occurs in over 20% *versus* 7.6% in the population without lupus; on the other hand, intrauterine growth restriction (IUGR) is also common, especially with pre-existing renal disease. Prematurity affects up to 33% of pregnancies and is associated with HBP, use of CS at the time of conception and during pregnancy, disease activity, and presence of nephrotic proteinuria and aPl **(C)**.[188,191]

The independent risk factors for pregnancy loss in the cohort at Johns Hopkins Hospital were: proteinuria in 1st

trimester, thrombocytopenia, APS and HBP (C).[192] A systematic review on the outcome of pregnancy in patients with SLE, which included 1842 patients and 2751 pregnancies, identified as main maternal complications: lupus activity (25.6%), HBP (16.3%), nephritis (16.1%), PE (7.6%) and eclampsia (0.8%). Fetal complications included abortion (16.0%), fetal death (3.6%), neonatal death (2.5%) and IUGR (12.7%). The pregnancy failure rate was 23.4% and that of preterm babies, 39.4%. The meta-analysis showed a positive association between active nephritis and prematurity, HBP and PE (D).[193]

The main risk factors for PE are current or previous LN, PE, lupus active at the time of conception, presence of native anti-ds-DNA, low blood levels of complement, obesity and HBP (A).[188,191,194–196]

It is mandatory to differentiate activity of lupus from physiologic changes of pregnancy, and activity of PE from activity of NL, since the therapeutic approach will be absolutely distinct: immunosuppression or interruption (D).[196,197] This challenge is even greater when these conditions coexist.

During pregnancy, the risk of LN reactivation goes from 20 to 30%[186] and a multicenter study identified that LN increases the risk of miscarriage, premature birth, PE and IUGR, but this disease is not a contraindication for pregnancy, provided that a careful planning of conception, monitoring and multidisciplinary treatment occur (C).[198] In a series of Brazilian female patients with SLE, the frequency of fetal loss was significantly higher in those patients with LN and aPl (37%) and also in those with LN but without aPl (26.6%) compared to patients both without LN and aPl (12.2%) (C).[199]

A literature review conducted between 1962 and 2009 identified that all maternal deaths during pregnancy in patients with LN occurred during disease activity and showed a correlation with infection (41.2%) or lupus complications (29.4%) (D) (Table 5).[200]

SLE therapy in pregnancy

Pregnancy in a patient with SLE does not require any specific treatment (D)[20,21]; however, if the woman is being treated with HCLQ before conception, this agent should be continued during pregnancy, because it reduces the chance of reactivation and possibly also the incidence of neonatal lupus. NSAIDs should not be used in female patients with LN; these drugs increase the risk of miscarriage, premature ductus arteriosus closure and prolonged labor (D).[196,201]

Given that prednisone suffers placental inactivation, this is the preferred CS for use in this period (D).[202] Fluorinated CS, as dexamethasone and betamethasone, cross the placental barrier and should be used to induce fetal lung maturation in premature births (D).[203]

Prednisone should be used according to the seriousness of symptoms (D),[204] but in doses >20 mg/day this medication is associated with gestational diabetes, HBP, PE and premature rupture of membranes.[191] When CS are used in the periconception period, these drugs are associated with a 1.7-fold increase in the risk of cleft lip and palate (D).[205]

AZA (≤2 mg/kg/day) is considered safe during pregnancy, although this drug has been associated with IUGR and with higher rates of pregnancy loss (D).[201]

Due to the increased risk of thrombosis in women with NS, the use of low-dose aspirin (100 mg/day) is indicated throughout pregnancy, regardless of the presence of aPl.[188] Methotrexate, CY, MMF, leflunomide, ACEI, ARB and coumarin are considered drugs with proven teratogenic risk (D)[201,202,205]; thus, ideally these agents should be discontinued at least 3 months before conception (Table 5).

Conflicts of interest

The authors declare that they have not received any kind of advantage that resulted in influence on the concepts presented in this consensus and introduce the support received for work done, related to the topic as potential conflicts of interest. EM Klumb participated in clinical trials or received personal/institutional aid sponsored by the pharmaceutical industry [PI (Aspreva Pharm., BMS, GSK, Roche)]. CCD Lanna participated in clinical trials or received personal/institutional aid sponsored by PI (GSK and Roche). JCT Brenol participated in clinical trials or received personal/institutional aid sponsored by PI (Abbott, Astra Zeneca, BMS, GSK, Janssen, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis, Wyeth). EMN Albuquerque participated in clinical trials or received personal/institutional aid sponsored by PI (Aspreva Pharm., BMS, GSK, Roche). OA Monticielo participated in clinical trials or received personal/institutional aid sponsored by PI (Abbott, Anthera, Aspreva Pharm., BMS, GSK, Pfizer, Roche). LTL Costallat participated in clinical trials or received personal/institutional aid sponsored by PI (GSK). LC Latorre participated in clinical trials or received personal/institutional aid sponsored by PI (Aspreva, GSK and Roche). FM Ribeiro participated in clinical trials or received personal/institutional aid sponsored by PI (Aspreva Pharm., GSK). CAA Silva; EI Sato; EF Borba Neto; MFLC Sauma and ESDO Bonfá declare no potential conflicts of interest.

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