Protocol for the diagnosis and treatment of LUPUS NEPHROPATHY

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LUPUS NEPHROPATHY

1. General aspects

Systemic lupus erythematosus (SLE) is a relapsing-remitting systemic autoimmune disease in which genetic, immunoregulatory, hormonal and environmental factors are involved. Its manifestations are associated with the presence of autoantibodies against nuclear and cytoplasmic antigens, which result in the formation and deposition of immune complexes and other immune processes that trigger an inflammatory response that affects different organs. To be classified as affected by SLE, a patient must have antinuclear antibodies (ANA) ≥1:80 and score at least 10 points from the 2019 *European League Against Rheumatism* (EULAR) / *American College of Rheumatology* (ACR) criteria. Kidney lesions secondary to SLE are known as lupus nephropathy (LN). LN is the most important predictor of morbidity and mortality and can be present in almost 30% at the onset of the disease and up to 50-60% during the first 10 years. Patients who achieve complete renal response (CRR) have a 10-year renal survival of around 90%, compared to 45% of those patients who achieve partial renal response (PRR), and 15% of non-responders. Globally, 10-30% of patients progress to end-stage chronic kidney disease (CKD) requiring renal replacement therapy.

2. Clinical presentation

Generally, LN presents early in the course of the disease, between the first 6 months and 3 years, and may also be the first manifestation of SLE. The form of presentation is wide, the most frequent being the presence of proteinuria (95%, up to 40-50% in the nephrotic range), microscopic hematuria (80%), renal dysfunction (30-50%), arterial hypertension (30-50%), hematic casts in urine (10-30%) and rapidly progressive glomerulonephritis (<15%). From a clinical point of view, it can present as a nephrotic or nephritic syndrome or be asymptomatic. In addition, the patient may present extrarenal involvement associated with SLE. Male, black, and non-caucasian patients tend to have a more aggressive course of the disease.

3. Classification

The LN classification is the one proposed by the ISN/RPS in 2003 and revised in 2018, which classifies patients according to renal histological findings, evaluated by light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM) (Table 1). Modified NIH Chronicity and Activity Index provide additional prognostic information through semiquantitative scoring of histologic features (Tables 2 and 3).

Table 1. ISN/RPS 2003 LN classification (revised in 2018).

Category	Description	
Class I	Normal glomerulus by LM, with the presence of minimal immune complexes in IF and EM.	
Class II	Mesangial hypercellularity (≥4 nuclei surrounded by matrix in the mesangial area) associated with mesangial immune deposits; mesangial matrix expansion (LM).	
Class III	Endocapillary hypercellularity in <50% of the glomeruli.	It may present other lesions such as cellular, fibrous or fibrocellular crescents (involvement >10% of Bowman's capsule), fibrinoid necrosis or tubulointerstitial involvement. The lesions can be active (A), chronic (C) or mixed (A/C).
Class IV	Endocapillary hypercellularity in ≥50% of the glomeruli.	
Class V	Subepithelial immune deposits with GBM thickening; mesangial deposits can coexist, as well as be combined with classes III and IV.	
Class VI	Advanced sclerosis (≥90% glomeruli).	

Table 2. Modified NIH Activity Index.

	Definition	Score
Endocapillary hypercellularity	in <25% (1+), 25%–50% (2+), or >50% (3+) of the glomeruli	0-3
Neutrophils and/or karyorrhexis		0-3
Fibrinoid necrosis		(0-3) x 2
Hyaline deposits (wire-loop lesions or hyaline thrombi)		0-3
Cellular/fibrocellular crescents		(0-3) x 2
Interstitial inflammation		0-3
Total		**0-24**

Table 3. Modified NIH Chronicity Index.

	Definition	Score
Glomerulosclerosis (global or segmental)	in <25% (1+), 25%–50% (2+), or >50% (3+) of the glomeruli	0-3
Fibrous crescents		0-3
Tubular atrophy		0-3
Interstitial fibrosis		0-3
Total		**0-12**

However, the ISN/RPS classification does not include some renal lesions also associated with SLE, some of them not always related to immune complex deposition, such as tubulointerstitial lesions (interstitial infiltrate, tubular basement membrane deposits), vascular disease [thrombotic microangiopathy (TMA), nephropathy associated with antiphospholipid antibodies (aPL), and even vasculitic lesions, with a poor prognosis], cryoglobulinemic glomerulonephritis or lupus podocytopathy (LP).

Lupus podocytopathy

This type of injury is not included in the ISN/RPS 2003 classification. It can be present in 1-2% of patients with SLE, presenting as nephrotic syndrome. Although clinically it may be difficult to distinguish LP from class V LN, it has distinct histological characteristics. LM reveals glomeruli with normal appearance or with a pattern of focal segmental glomerulosclerosis, with or without mesangial proliferation. EM shows diffuse podocyte effacement and the absence of subendothelial or subepithelial deposits.

4. Diagnosis

In all patients with SLE without biological evidence of renal involvement, but with high titers of anti-double-stranded DNA (anti-dsDNA) antibodies and sustained consumption of complement, tight monitoring of renal function, proteinuria and urinary sediment is required.

Importantly, in patients with SLE and kidney involvement, it should also be considered other causes that are not secondary to SLE, such as acute tubular necrosis, renovascular disease, drug nephrotoxicity, nephroangiosclerosis associated with arterial hypertension and other cardiovascular risk factors, or tubulointerstitial nephritis secondary to drugs.

4.1. Renal biopsy indications

- 24h proteinuria >0.5 gr confirmed in two determinations, or, unexplained worsening of proteinuria in case of patients with a high level of baseline proteinuria due to previous established CKD,.
- Impaired renal function not explained by other causes, regardless of the degree of proteinuria.
- Persistent active sediment (hematuria or leukocyturia of glomerular origin, hematic or leukocyte casts, etc).

4.2. Complementary tests

– A complete medical history and physical examination should be performed.

– *General analysis*: ESR, CRP, blood count, glucose, creatinine, BUN, uric acid, cholesterol, triglycerides, GOT, GPT, GGT, alkaline phosphatase, bilirubin, LDH, CK, proteins, albumin, ionogram, proteinogram, coagulation, urine sediment and 24-hour proteinuria; TSH; ferritin, transferrin, serum iron, transferrin saturation index. Depending on the history of previous immunosuppressive treatment, especially in patients who have received rituximab, the quantification of immunoglobulins will be assessed.

– *Immunology*: In patients without known SLE, antinuclear antibodies (ANA) will be determined by indirect immunofluorescence in rat triple tissue cells and HEp2 cells; anti-dsDNA antibodies, anti-nucleosome; selected profile of antibodies against extractable nuclear antigens (anti-ENA): Sm, RNP, Ro, La; C3, C4 and CH50 fractions of complement; anti-C1q, according to center availability. If the patient was already classified as SLE, the ANA should not be repeated, and with a previous positive result of the anti-ENA, these will not be repeated. In patients with abundant histological lesions of extracapillary proliferation or necrosis, it is recommended to determine anti-neutrophil cytoplasmic antibodies (ANCA).

– *Antiphospholipid antibodies* (aPL): lupus anticoagulant (LA), anticardiolipin antibodies (aCL) IgG and IgM and anti-beta-2-glycoprotein-I (aβ2GPI) IgG and IgM (annually).

– *Serologies*: In our hospital, there is a specific profile called BIOINF which includes HAV, HBV, HCV, HIV, syphilis, measles, mumps, rubella, varicella-zoster, quantiferon TB. A referral will be held with the Department of Preventive Medicine and Epidemiology in order to update the vaccination schedule. Depending on the geographical origin, an interconsultation with the Department of International Health will also be requested to rule out imported infections.

– It is recommended to perform a renovesical ultrasound to rule out concomitant urological pathology. Likewise, Doppler of the renal arteries should be considered in patients with refractory arterial hypertension or the presence of aPL.

5. Treatment schedule. Algorithms and clinical care strategy.

Measures should be established to achieve the following objectives:

1. Control disease activity.
2. Prevent recurrences.
3. Avoid pharmacological toxicity.
4. Prevent the accumulation of organ damage and preserve long-term kidney function.
5. Manage the comorbidities of the disease and those associated with the treatment.
6. Improve the quality of life and survival of the patient.

As a guide, the evolution of the disease will be defined by the renal response criteria:

- *Complete renal response (CRR):* normal renal function (or GFR ±15% of baseline value in the case of previous dysfunction), proteinuria ≤0.5 g/day, inactive sediment and serum albumin >3 g/day.
- *Partial renal response (PRR):* reduction in proteinuria by >50% and always <3 g/day, with stabilization (GFR ±15%) or improvement in GFR.
- If after 6 – 12 months of treatment the criteria for CRR or PRR are not met, it will be considered as *refractory* or *non-responsive*.

The aim of the therapeutic management is to reach PRR maximum at the first 3 – 6 months and CRR at 6 – 12 months.

5.1. General measures

1. Control and suppression of **cardiovascular risk factors**: stop smoking, maintain a balanced diet according to the patient's metabolic profile, maintain blood pressure ≤120/80 mmHg, plasma LDL-cholesterol ≤80 mg/dL, perform activity regular physical (appropriate to their clinical situation), and achieve a normal weight. In case of arterial hypertension and/or proteinuria, salt restriction is recommended (<2 gr sodium per day, or <90 mmol sodium per day, or <5 gr sodium chloride per day).

2. It is advisable to **avoid exposure to UVA rays** (solar or artificial) both directly and indirectly (swimming pool or seawater, sand, snow, UVA devices, fluorescent tubes). It is essential to apply a sun protection cream to the exposed parts and wear suitable clothing. Sunscreens (protection factor greater than 30) should be applied approximately one hour before sun exposure and again after bathing or profuse sweating.

3. In the most intense phase of the kidney flare, it is essential to ensure rest, maintain sufficient hours of sleep and avoid situations of disproportionate physical or mental fatigue. Once this phase is over, the patient can gradually resume a normal life.

4. All patients should have an optimized **renal protective treatment.** In the event of proteinuria, blockade of the renin-angiotensin-aldosterone system (with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) should be performed at the maximum tolerated dose (depending mainly on blood pressure and renal function) to achieve proteinuria <500 mg/g. Alternatives or complementary treatments, depending on the patient's profile, include among others anti-aldosterone drugs (spironolactone, eplerenone, finerenone), sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP1) agonists.

5. **Hormonal treatment**: in general, and especially in situations of renal flare, it is recommended to avoid pharmacological contraceptives, especially estrogens in patients with aPL. Barrier contraceptives or progestogen-based contraceptives would be the first option.

6. **Vaccination and infectious prophylaxis**: since the vaccination process is prolonged, an early consultation with the Department of Preventive Medicine and Epidemiology is preferred. It is recommended:
- Screening for latent tuberculosis infection (quantiferon, chest x-ray, clinical history), to adequate prophylaxis if necessary.
- To assess the history and risk of herpes zoster infection. The vaccination with the inactivated recombinant vaccine will be individualized.
- Screening for HAV, HBV, HCV and HIV will be carried out. In the case of anti-HBs IgG <10 IU/mL, vaccination against HBV is recommended.
- Vaccination against *Influenza* virus (annually), *Streptococcus pneumoniae* (quinquennial) and COVID19.
- Gynecological examinations with a vaginal cytology study and vaccination against the human papillomavirus, according to age and risk factors.
- The administration of live attenuated vaccines is contraindicated during immunosuppressive treatment. Therefore, in patients with no antibodies against measles, rubella or mumps, an individualized patient's approach must be agreed with Preventive Medicine, always before starting immunosuppressive treatment.
- As a general recommendation, given that these are generally young patients without underlying lung disease, infectious prophylaxis against *Pneumocystis jirovecii* is not recommended, but each case will be individualized, especially in patients with underlying lung disease, prednisone >15 mg/day for more than three months and lymphopenia $<600 \cdot 10^9$/L (CD4 $<200 \cdot 10^9$/L).
- Depending on the geographical origin, screening for other imported infections will be carried out.

7. The use of **antiaggregants** with acetylsalicylic acid should be considered in patients with aPL and in women with a history of LN in case of pregnancy to reduce the risk of preeclampsia. In patients with nephrotic syndrome and serum albumin <20 gr/L, **anticoagulation** will be considered.

8. All patients should take calcium supplements between 1 – 1.2 g/day, especially while under treatment with corticosteroids. Vitamin D will be supplemented in case of deficiency. The individualized use of

bisphosphonates will be considered in those patients with osteoporosis despite correct supplementation, and in those with osteopenia who require prolonged GC treatment. It is recommended to reduce the dose of bisphosphonates by half in patients with GFR <30 ml/min/1.73m^2.

9. **Fertility:** Cyclophosphamide (CYC) has been associated with premature ovarian failure (POF), amenorrhea, and oligozoospermia. However, the dose used according to the *Euro-Lupus Nephritis Trial* (ELNT) guideline is not generally associated with these disorders. To minimize this risk, it is recommended not to exceed a cumulative dose of 10 gr of CYC. In selected cases of patients at high risk of FOP, protection of fertility with gonadotropin-releasing hormone (GnRH) agonists will be evaluated.

5.2. Pharmacotherapy:

Algorithms 1 to 3 and section 5.3 (*Treatment algorithms according to histological class*) contain the initial treatment guideline for LN. It is convenient to adapt and individualize the treatment according to the particularities and safety profile of each patient.

The treatment will be guided according to the objectives to be achieved (*treat-to-target* or *treatment goal approach*), with an initial and a subsequent treatment, unlike the traditional induction-maintenance guideline. Therefore, it will require continuous reassessment of disease activity and adaptation of treatment until the desired result is achieved. Algorithms reflect initial and sequential treatment (including combination therapies) based on disease progression.

These algorithms propose modifications in the therapeutic approach based on the response every 3 months. However, we recommend not sticking to them "blindly" but considering them as guides, evaluating the patient as a whole and its evolution over time. In addition, it must be considered that a good immunological response does not always correlate temporally with histological resolution, especially in the most aggressive histological lesions or those with a large amount of immune complex deposits. The histological lesion may take longer to resolve. In some cases, the kinetics of the decrease in proteinuria may be an argument for a vigilance attitude. Thus, in highly nephrotic patients at diagnosis, failure to achieve the goal of proteinuria must be put into perspective, and the correct attitude may consist of allowing a few more weeks of observation before making a therapeutic decision, especially if the kinetics of decreasing proteinuria suggests that the target is in sight.

Consider the following points of special importance when reading the algorithms:

1. All patients, unless contraindicated, should take antimalarials.
2. Before considering "no response" or therapeutic failure, ensure a correct pharmacological dosage and therapeutic adherence. Up to 60% of patients with SLE may be non-compliant with treatment.
3. Always consider, at each visit, whether renal protection therapy is optimized.
4. The algorithms indicate an initial and sequential treatment until reaching the RCC. When the latter is reached, the immunosuppressive treatment with which the CRR has been achieved will be continued with the doses established in section 5.2.1 (*Specific aspects of pharmacological treatment*), and for the time indicated in section 6.1 (*Duration of treatment*).

5.2.1. Specific aspects of pharmacological treatment:

Hydroxychloroquine

- All patients, unless contraindicated, should take antimalarials, ideally hydroxychloroquine at ≤5 mg/kg/day (up to a maximum of 400 mg/d). In patients with eGFR <30 ml/min/1.73m ^{2}, the dose will be reduced by 25%.

- Occasionally, prolonged use of HCQ can cause pigmentation in the macula of the retina, which can lead to loss of vision. Therefore, all patients under treatment with antimalarials will undergo ophthalmological follow-ups, at the diagnosis of SLE (start of treatment), 5 years after starting treatment, and annually thereafter. Patients with risk factors for macular involvement, such as those with underlying retinal or macular disease, age > 60 years, and renal or hepatic dysfunction (drug elimination pathways) will undergo annual follow-ups from the beginning. Other risk factors for macular involvement are consumption > 400 mg/day of HCQ and a cumulative dose > 1,000 g.

- Another less common adverse effect of antimalarials is skin pigmentation. Cardiac conduction disorders, myopathy and peripheral neuropathy are considered rare adverse effects.

Glucocorticoids

- Glucocorticoids (GC) are used as the initial treatment regimen along with other immunosupressants, with the main objective of achieving doses ≤5 mg/day at 4 months, regardless of the evolution of LN. In case of refractoriness to treatment, optimization of immunosuppressive therapy will be prioritized before intensification of treatment with GC.

- As a general rule, a low-dose GC regimen should be considered for the treatment of LN, such as the one proposed below:

	Dose
Initial bolus of methylprednisolone	125 – 500 mg/day x 3 days
Oral prednisone	
Week 0 to 2	20 – 30 mg
Week 2 to 4	20 mg
Week 4 to 6	15 mg
Week 6 to 10	10 mg
Week 10 to 14	7,5 mg
From week 14	5 mg*

* It may be considered to progressively decrease to 2.5 mg (every other day 5/2.5 mg) or maintain this dose of 5 mg/day, depending on the presence of extrarenal symptoms from week 16 (month 4). The lowest possible dose will be maintained for at least 12 months after reaching the CRR, after which its progressive reduction can be considered until discontinuation in some patients.

Cyclophosphamide

- This fast-acting and effective alkylating agent on B and T cells is of choice, as initial treatment associated with GC, in cases of severe renal disfunction or in cases of histological lesions with a poor prognosis (for example, fibrinoid necrosis, crescents >50% of the glomeruli).
- The administration scheme of reduced doses of CYC is recommended, according to the ELNT: bolus of 500 mg of intravenous CYC every two weeks up to a total of 6 doses (equivalent to 3 months of treatment).
- In severe cases, combining bolus administration of methylprednisolone (125 mg) with each bolus of CYC should be considered.
- As it is a low dose of CYC, its administration is generally well tolerated, with no notable adverse effects at these doses. The main adverse effect is bone marrow suppression, with leukopenia predominating over anemia and thrombocytopenia. This effect is observed more markedly on days 8-14, especially in those patients with renal dysfunction, since they have less drug clearance. It is recommended to monitor the hematological series before each infusion. CYC can also cause damage to the epithelium of the bladder, manifesting as hemorrhagic cystitis and, in the long term, transitional cell carcinoma of the bladder or bladder fibrosis. These effects are minimized by adequate hydration and administration of mesna during the infusion.
- Finally, CYC is associated with infertility, in the form of amenorrhea, FOP and oligozoospermia, although it is not usually observed at the doses used in ELNT. It is recommended not to exceed a cumulative dose of 10 gr of CYC to minimize the risk of infertility.

Mycophenolate

- It is an antimetabolite with high oral bioavailability (>90%). It can be used as an alternative to CYC as initial treatment (ALMS trial). It is of choice in the case of patients with high risk of infertility or exposure to high accumulated doses of CYC.
- Clinical trials were generally performed with mycophenolate mofetil (MMF), but in case of digestive intolerance, mycophenolate sodium (MPA) can be used interchangeably at the equivalent dose.
- The recommended dose for initial treatment is MMF 2–3 g/day (divided into two doses) or MPA 1440–2160 mg/day (divided into two doses). To improve digestive tolerance, titration can be performed during the first two weeks.
- Once CRR is achieved, subsequent treatment can be maintained at a dose of MMF 1.5–2 g/day or MPA 1080–1440 mg/day.
- The main adverse effects are digestive intolerance (nausea, vomiting) and leukopenia.
- In patients with severely impaired renal function (eGFR <25 ml/min/1.73m^2), MMF/MPA dose reduction should be considered.

Calcineurin inhibitors: tacrolimus and voclosporin

- Treatment with triple immunosuppressive therapy including a calcineurin inhibitor (CNI) (tacrolimus or voclosporin) with reduced doses of MMF and GC may be considered in patients who do not tolerate the standard dose of MMF, or in those patients with podocyte injury and high proteinuria. Monotherapy treatment may also be considered in patients with class V LN.
- The CNI of choice are tacrolimus (approximately 0.10 – 0.15 mg/kg/day, for plasma levels 5–7 ng/mL) and voclosporin (approved by the FDA and the EMA for the treatment of LN in combination with MMF) (23.7 mg/12h orally, does not require monitoring of plasma levels). The use of cyclosporine is not recommended due to the higher rate of recurrence after withdrawal and greater nephrotoxicity.
- The main adverse effects to monitor in these patients are impaired renal function, poor blood pressure control, headache, diarrhea, metabolic syndrome and hematological disorders.
- The use of CNI is not recommended in patients with eGFR ≤45 ml/min/1.73m^2 or with signs of high chronicity in renal biopsy (IFTA >25-30%, CI >5, etc).

Azathioprine

- Azathioprine (AZA) is not recommended as initial treatment in LN, since it has shown less efficacy than MMF (ALMS trial) and higher recurrence (ALMS and MAINTAIN trials). Its use is reserved for those patients with intolerance or lack of access to MMF or with a desire to become pregnant. The recommended daily oral dose is 1.5 – 2 mg/kg/day (maximum 2.5 mg/kg/day), and the taper-off schedule is similar to that for MMF.
- The main adverse effects are hematological series disorders, especially leukopenia, and gastrointestinal disorders. Its combined use with allopurinol is contraindicated due to the risk of bone marrow aplasia.

Anti-CD20 therapy: rituximab and obinutuzumab

- The compassionate use of rituximab or obinutuzumab should be considered in patients with persistent active LN refractory to treatment, as well as in the case of frequent recurrences.
- Rituximab has not shown efficacy in LN in randomized controlled trials (LUNAR), although it may be an effective and safe alternative for the treatment of refractory LN, based on observational studies. The usual dose of rituximab is two doses of 1 gr separated by 15 days. The need of a new infusion of 500 mg will be reassessed after 6 months.
- The dose of obinutuzumab currently being evaluated in a phase 3 clinical trial for LN (NCT04221477) is two doses of 1 gr separated by 15 days with retreatment at 6 months.
- For safety aspects, adverse effects and follow-up in patients undergoing anti-CD20 therapy, we recommend reading the Hospital Clínic protocol "Rituximab – Indications in renal pathology not approved in the data sheet".

- It should be noted that in patients with nephrotic syndrome and very high levels of proteinuria, urinary loss of rituximab may occur, reaching lower levels than desired with a possible loss of efficacy.

Anti-BLyS/BAFF therapy: belimumab

- Belimumab is indicated for the treatment of active LN in combination with standard immunosuppressive treatment. Its main benefit from a renal point of view has been observed in patients treated in combination with MMF, with proliferative histological lesions and proteinuria <3 gr/24h (BLISS-LN trial). In these patients, its use associated with standard therapy decreases the risk of relapse and slows the decline in GFR. Other patients who may benefit from its use are those with recurrent LN and steroid-dependent patients.
- Likewise, belimumab is indicated as adjuvant treatment, regardless of kidney damage, in patients with SLE with high anti-dsDNA levels and complement consumption and a high degree of disease activity despite standard treatment.
- The recommended dose is 10 mg/kg on days 0, 14 and 28, and subsequently at 4-week intervals (intravenously), or 200 mg weekly (subcutaneously) for at least two years.
- It is a drug with good tolerance and a low profile of adverse effects (generally related to administration).

5.3. Treatment algorithms based on histological class

- Algorithms 1 to 3 refer to treatment recommendations for **proliferative LN (III/IV ± V)** with or without poor prognosis criteria (clinical, analytical or histological), and for **pure class V LN**. Regarding the latter, it represents 5-10% of LN, and unlike primary membranous nephropathy, it does not usually remit spontaneously, so initial immunosuppressive treatment is recommended.

- In **class I and II LN,** patients generally have normal renal function, with generally low-grade proteinuria, sometimes associated with hematuria. For these patients, specific immunosuppression beyond that necessary for the treatment of extrarenal manifestations (other than HCQ and nephroprotection) is generally not necessary. In those patients with class I and II with proteinuria in the nephrotic range, the presence of LP should be ruled out.

If specific renal treatment is considered in these patients, the treatment of choice is GC (prednisone 20 mg/day initially, with subsequent tapering) associated with MMF or CNI (of choice in the case of coexisting LP), for at least 6 – 12 months, with progressive decline for another 6 months.

- **Lupus podocytopathy**: the clinical course of these patients is similar to that of those with optically normal nephrotic syndrome or minimal change disease, with a good response to treatment with GC monotherapy, reaching CRR in approximately 4 weeks of treatment. In case of recurrence after reduction of GC or resistance to them, the use of CNI can be considered for at least 6 – 12 months, with progressive reduction for another 6 months, or treatment with rituximab.

6. Follow-up

- Multidisciplinary follow-up of these patients with a team composed by nephrologists, specialists in systemic autoimmune diseases (internal medicine, rheumatology), pathologists specialized in renal histopathology, and advanced practice nursing is recommended.

- Patients will be evaluated monthly until reaching PRR during the first 3 – 4 months. Subsequently, the visits can be progressively spaced out. Weight, blood pressure, kidney function, serum albumin, urine sediment, proteinuria (recent or 24h CPR), complete blood count, and complement factors (C3, C4, CH50) will be monitored at each follow-up visit. Anti-dsDNA antibodies will be requested every 3-6 months. The aPL will be determined for guidance each year.

- A real goal is to reach the PRR maximum in the first 3 – 6 months and CRR at 6 – 12 months.

- Patients undergoing treatment with antimalarials should have a baseline ophthalmological review, and an annual review will be carried out after the fifth year of treatment.

- A baseline densitometry will be performed. Likewise, an estimation of the risk of fracture (FRAX-adjusted score) will be made annually in all patients under treatment with GC. There is currently no consensus on the frequency of performing densitometry in patients with LN, so those recommended for the general population will be followed (every 2 – 3 years in patients with high risk of fracture: prolonged GC therapy, post-menopausal, previous fractures, smoking, underweight, etc).

- It is recommended to repeat a kidney biopsy during follow-up in the following cases: suspicion of histological change or new lesions such as TMA; refractoriness to treatment; unexplained worsening of proteinuria, creatinine, or urine sediment; suspected pathology not related to SLE and uncertainty regarding the degree of activity/chronicity of kidney lesions for changes in therapeutic decisions. We also recommend conduct a repeated kidney biopsy once renal response is achieved at approximately 24 months to guide subsequent treatment, by assessing histological response and the persistence of subclinical activity and the degree of chronicity, among others.

6.1. Treatment duration

- Class I and II: in the event of using immunospuressant treatment, consider a period of 12 months with subsequent progressive reduction until completing at least a total of 18 months, depending on the evolution.

- LP: in the event of treatment with monotherapy with GC, consider a minimum of 4 weeks if the CRR is reached. If CRR is not reached at 4 weeks, it is recommended the early addition of a CNI as a GC sparing agent for at least 6-12 months, tapering over another 6 months. It must take into account that LP can overlap with the different histological classes, so the treatment will have to be adapted accordingly.

- Class III/IV (±V) and pure V: as a general rule, treatment in its different combinations should be maintained for around 3-5 years, although in some patients, especially in cases of recurrent LN and high immunological activity, it should be maintained for longer periods or even indefinitely.

- **GC**: ideally, and in case of no extrarenal symptoms, patients should reach a dose of 2.5–5 mg/day at 4 – 6 months. The lowest possible dose will be maintained for 12 months after reaching CRR, afterwards a progressive reduction can be assessed until withdrawal in some patients.

- **MMF/MPA**: progressive decrease from 18 to 24 months of treatment (provided that CRR has been reached) for suspension at 3 to 5 years of treatment.

- **CNI**: It must be differentiated when the CNI is used in association with another immunosuppressant (for example, MMF) from its use in monotherapy. In the first case, a progressive reduction of the CNI can be considered after 12 – 18 months of treatment (provided that the CRR has been reached) and try to withdraw it after a total of 18 – 24 months of treatment (maintaining, meanwhile, the other immunosuppressant until completing the global 3 – 5 years of treatment). In the event of use in monotherapy, a longer course is recommended, between 24 – 36 months (avoid prolonged use of CNI beyond 3 years).

- **Belimumab**: clinical trials for the use of belimumab in LN have lasted 2 years, although there is reported experience of the safe use of belimumab with series of more than 10 years.

- **Rituximab**: there is not an established regimen for the use of rituximab in LN over time, but its use is recommended to be reassessed every 6 months based on the characteristics of the patient, the concomitant immunosuppressive treatment, the time of evolution of the disease and the degree of activity.

7. Special situations

7.1. Pregnancy

- Patients with inactive LN can plan pregnancy, ideally with proteinuria <500 mg/day. If they are being treated with MMF, it should be withdrawn (or replaced by AZA) and wait 3 – 6 months to rule out recurrence and assess tolerance.
- In the case of patients with active LN, pregnancy is not recommended for a minimum of 6 months after reaching CRR. In case of pregnancy, multidisciplinary follow-up should be carried out with obstetrics, due to the increased risk of adverse perinatal outcomes, especially the development of pre-eclampsia.
- In the event of pregnancy planning, patients should be treated with immunosuppressants compatible with pregnancy for at least 3 months before conception. The therapeutic options in this case are AZA, tacrolimus, GC, HCQ and IV IgG. The safety of rituximab and belimumab in pregnancy has not been established, so they are not recommended in the data sheet.
- The antihypertensives allowed in case of pregnancy are alphamethyldopa, labetalol and nifedipine. ACE inhibitors and angiotensin II receptor blockers are contraindicated.
- It is recommended to start aspirin 150 mg/d in the 12th week of pregnancy.
- In the event of a renal flare during pregnancy, a kidney biopsy can be performed safely up to the 20th week of pregnancy.
- In case of suspicion of preeclampsia versus LN, the determination of angiogenic factors (sFlt-1/PlGF ratio) will be assessed.

7.2. Lupus nephritis and thrombotic microangiopathy

Patients with LN and thrombotic microangiopathy (TMA) will be managed according to the etiology of the TMA (we recommend to read the specific protocol of TMA of the Department of Nephrology Service of the Hospital Clínic). Thus, the differential diagnosis will be made between the most frequent causes of TMA in these patients [APS, thrombotic thrombocytopenic purpura (TTP) associated with SLE, atypical hemolytic uremic syndrome (aHUS), TMA associated with dysregulation of the alternative complement pathway]. In this chapter, mention will only be made of TMA secondary to APS.

7.2.1. APS-associated nephropathy

- APS is defined as the presence of thrombosis (arterial, venous and/or small vessel) and/or obstetric complications (miscarriage, stillbirths and/or prematurity due to placental insufficiency), together with sustained positivity for aPL: LA, aCL and aB2GPI. Around 30-40% of patients with SLE have circulating aPL.

- Kidney involvement of APS can be diverse, with thrombosis of the renal arteries or veins, stenosis of the renal arteries with renovascular hypertension, in addition to a specific type of nephropathy associated with APS consisting of the presence of glomerular, arteriolar or interlobular thrombotic lesions other than large vessel involvement. In the acute forms thrombosis is observed at the level of arterioles and glomerular capillaries of the TMA type, and in the chronic form we can find lesions with thickening and fibrosis of the intima, sclerosis and capsular atrophy.

- Although there is no solid evidence on the benefits of anticoagulation in patients with nephropathy associated with APS, the administration of anti-vitamin K drugs (acenocoumarol or warfarin) is recommended in these patients with an INR target of 2–3.

- In the case of nephropathy associated with APS in a patient with catastrophic APS, in addition to treatment with anticoagulation and GC, the association of plasma exchanges, intravenous IgG and, in refractory cases, rituximab or eculizumab should be assessed.

7.3. Refractory lupus nephropathy

- We define refractory LN by the absence of response after 3 – 6 months of treatment according the algorithms 1 – 3 (or 4 weeks if there is acute kidney failure or rapidly progressive glomerulonephritis).

- Firstly, a correct diagnosis should always be verified. If necessary, it will be performed a genetic study to verify that there is no coexistence with other renal pathologies such as genetic podocytopathies, diseases associated with complement system dysregulation, or other diseases (APOL-1, etc.).

- Adequate adherence to treatment should always be verified and a correct pharmacological dosage ensured.

- If a change in histological class is suspected, new diagnoses (eg TMA associated with APS) or doubts about a possible progression of chronic lesions, consider a new kidney biopsy.

- In terms of treatment, patients who receive an MMF analogue-based treatment regimen will be switched to a CYC-based regimen, and vice versa. Prolongation of CYC treatment (up to 9 bolus) may also be considered. For LN resistant to proven efficacy treatments, it can be considered the use of alternative treatments (compassionate use) such as anti-CD20 (rituximab, obinutuzumab or ocrelizumab), anifrolumab, complement system inhibitors (eculizumab, ravulizumab), IV IgG, leflunomide, secukinumab, combined therapies, or the compassionate use of drugs directed against plasma cells (bortezomib, daratumumab) or, in selected cases, CAR-T cell therapy.

7.4. Recurrence of lupus nephropathy

- About 10-50% of patients with LN will have recurrences. LN recurrences will always occur in patients with at least partial response to the previous episode of LN. They are characterized by an increase of proteinuria, changes in the urinary sediment or worsening of renal function. These recurrences are treated with the same initial therapy regimen, if it was effective.
- It is recommended not to exceed a total accumulated dose of 10 gr of CYC.
- *Add-on* treatment with belimumab will be considered in those patients with proliferative lesions in the kidney biopsy.
- It is recommended to extend the duration of treatment or a more gradual decrease before its withdrawal, or in case of multiple relapses, maintain low doses of immunosuppressants indefinitely.

7.5. Lupus nephropathy and end-stage chronic kidney disease

- The main risk factors for progression to end-stage chronic kidney disease are: histological class (up to 25% of patients with classes III and IV; 10% in class V; less than 2% in class I and II), failure to achieve renal response at least partial, and the concomitant presence of cardiovascular risk factors.
- In patients who require renal replacement therapy, any modality (hemodialysis, peritoneal dialysis, renal transplantation) can be used indistinctly, being the latter of choice.
- To perform a kidney transplant, at least 6 – 12 months of clinical (and, ideally, serological) inactivity are recommended.
- It is recommended to monitor aPL levels during the pre-transplant study given the increased risk of vascular complications if they are present.
- Immunosuppression in patients with stage 5 CKD on dialysis will be guided by extrarenal symptoms. It is recommended to maintain HCQ unless contraindication, although the dose will be reduced by 25-50%, without exceeding 200 mg/day. In these patients, annual ophthalmological controls are especially important.

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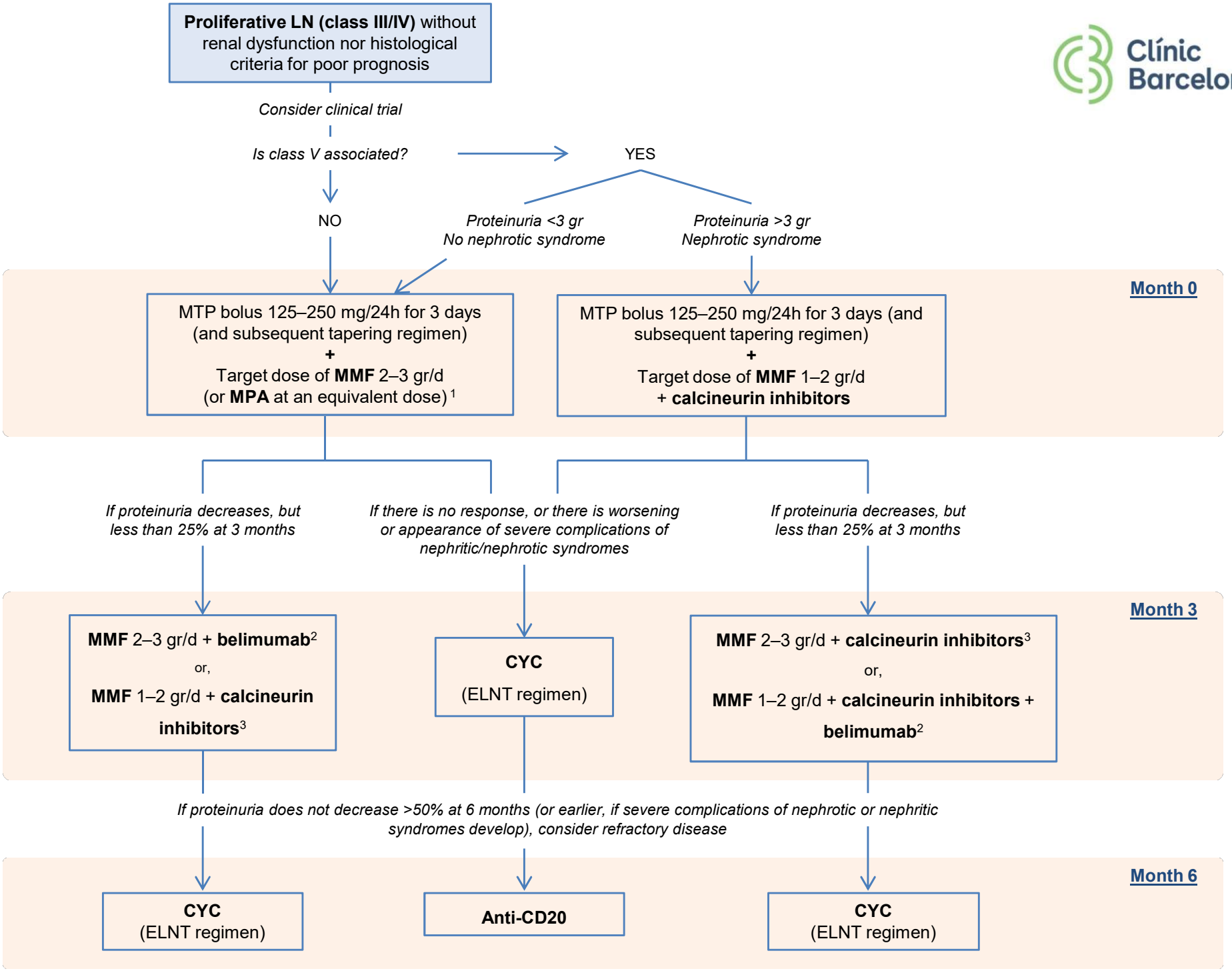
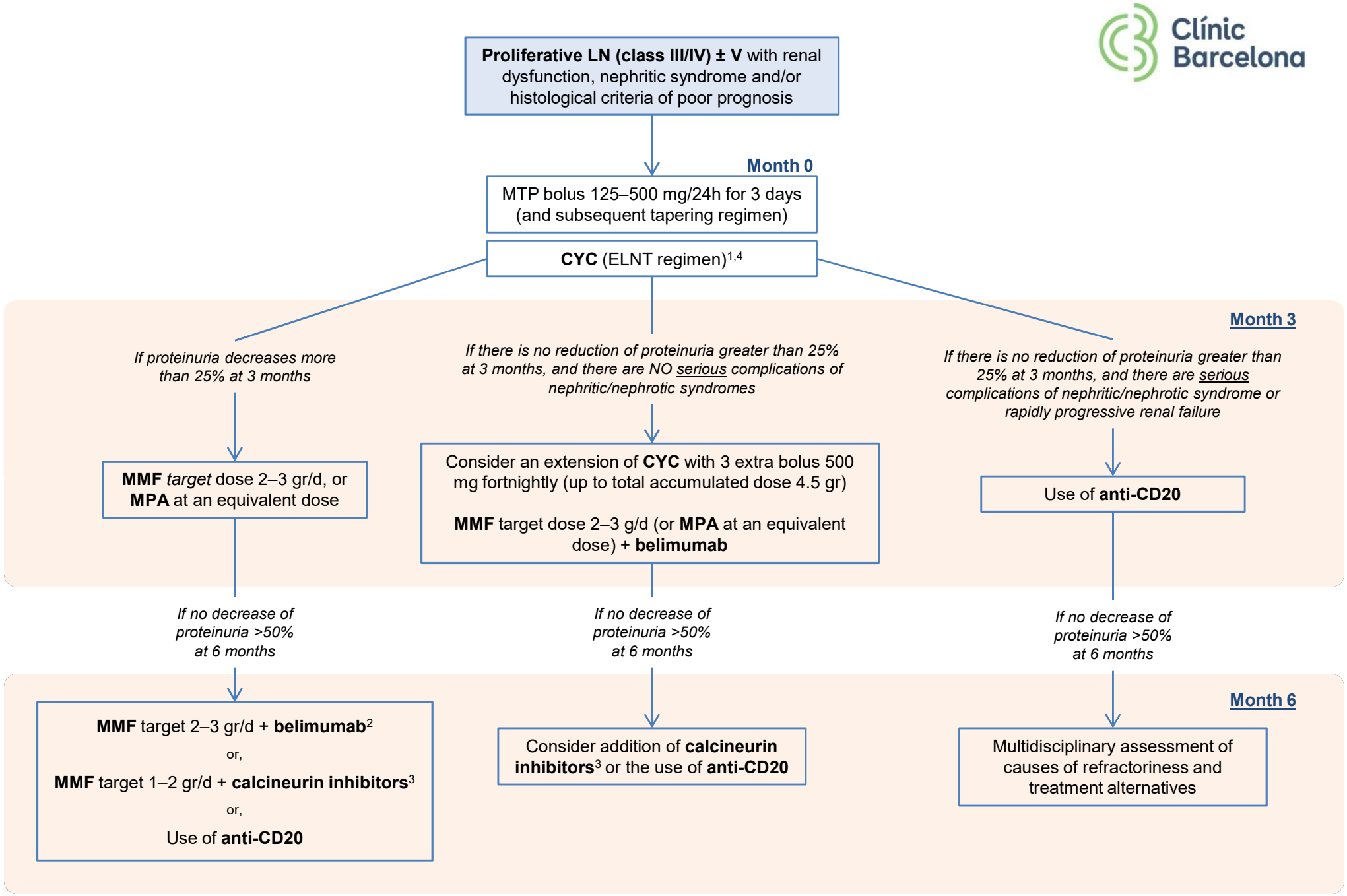
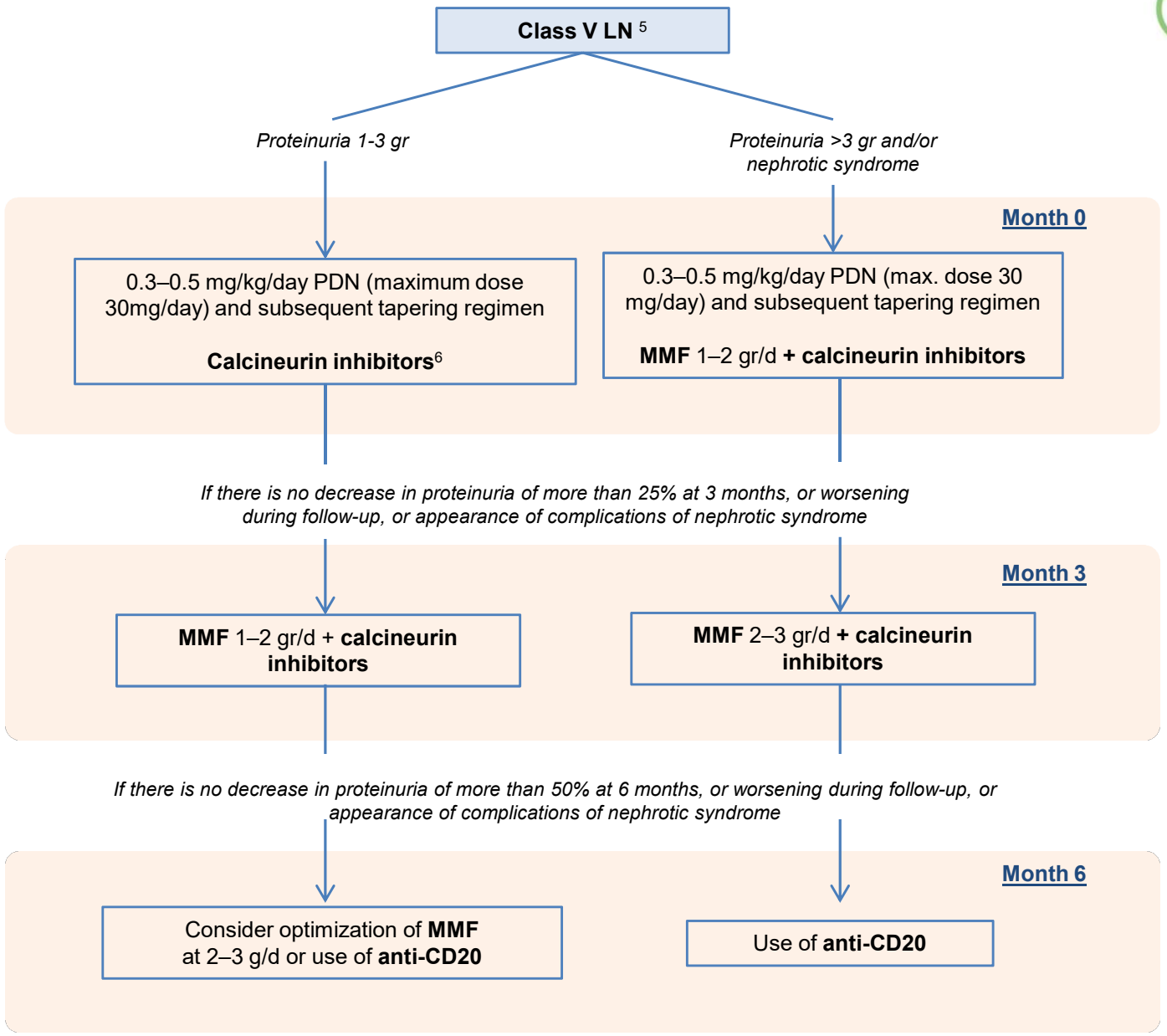


Algorithm 1. Treatment of proliferative LN without poor prognosis criteria (legend on the last page)



Algorithm 2. Treatment of proliferative LN with poor prognosis criteria (legend on the last page)



Algorithm 3. Treatment of class V NL (legend on the last page)

LEGEND

[1] Consider **belimumab** initially from month 0 in case of: (1) extra-renal involvement (joint, skin); (2) patients with recurrence of LN; (3) patients who are expected, based on their clinical and immunological profile, that they will not reach CRR in 6 – 12 months; (4) patients with previous chronic kidney disease, in order to maximize the chances of slowing the decline in eGFR slope due to the current LN flare; (5) steroid-dependent patients.

[2] **Belimumab:** it is of choice if extra-renal symptoms are present.

[3] **Calcineurin inhibitors:** they are of choice in case of proteinuria > 3g, nephrotic syndrome or podocyte lesions.

[4] Consider the association of MTP 125 mg with each CYC bolus. In selected cases with criteria of poor prognosis or refractory renal disease, it may be considered to extend 500 mg bolus of CYC from 6 to 9.

[5] In the event of proteinuria <1 gr, immunosuppressants will be guided by extra-renal symptoms.

[6] In patients with associated extra-renal manifestations, a combination therapy of a calcineurin inhibitor with MMF (target dose 1-2 g/d), or MPA at an equivalent dose, can be used; even in the event of low grade proteinuria, the use of MMF in monotherapy can also be considered (target dose 2-3 g/d).