Lupus Nephritis

Summary of KDIGO 2024

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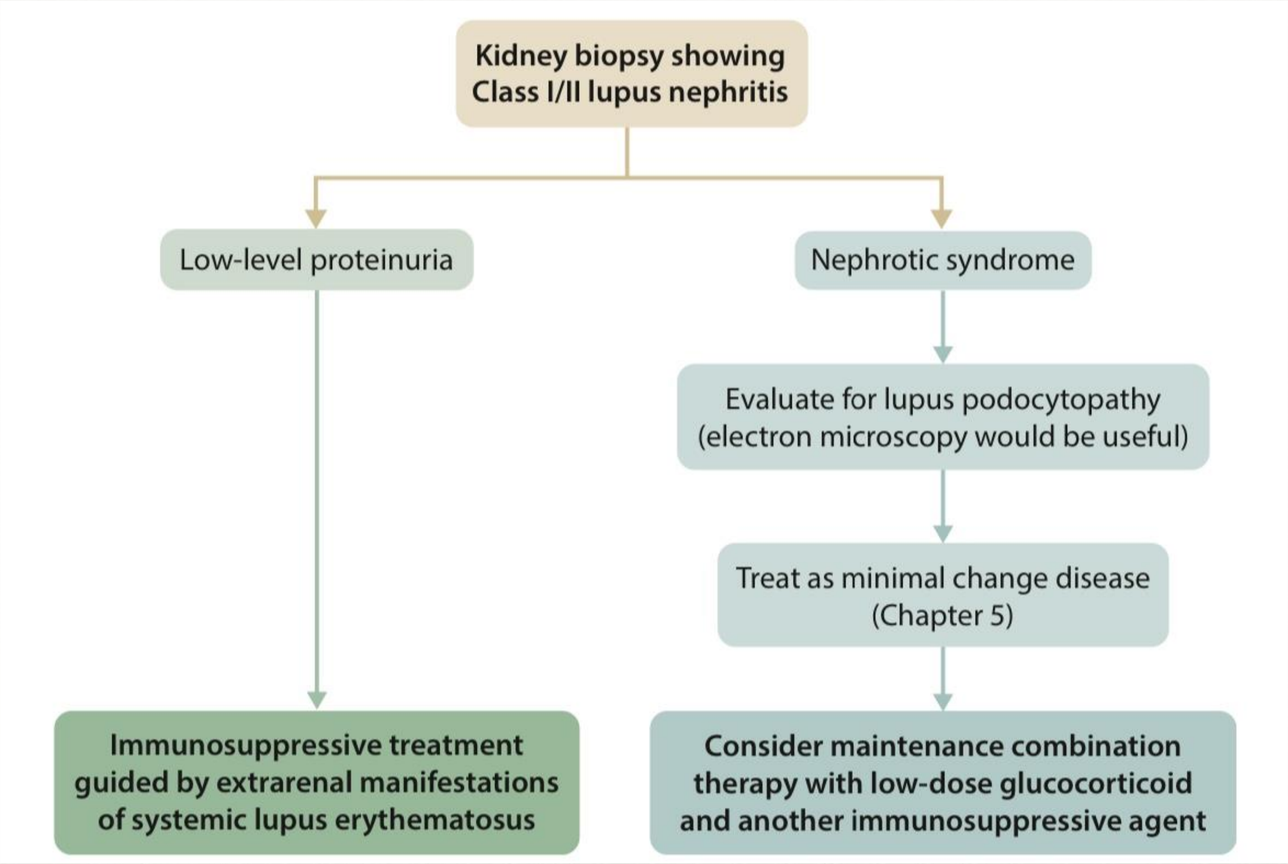
Treatment of lupus nephritis

- Proliferative lupus nephritis :
- Class I/II
- Class III/IV
- Membranous lupus nephritis
- Thrombotic microangiopathies
- Special conditions(pregnancy)

Class I/II proliferative LN



Class I/II proliferative LN

- If low grade proteinuria : no specific immunosuppression

Patients with Class I or Class II LN generally have normal kidney function, or at most, low-grade proteinuria that is well below the nephrotic range, and sometimes microscopic hematuria. For these patients, no specific immunosuppressive therapy beyond what is being given for nonrenal lupus is needed.[84]

Class I/II proliferative LN

- If nephrotic range proteinuria or nephrotic syndrome (due to lupus podocytopathy): GC+MPAA/Aza/CNI

Although there have been no RCTs, observational data showed that over 90% of patients given glucocorticoid monotherapy achieved remission within a median time of 4 weeks.[85,88–92] Data on relapse are even more limited, but there appears to be a significant risk of relapse after glucocorticoids are tapered.[93] Although optimal duration is not known, maintenance with low-dose glucocorticoid plus an additional agent such as mycophenolic acid analogs (MPAA), azathioprine, or a CNI is suggested, especially in patients with a history of relapse.

Class III/IV proliferative LN

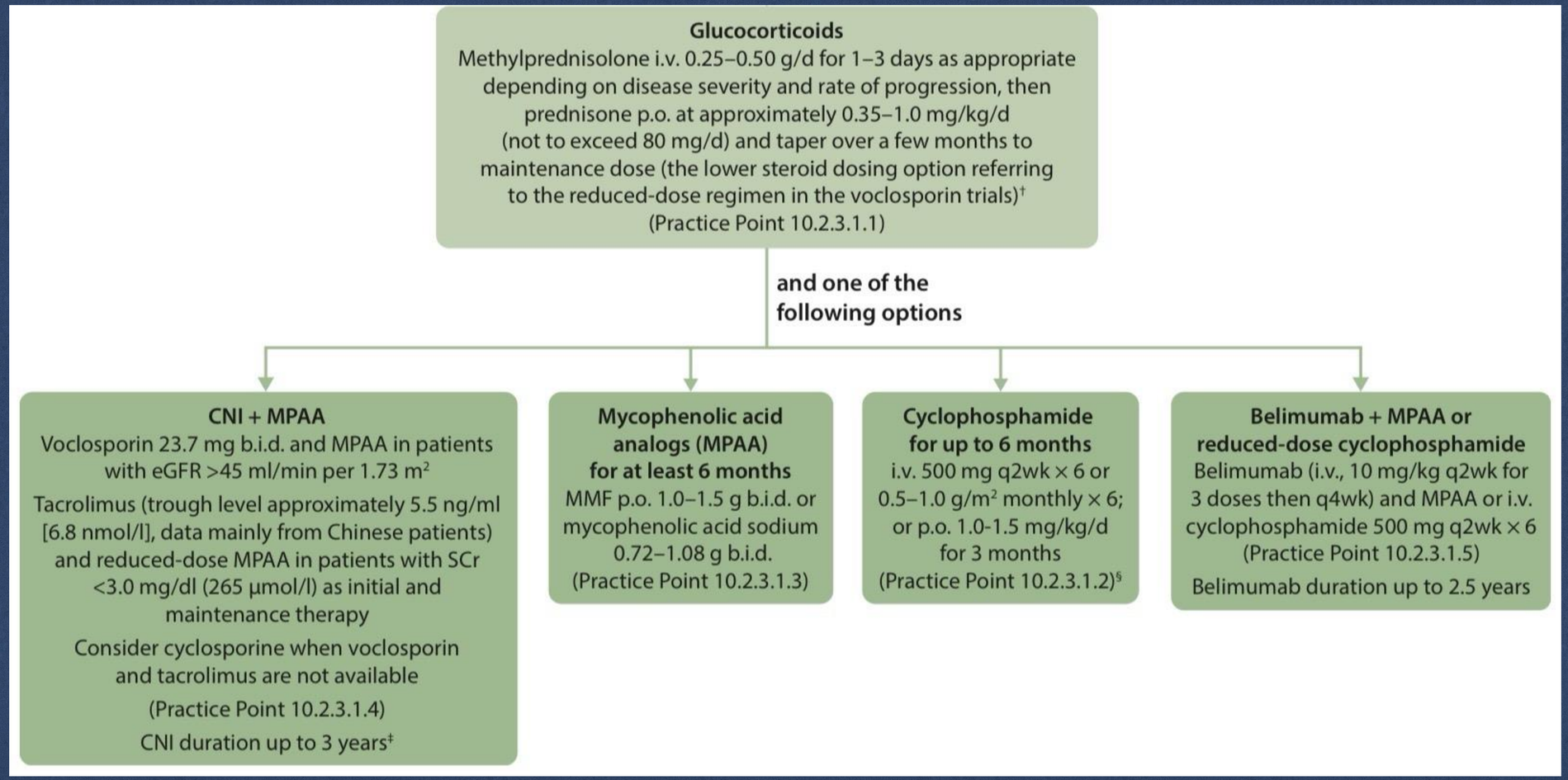
- <u>Induction phase:</u>
- Dual immunosuppressive: GC+Cyclophosphamide

  GC+MPAA
- Triple immunosuppressive: GC+MPAA+CNI

GC+MPAA/Cyclophosphamide+Belimumab

- Others

Class III/IV proliferative LN-induction phase



Glucocorticoids

Glucocorticoids are used in all current treatment regimens for LN. These drugs have both immunosuppressive and anti-inflammatory effects and provide immediate treatment for the often-extensive intrarenal inflammation that is seen in patients with Class III and Class IV LN. This regimen is necessary because there is a lag before the immunosuppressive effects of cyclophosphamide, MPAA, CNIs, or B cell–directed therapies are seen. The dose, tapering regimen, and duration of glucocorticoid schemes vary considerably among clinicians and are largely opinion-based. Examples are given in Figure 7. In view of the established efficacy associated with combined immunosuppression, there is a move towards reducing glucocorticoid exposure.

Glucocorticoids

- A regimen of reduced dose GC following a short course of methylprednisolone pulses may be considered during the initial treatment of active LN when both the kidney and extra renal disease manifestations show satisfactory improvement.

	High-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

Cyclophosphamide

- The choice of which regimen to use depends on several factors and can be individualized.
- Intravenous cyclophosphamide can be used as the initial therapy for active classIII/IV LN in patients who may have difficulty adhering to an oral regimen.

	High-dose intravenous cyclophosphamide (NIH regimen)	Low-dose intravenous cyclophosphamide (Euro-Lupus regimen)	Oral cyclophosphamide
Cyclophosphamide	i.v. 0.5–1 g/m^2 monthly for 6 months	i.v. 500 mg every 2 weeks for 3 months	p.o. 1.0–1.5 mg/kg/d (max 150 mg/d) for 2–6 months
Comments	Efficacy data included patients of different races/ethnicities	Efficacy data mainly in Caucasian patients, with some data from patients of African or Caribbean descent, Hispanic descent, Indian patients, and other Asian countries	Efficacy data included patients of different races/ethnicities

MPAA

- An MPAA-based regimen is the preferred initial therapy of proliferative LN for patients at high risk of infertility, such as patients who have a moderate-to-high prior cyclophosphamide exposure.

Mycophenolic acid analogs (MPAA) for at least 6 months

MMF p.o. 1.0–1.5 g b.i.d. or mycophenolic acid sodium 0.72–1.08 g b.i.d. (Practice Point 10.2.3.1.3)

MPAA

Cyclophosphamide has historically been the first-choice treatment for very severe proliferative LN. An analysis of pooled data from various clinical trials of patients with Class III/IV LN, crescents in >15% of glomeruli, and abnormal SCr level at presentation showed a comparable early response to glucocorticoids plus either cyclophosphamide or MMF.[161] However, the analysis also suggested that initial treatment with cyclophosphamide might be associated with a more sustained response and more favorable long-term kidney outcome than initial treatment with MMF.

CNI

- Initial therapy with an immunosuppressive regimen that includes a CNI (voclosporin, tacrolimus, or cyclosporine) may be preferred in patients with relatively preserved kidney function and nephrotic-range proteinuria likely due to extensive podocyte injury, as well as patients who cannot tolerate standard-dose MPAA or are unfit for or will not use cyclophosphamide-based regimens.

CNI + MPAA

Voclosporin 23.7 mg b.i.d. and MPAA in patients with eGFR >45 ml/min per 1.73 m^2

Tacrolimus (trough level approximately 5.5 ng/ml [6.8 nmol/l], data mainly from Chinese patients) and reduced-dose MPAA in patients with SCr <3.0 mg/dl (265 µmol/l) as initial and maintenance therapy

Consider cyclosporine when voclosporin and tacrolimus are not available

(Practice Point 10.2.3.1.4)

CNI duration up to 3 years‡

Belimumab

- A triple immunosuppressive regimen of belimumab with glucocorticoids and either MPAA or reduced-dose cyclophosphamide may be preferred in patients with repeated kidney flares or at high-risk for progression to kidney failure due to severe chronic kidney disease.

Belimumab + MPAA or reduced-dose cyclophosphamide

Belimumab (i.v., 10 mg/kg q2wk for 3 doses then q4wk) and MPAA or i.v. cyclophosphamide 500 mg q2wk × 6 (Practice Point 10.2.3.1.5)

Belimumab duration up to 2.5 years

Class III/IV proliferative LN

- Other therapies: GC+Aza

  GC+Leflunomide

- Other therapies, such as azathioprine or leflunomide combined with GC, may be considered in lieu of the recommended initial drugs for proliferative LN in situations of patient intolerance, lack of availability, and/or excessive cost of standard drugs, but these alternatives may be associated with inferior efficacy, including increased rate of disease flares and/or increased incidence of drug toxicities.

Class III/IV proliferative LN

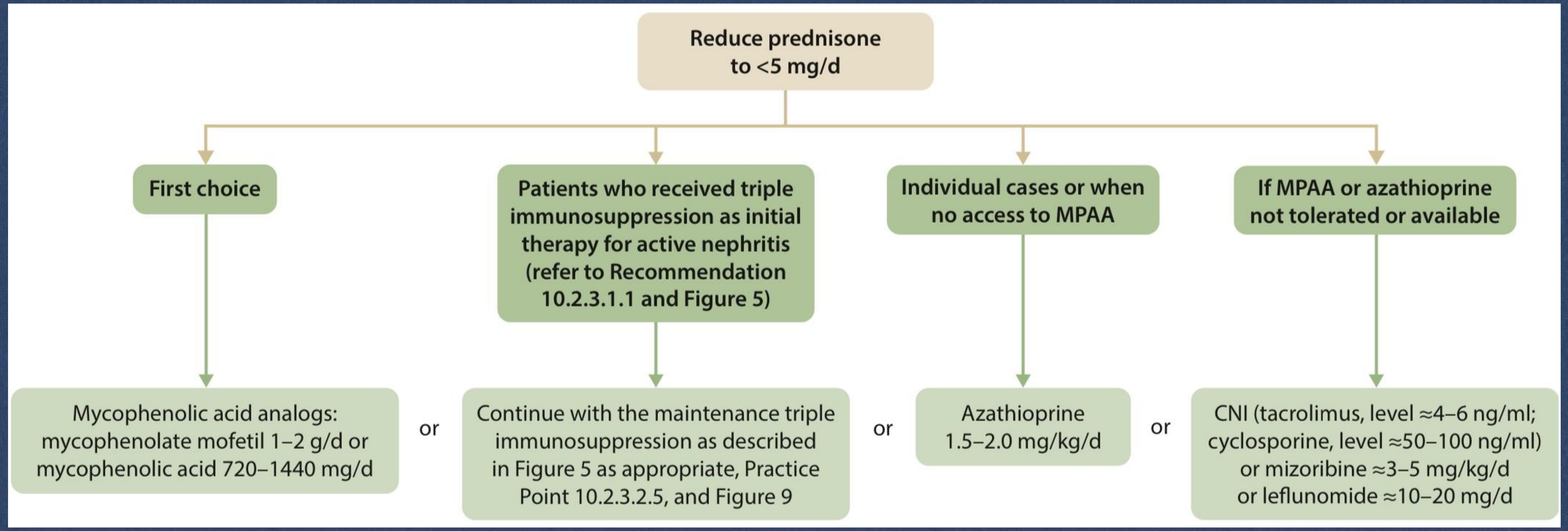
- <u>Maintenance phase:</u>
- Dual immunosuppressive: GC+MPAA \ Aza
- Triple immunosuppressive: GC+MPAA+CNI

  GC+MPAA/Aza+Belimumab
- Others: GC+CNI

  GC+Mizoribine

  GC+Leflunomide

Class III/IV proliferative LN-maintenance phase



MPAA

The dose of mycophenolate mofetil (MMF) in the early maintenance phase is approximately 750–1000 mg twice daily, and for mycophenolic acid (MPA), approximately 540–720 mg twice daily.

The suggested dosages are largely based on data from the ALMS and MAINTAIN trials.[16,203] As mentioned before, the Work Group recommends maintenance of these doses until achievement of complete response, and then tapering. Due to pharmacogenetic differences, the level of MPA exposure varies considerably among patients receiving the same dose of MPAA. The dose of MPAA may need to be reduced when kidney function is significantly impaired, as patients with CKD are more susceptible to the adverse effects of MPA.

Aza

- Azathioprine is an alternative to MPAA after completion of initial therapy in patients who do not tolerate MPAA, who do not access to MPAA, or who are considering pregnancy.

Azathioprine
1.5–2.0 mg/kg/d

Triple immunosuppressive

- Patients treated with triple immunosuppressive regimens that include belimumab or a CNI in addition to standard immunosuppressive therapy can continue with a triple immunosuppressive regimen as maintenance therapy.

- These results suggest that triple immunosuppressive regimens that include belimumab or a CNI in addition to standard maintenance immunosuppression can be continued for 2-3 years.

Others

- If MPAA and azathioprine cannot be used for maintenance, CNIs or mizoribine or leflunomide can be considered.

CNI (tacrolimus, level ≈4–6 ng/ml;
cyclosporine, level ≈50–100 ng/ml)
or mizoribine ≈3–5 mg/kg/d
or leflunomide ≈10–20 mg/d

Assessing treatment response in LN

Criteria	Definition
Complete response*	• Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy, but could take more than 12 mo
Primary efficacy renal response	• PCR ≤0.7 g/g (70 mg/mmol) • eGFR that was no worse than 20% below the pre-flare value or ≥60 ml/min per 1.73 m^2 • No use of rescue therapy for treatment failure
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6–12 mo of starting therapy

Management of unsatisfactory response to treatment

1	Verify adherence to treatment
2	Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)
3	Repeat biopsy if concern for chronicity or other diagnosis (e.g., thrombotic microangiopathy)
4	Consider switching to an alternative recommended treatment regimen when there is persistent active disease
5	Consider the following in patients refractory to first-line treatment regimens: • Addition of rituximab or other biologic therapies • Extended course of i.v. pulse cyclophosphamide • Enrollment in clinical trials if eligible

Treatment of LN relapse

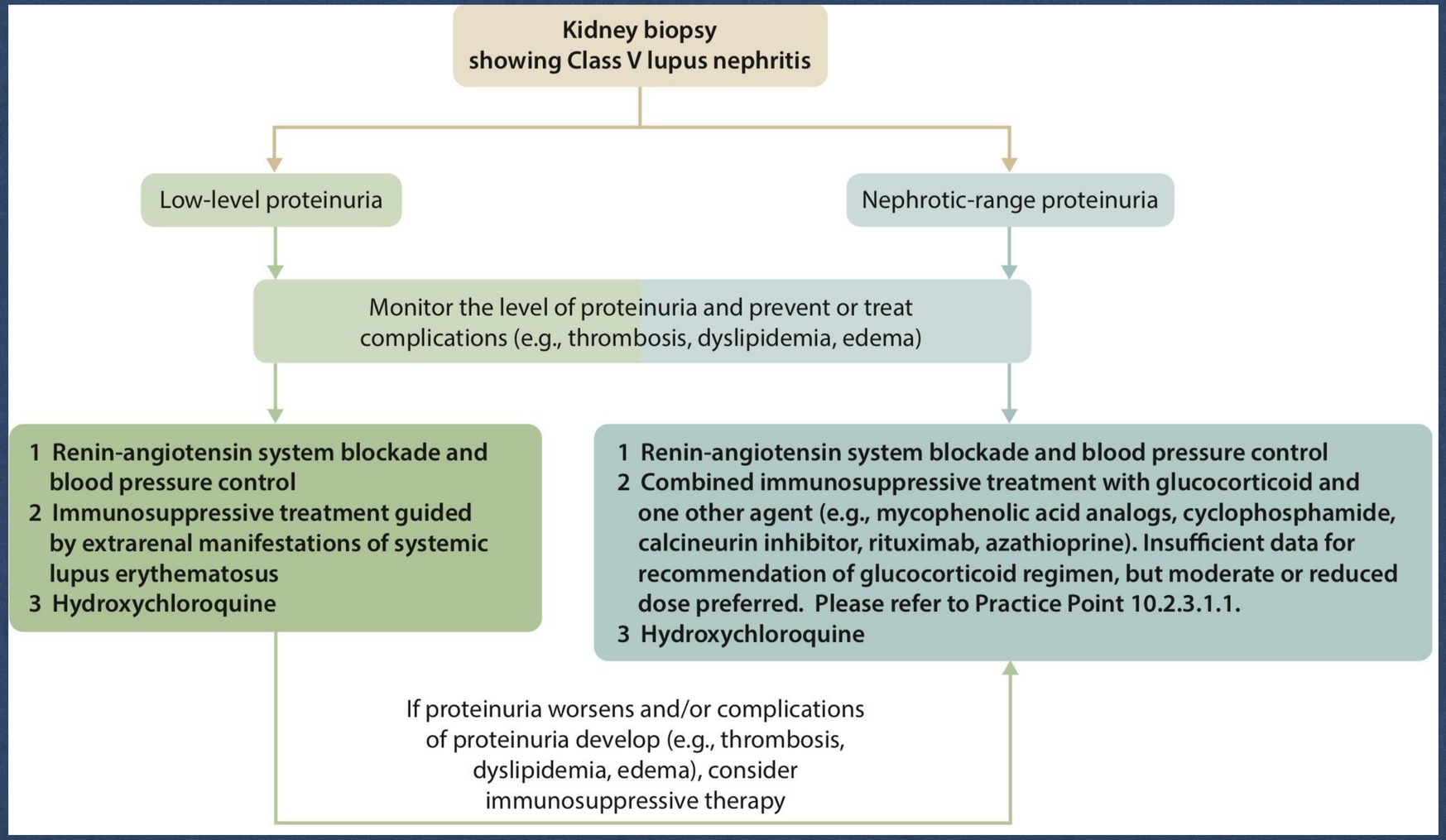
- After a complete or partial remission has been achieved, LN relapse should be treated with the same initial therapy used to achieve the original response, or an alternative recommended therapy.

There are no data that focus on the treatment of LN flares alone. However, it is generally agreed that there is no major difference between management of an LN flare and that of *de novo* active LN, and initial therapies are the same as outlined above.

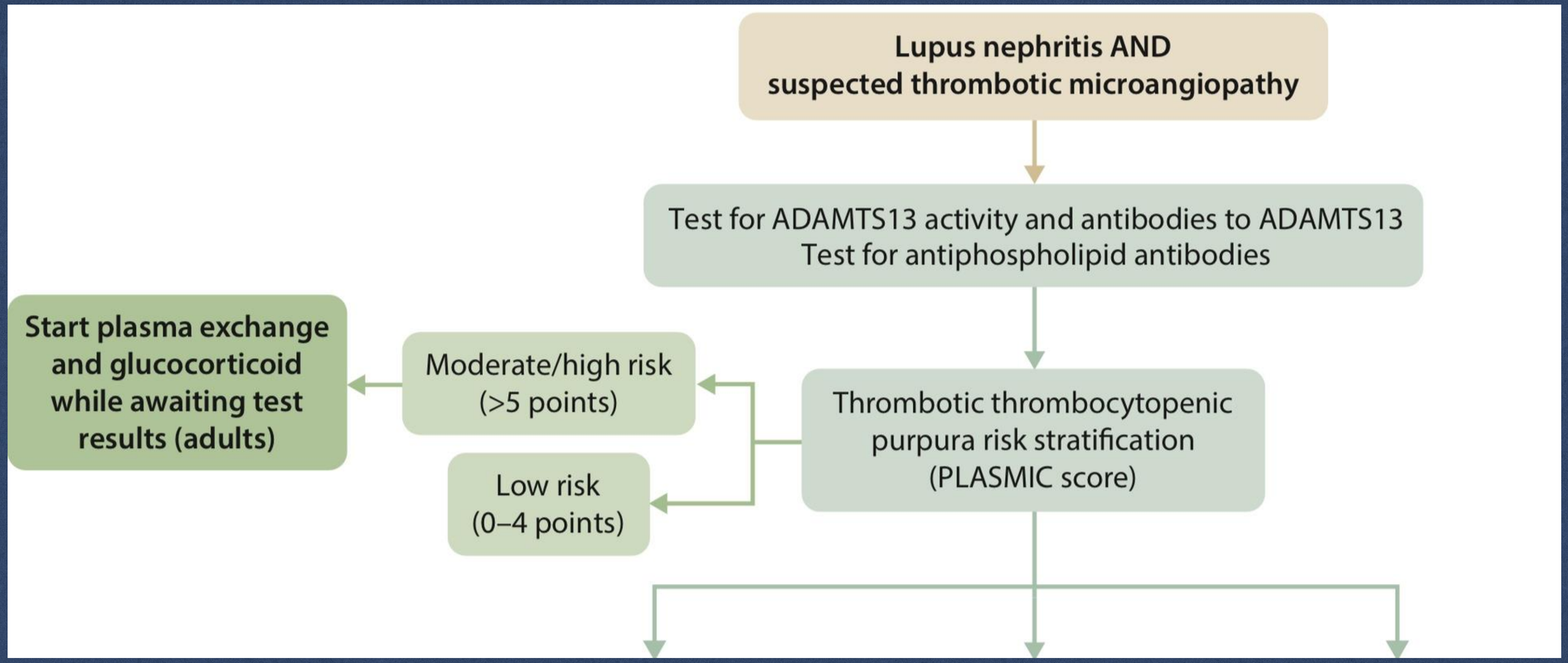
Treatment of LN relapse

The last point is critical but complex. The same clinical criteria used to diagnose *de novo* LN are used to diagnose LN flares, absent a kidney biopsy. That is, flares are generally considered when proteinuria increases beyond a certain threshold, with or without an active urinary sediment or deterioration of kidney function. Without histology, it is sometimes difficult to determine whether changes in proteinuria are due to active inflammatory kidney injury or reflect progression of chronic damage incurred during preceding episodes of active LN, because there is often discordance between clinical findings and histologic findings.[10,11]

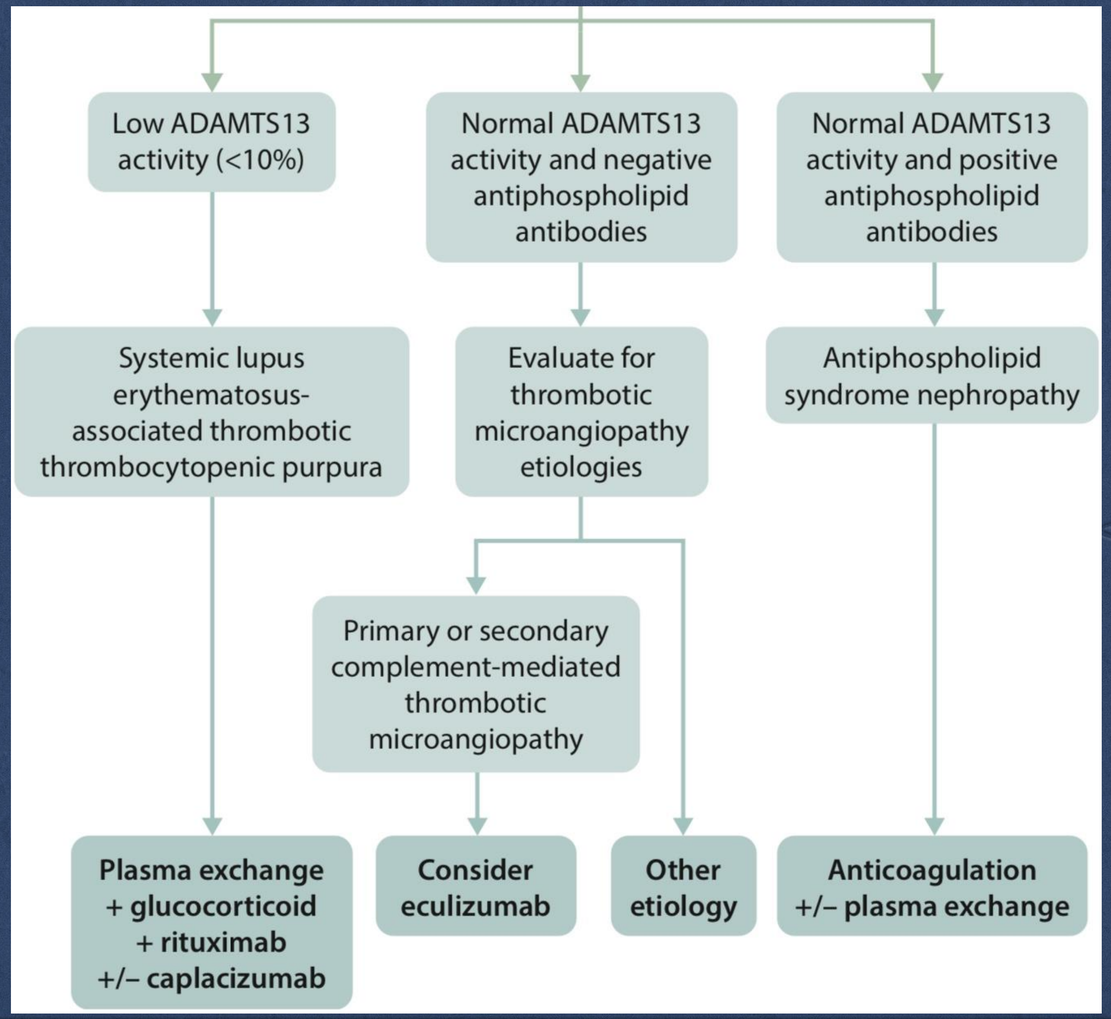
Class V LN


Kidney biopsy
showing Class V lupus nephritis
Low-level proteinuria
Nephrotic-range proteinuria
Monitor the level of proteinuria and prevent or treat complications (e.g., thrombosis, dyslipidemia, edema)
1 Renin-angiotensin system blockade and blood pressure control
2 Immunosuppressive treatment guided by extrarenal manifestations of systemic lupus erythematosus
3 Hydroxychloroquine
1 Renin-angiotensin system blockade and blood pressure control
2 Combined immunosuppressive treatment with glucocorticoid and one other agent (e.g., mycophenolic acid analogs, cyclophosphamide, calcineurin inhibitor, rituximab, azathioprine). Insufficient data for recommendation of glucocorticoid regimen, but moderate or reduced dose preferred. Please refer to Practice Point 10.2.3.1.1.
3 Hydroxychloroquine
If proteinuria worsens and/or complications of proteinuria develop (e.g., thrombosis, dyslipidemia, edema), consider immunosuppressive therapy

LN and TMA


Lupus nephritis AND
suspected thrombotic microangiopathy
Test for ADAMTS13 activity and antibodies to ADAMTS13
Test for antiphospholipid antibodies
Thrombotic thrombocytopenic purpura risk stratification (PLASMIC score)
Moderate/high risk (>5 points)
Low risk (0–4 points)
Start plasma exchange and glucocorticoid while awaiting test results (adults)

LN and TMA


Low ADAMTS13 activity (<10%)
Normal ADAMTS13 activity and negative antiphospholipid antibodies
Normal ADAMTS13 activity and positive antiphospholipid antibodies
Systemic lupus erythematosus-associated thrombotic thrombocytopenic purpura
Evaluate for thrombotic microangiopathy etiologies
Antiphospholipid syndrome nephropathy
Primary or secondary complement-mediated thrombotic microangiopathy
Plasma exchange + glucocorticoid + rituximab +/– caplacizumab
Consider eculizumab
Other etiology
Anticoagulation +/– plasma exchange

LN and pregnancy

- Patients with active LN should be counseled to avoid pregnancy while the disease is active or when treatment with potentially teratogenic drugs is ongoing, and for>6 months after LN becomes inactive.

- To reduce the risk of pregnancy complications, HCQ should be continued during pregnancy, and low dose ASA should be started before 16 weeks of gestation.

- GC, HCQ, Aza, tacrolimus, and cyclosporine are considered safe immunosuppressive treatments during pregnancy.

LN and breastfeeding

Hydroxychloroquine, tacrolimus, low-dose azathioprine, and prednisone have limited transfer into breast milk and are considered safe with breastfeeding. MPAA are contraindicated when patients are breastfeeding.[340]