

NfN Richtlijn Lupus Nefritis

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Verantwoordelijk lid NfN kwaliteitscommissie:
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De richtlijn bevat aanbevelingen van algemene aard. Het is mogelijk dat in een individueel geval deze aanbevelingen niet van toepassing zijn. Het is de verantwoordelijkheid van de behandelend arts te beoordelen of de richtlijn in de praktijk toepasbaar is. Er kunnen zich feiten of omstandigheden voordoen waardoor, in het belang van een goede zorg voor de patiënt, van een richtlijn moet worden afgeweken.

Voorwoord

Deze richtlijn is gebaseerd op de KDIGO (Kidney Disease Improving Global outcomes) Clinical Practice Guidelines for Glomerulonephritis, Chapter 12: Lupus nephritis.

In het voorliggende document is alleen de KDIGO samenvatting opgenomen met de aanbevelingen. Voor de uitgebreide onderbouwing van de richtlijnen raadplege men de volledige richtlijn, gepubliceerd in *Kidney International Supplements* 2012;2:221-232, en op www.kdigo.org

De KDIGO richtlijn is door de Landelijke Werkgroep Systemische Lupus Erythematosus en subcommissie van de NfN kwaliteitscommissie beoordeeld. Waar nodig heeft de Werkgroep en subcommissie commentaar of aanvulling op de KDIGO richtlijn gegeven. Het commentaar en aanvullingen zijn gebaseerd op drie andere richtlijnen welke onlangs zijn gepubliceerd:

- Van Tellingen A, Voskuyl AE, Vervloet MG, et al. Dutch guidelines for diagnosis and therapy of proliferative lupus nephritis, *The Netherlands Journal of Medicine* 2012;70:199-207 namens de Landelijke Werkgroep Systemische Lupus Erythematosus, <http://www.njmonline.nl/getpdf.php?id=10000838>
- Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology Guidelines for screening, treatment and management of lupus nephritis. *Arthritis Care and Research* 2012;64:797-808
- Bertsias GK, Tektonidou M, Amoura A, et al. Joint European League Against Rheumatism and European Renal Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Annals Rheum Disease* 2012;71:1771-1782

In de appendix, blz 16 e.v. is toegevoegd het advies van de Landelijke werkgroep SLE betreffende het verrichten van een nierbiopsie bij patiënten met SLE.

KDIGO Clinical Practice Guideline for Glomerulonephritis

The 2011 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis (GN) aims to assist practitioners caring for adults and children with GN. Guideline development followed an explicit process of evidence review and appraisal. Treatment approaches are addressed in each chapter and guideline recommendations are based on systematic reviews of relevant trials. Appraisal of the quality of the evidence and the strength of recommendations followed the GRADE approach. (zie bijlage blz 13)

Chapter 12: Lupus nephritis

Summary of recommendation statements

12.1: Class I LN (minimal-mesangial LN)

12.1.1: We suggest that patients with class I LN be treated as dictated by the extrarenal clinical manifestations of lupus. (2D)

Rationale

- Class I LN has no clinical kidney manifestations.
- Class I LN is not associated with long-term impairment of kidney function.

Comment

There are no data to suggest that treatment of class I LN is indicated, unless necessitated by extra-renal lupus activity. However, the EULAR-EDTA recommendations establish that in cases of class I LN with podocytopathy on the electron microscopy (minimal change nephropathy) or with interstitial nephritis, corticosteroids alone or in combination with immunosuppressive agents may be considered. The Dutch Working Party on SLE supports this advice.

12.2: Class II LN (mesangial-proliferative LN)

12.2.1: Treat patients with class II LN and proteinuria <1 g/d as dictated by the extra-renal clinical manifestations of lupus. (2D)

12.2.2: We suggest that class II LN with proteinuria >3 g/d be treated with corticosteroids or CNIs as described for minimal change nephropathy. (2D)

Rationale

- There are no evidence-based data on the treatment of class II LN.
- Podocytopathies, characterized histologically by diffuse foot process effacement in the absence of glomerular capillary wall immune complex deposition or endocapillary proliferation, have been observed in patients with class II LN.

Comment

There is no prospective study on the treatment of nephrotic range proteinuria in class II LN. However, the KDIGO guideline mentions that it is reasonable to treat these patients as for MCD/FSGS in case of nephrotic syndrome, or if proteinuria cannot be controlled using RAS

blockade. In addition, The EULAR-EDTA guideline recommends low-to moderate doses of corticosteroids alone or in combination with azathioprine if proteinuria > 1 g/day persists despite RAS-blockade and salt restriction, especially in the presence of glomerular hematuria. Both recommendations are not graded. The Dutch Working Party on SLE supports the EULAR/EDTA recommendation. We also recommend that treating physicians are watchful for signs of conversion to proliferative forms of lupus nephritis.

12.3: Class III LN (focal LN) and class IV LN (diffuse LN)—initial therapy

12.3.1: We recommend initial therapy with corticosteroids (1A), combined with either cyclophosphamide (1B) or MMF (1B).

12.3.2: We suggest that, if patients have worsening LN (rising SCr, worsening proteinuria) during the first 3 months of treatment, a change be made to an alternative recommended initial therapy, or a repeat kidney biopsy be performed to guide further treatment. (2D)

Rationale

- Proliferative LN (class III or IV) is an aggressive disease.
- Patient and kidney survival in class III and IV LN have dramatically improved through the use of intensive immunosuppression.
- The treatment recommendations are for active or active plus chronic lesions, based on the International Society of Nephrology/Renal Pathology Society classification of LN.
- The term 'initial' treatment is preferred.
- The evolution of initial therapy in proliferative LN has been to reduce toxicity while maintaining efficacy.
- The efficacy of newer initial treatment regimens should be assessed not only by initial responses, but also by long-term effects on kidney relapse, and development of chronic kidney disease.

Comment

The results of the Euro-Lupus Nephritis trial showed that the low-dose iv cyclophosphamide (500 mg fixed dose, six pulses every two weeks) in combination with methylprednisolon (three days, 750 mg) achieves good clinical results in the long-term in a European (mainly Caucasian) population with a moderately severe disease. After ten years of follow-up, no significant differences were found between low-dose iv cyclophosphamide and high dose iv cyclophosphamide (NIH-regimen) with regard to survival, ESRD or doubling of serum creatinine.

In addition, the results of the first Dutch Lupus Nephritis Study indicate that azathioprine can not be considered the first choice induction therapy in patients with proliferative LN.

Moreover, two randomized, controlled trials did not show any additional significant effect of anti-CD20 therapy (i.e. rituximab) as add-on therapy in patients with LN treated with MMF and corticosteroids. Therefore, the use of rituximab as a first line adjunctive agent in induction therapy currently is not justified.

Based on these results, the Dutch Working Party proposes for initial treatment in Caucasian patients with proliferative LN either the low-dose cyclophosphamide Euro-lupus regimen or MMF together with (methyl)prednisolone, as outlined in *Table I and II, blz 14*. In non-Caucasians initial therapy with MMF is recommended.

In case of *failure* of the initial induction therapy (i.e. a doubling of serum creatinine compared with the baseline value at three months after the start of the induction therapy), and/or in patients who do not meet the response criteria of partial/complete remission after 12 months

of induction treatment, we recommend switch of the immunosuppressive agent from either cyclophosphamide to MMF, or from MMF to cyclophosphamide, accompanied by iv methylprednisolone (750 mg) for three days.

Several definitions of treatment response have been assessed for class III and IV LN. However, no single renal parameter has been validated as a marker for determining response. Nonetheless, changes in renal function have been associated with renal outcome in several studies. Based on the available literature, the Dutch Working Party assigned the following definitions for response as a guide to the success of therapy:

A complete response includes no disease activity, i.e. proteinuria less than 0.5 gram/24h, and a serum creatinine within 125% of the baseline value at 6 to 12 months after the start of induction therapy.

A partial response is defined as an improvement not sufficient for the definition of a complete response, i.e. a reduction of proteinuria of more than 50% (and at least less than 3 gram/24h), and a serum creatinine within 125% of the baseline value at 6 to 12 months after the start of the induction therapy.

A failure of the initial induction therapy has been defined as a doubling of serum creatinine compared to the baseline value at 3 months after the start of the induction therapy.

A flare is an increase in disease activity that requires intensification of the therapy and is defined as an increase of 25% or more in the lowest serum creatinine level measured during the period of induction therapy and/or the development of either a nephrotic syndrome (proteinuria > 3.5 g/24h and serum albumin < 30 g/l), while the lowest protein excretion so far has been ≤ 2.0 g/24h repeatedly, or proteinuria > 1.5 g/24h in a previous non-proteinuric patient.

12.4: Class III LN (focal LN) and class IV LN (diffuse LN)—maintenance therapy

12.4.1: We recommend that, after initial therapy is complete, patients with class III and IV LN receive maintenance therapy with azathioprine (1.5–2.5 mg/kg/d) or MMF (1–2 g/d in divided doses), and low-dose oral corticosteroids (≤10 mg/d prednisone equivalent). (1B)

Rationale

- There is a moderate-quality evidence from randomized clinical trials in patients with class III/IV LN that prolonged maintenance therapy after initial treatment is required.
- There is a moderate-quality evidence that maintenance therapy with azathioprine or MMF is superior to cyclophosphamide as judged by risk of death, and risk of development of CKD.
- There is a moderate-quality evidence that azathioprine and cyclosporine A have comparable efficacy as maintenance therapies for class III/IV LN.
- There is very low-quality evidence to guide the duration of maintenance therapy after complete remission, but most randomized studies of class III/IV LN have given therapy for several years.

Comment

Two randomized controlled trials with different study designs have been conducted to assess the optimal maintenance treatment in proliferative LN.

In the MAINTAIN Nephritis Trial, MMF (2 g/day) was compared with azathioprine (2 mg/kg/day) as maintenance treatment after induction treatment with low-dose i.v. cyclophosphamide (Euro-Lupus regimen). MMF and azathioprine were equally effective in

preventing renal flares. In this study, patients were randomized at the start of the induction treatment.

Recently, data from the ALMS Maintenance Trial were published. In contrast to the MAINTAIN Nephritis Trial, only patients achieving partial or complete remission during a 6-month induction phase were re-randomized to corticosteroids plus MMF (2 g/day) or azathioprine (2 mg/kg/day) for up to 36 months. In this study, MMF was superior to azathioprine in delaying the time to treatment failure, which was defined as either renal flare, necessity of rescue therapy, doubling of serum creatinine, ESRD or death (16.4% versus 32.4%). The completion rate at 36 months was higher in the MMF group compared to the azathioprine group (62.9% versus 48.6%). Superiority of MMF was consistent regardless of type of induction treatment, race or region. The discrepancy in the results between the MAINTAIN and the maintenance phase of the ALMS trial can have several explanations, such as the number of and the difference in ethnicity of the patients included in both studies, a different trial design and differences in study endpoints. Moreover, the randomization procedure in the ALMS Maintenance Trial selected for those patients with a good clinical response. As indicated before a considerable proportion of patients does not show such a favorable response at 6 months.

Based on the above mentioned studies, The Dutch Working Party suggests that azathioprine and MMF are equally effective in maintaining a renal response and in preventing a renal flare in Caucasian patients. In non-Caucasian patients maintenance treatment with MMF is preferred.

Monitoring MPA blood levels to individualize treatment with MMF is not widely accepted yet. Gradual dosage up titration to ensure the best possible efficacy/toxicity ratio has been proposed by the EULAR/ERA-EDTA recommendations. In addition, monitoring of MPA blood levels in cases with GFR <30 ml/min is recommended by this paper.

Awaiting the results of further prospective controlled trials in patients with LN, the target range derived from the current available literature (MPA-AUC value of 35 mg*h/L ~ pre-dose concentration of 3.0 mg/L) may serve as a initial guidance for MPA monitoring. The Dutch Working Party advises that before concluding MPA treatment has failed at least one adequate drug exposure assessment is made.

12.4.2: We suggest that CNIs with low-dose corticosteroids be used for maintenance therapy in patients who are intolerant of MMF and azathioprine. (2C)

Comment

A pilot RCT in 69 patients with class III/IV LN suggested that 2 years of cyclosporine may be as effective as 2 years of azathioprine for maintenance, after initial treatment with prednisone and oral cyclophosphamide, in terms of relapse prevention and reduction of proteinuria.

12.4.3: We suggest that, after complete remission is achieved, maintenance therapy be continued for at least 1 year before consideration is given to tapering the immunosuppression. (2D)

Rationale

- There is a moderate-quality evidence from RCTs in patients with class III/IV LN that prolonged maintenance therapy after initial treatment is required.
- There is a moderate-quality evidence that maintenance therapy with azathioprine or MMF is superior to maintenance cyclophosphamide as judged by risk of death, and risk of development of chronic kidney disease.
- There is very low-quality evidence to guide the duration of maintenance therapy after complete remission, but most randomized studies of class III/IV LN have given therapy for several years.

Comment

It is difficult to define precisely the criteria that allow the identification of patients in whom the dose of immunosuppression can be reduced safely. If the disease is clinically and serologically quiescent for at least a year following induction therapy the immunosuppression could be tapered slowly. However, based on the Dutch Lupus Nephritis trials duration of therapy of at least 5 years seems warranted. In this context, the 10-year follow-up data of the Euro-Lupus Nephritis Trial showed that 53% of the patients were still on maintenance immunosuppressive therapy. The Dutch Working Party proposes the following reduction schedule as a guidance in clinical practice (Level C): taper the dose of prednisone to 10 mg every other day at 4 years after the start of the induction therapy, followed by a 50% dose reduction of azathioprine/MMF 6 months later and continue this treatment regimen for at least two more years. After this period (6.5 years), the decision to stop immunosuppressive treatment will be left at the discretion of the treating physician and the patient.

This advice differs from the tapering schedule as proposed in the ALMS and MAINTAIN trial. In the ALMS trial the dose of corticosteroids was maximally 10 mg until 36 months with no data after 36 months. In the MAINTAIN trial prednisone was dosed at 7.5 mg at 6 months, 5 mg at 12 months, with further tapering after 24 months. There are no data available from controlled studies, allowing a more clear advice.

- 12.4.4: If complete remission has not been achieved after 12 months of maintenance therapy, consider performing a repeat kidney biopsy before determining if a change in therapy is indicated. (*Not Graded*)

Comment

The benefit of a repeat biopsy during the disease course of proliferative LN is questionable since there is no consensus in the literature. The opinion of the Dutch Working Party is that only in those patients where it is anticipated that the findings have therapeutic consequences a repeat biopsy is justified (Level C).

First, the persistence of proteinuria after reaching a partial response, despite optimal supportive treatment including salt restriction and treatment with ACEi or ARBs to differentiate between active disease, chronic lesions or transition to focal segmental glomerulosclerosis.

Second, failure to respond (either complete or partial response) at 12 months after the start of the initial induction treatment to differentiate between active and chronic lesions.

- 12.4.5: While maintenance therapy is being tapered, if kidney function deteriorates and/or proteinuria worsens, we suggest that treatment be increased to the previous level of immunosuppression that controlled the LN. (*2D*)

Comment

The Dutch Working Party recommends that a repeat biopsy can be considered to evaluate whether re-induction therapy is necessary if active lesions are detected.

12.5: Class V LN (membranous LN)

- 12.5.1: We recommend that patients with class V LN, normal kidney function, and non-nephrotic-range proteinuria be treated with antiproteinuric and antihypertensive medications, and only receive corticosteroids and immunosuppressives as dictated by the extrarenal manifestations of systemic lupus. (*2D*)
- 12.5.2: We suggest that patients with pure class V LN and persistent nephrotic proteinuria be treated with corticosteroids plus an additional

immunosuppressive agent: cyclophosphamide (2C), or CNI (2C), or MMF (2D), or azathioprine (2D).

Rationale

- Pure class V LN, although regarded as indolent compared to class III and IV LN, is still associated with the development of CKD and ESRD, especially if there is heavy proteinuria.
- Nephrotic range proteinuria in class V LN generally does not spontaneously remit.
- There have been no studies of the effect of treatment of class V LN on long-term kidney outcomes.
- The prognosis for patients with mixed membranous and proliferative lesions is less favorable than pure class V LN, and similar to that of patients with class III or IV LN.

Comment

A decrease in GFR occurs in about 20% of cases of class V LN, and ESRD in about 8-12% after 7-12 years. Given the adverse effects of proteinuria on the kidney, it is reasonable to treat patients with class V LN independent of the amount of proteinuria (non-nephrotic or nephrotic) with antiproteinuric and antihypertensive medications. These therapies may reduce proteinuria by 30-50%.

Both the EULAR-EDTA and the ACR guidelines recommend MMF in combination with glucocorticoids as initial treatment of pure class V LN with nephrotic range proteinuria. This recommendation is based on a combined analysis of two RCTs in a subgroup of patients with pure class V LN which shows a comparable antiproteinuric effect of MMF versus high-dose cyclophosphamide (Radhakrishnan, et al. KI 2010). The Dutch Working Party suggests to follow this recommendation for those with nephrotic range proteinuria and/or deterioration of renal function in whom conservative treatment (salt restriction, blood pressure control and RAS blockade) failed to reduce proteinuria < 1 gram/24 hours. We also recommend that treating physicians are watchful for signs of conversion to proliferative forms of lupus nephritis.

12.6: General treatment of LN

12.6.1: We suggest that all patients with LN of any class are treated with hydroxychloroquine (maximum daily dose of 6–6.5 mg/kg ideal body weight), unless they have a specific contraindication to this drug. (2C)

Rationale

- There is low-quality evidence that hydroxychloroquine may protect against the onset of LN, against relapses of LN, ESRD, vascular thrombosis, and that it has favorable impact on lipid profiles.

Comment

Both the KDIGO and the EULAR/EDTA guidelines recommend yearly eye examinations for retinal toxicity, especially after five years of continuous use. The Dutch Working Party advises a baseline ophthalmic examination within the first year of use and an annual screening after five years of use to detect retinal toxicity. Moreover, for patients with maculopathy or additional risk factors for retinal toxicity (cumulative dose of hydroxychloroquine >1000 g, elderly, kidney and/or liver dysfunction) annual screening should be performed from the initiation of the therapy. Hydroxychloroquine should be used during pregnancy to a maximum of 400 mg/day.

Moreover, the indication for supportive treatment depends on the stage of chronic kidney disease and the presence of proteinuria. In general, the strategy aims at reduction of cardiovascular risk factors and should comprise lifestyle modifications (smoking cessation, weight reduction, increased physical activity and dietary changes, especially salt reduction) together with adequate control of blood pressure (target of <130/80 mmHg) with angiotensin inhibitors (ACEi) of angiotensin receptor blockers (ARBs), and treatment of hyperlipidemia. To reduce the risk for corticosteroid-induced osteoporosis The Dutch Working Party advises the recommendations of the CBO Consensus Osteoporosis 2011.

In addition to the supportive treatment options mentioned above, low-dose acetylsalicylic acid seems warranted in patients with positive anti-phospholipid antibodies for primary prevention of thrombosis and pregnancy loss (expert opinion). Furthermore, coumarines should be considered in patients with a nephrotic syndrome and serum albumin <20 g/l.

12.7: Class VI LN (advanced sclerosis LN)

12.7.1: We recommend that patients with class VI LN be treated with corticosteroids and immunosuppressives only as dictated by the extrarenal manifestations of systemic lupus. (2D)

Rationale

- Class VI LN reflects chronic injury, and the consequences of the loss of functional kidney mass, without active immune-mediated injury. Therefore, immunosuppression is not indicated.
- Despite the absence of active LN, patients may still have extra-renal manifestations of systemic lupus requiring immunosuppression.
- As with CKD from any etiology, antiproteinuric and antihypertensive therapies are indicated to preserve residual kidney function and delay ESRD as long as possible.

Comment

No additional comment.

12.8: Relapse of LN

12.8.1: We suggest that a relapse of LN after complete or partial remission be treated with the initial therapy followed by the maintenance therapy that was effective in inducing the original remission. (2B)

12.8.1.1: If resuming the original therapy would put the patient at risk for excessive lifetime cyclophosphamide exposure, then we suggest a non-cyclophosphamide-based initial regimen be used. (2B)

12.8.2: Consider a repeat kidney biopsy during relapse if there is suspicion that the histologic class of LN has changed, or there is uncertainty whether a rising SCr and/or worsening proteinuria represents disease activity or chronicity. (Not Graded)

Rationale

- LN is a relapsing condition.
- Relapses are associated with development of CKD.
- The pathologic findings in LN may change with relapse, and such changes cannot, with certainty, be predicted clinically.

Comment

The treatment of relapse of LN is not described in the Dutch guideline, the ACR guideline and the EULAR-EDTA recommendations. To prevent long-term cyclophosphamide induced toxicities, a maximal lifetime cyclophosphamide exposure of 15 g is recommended by the Dutch Working Party.

12.9: Treatment of resistant disease

- 12.9.1: In patients with worsening SCr and/or proteinuria after completing one of the initial treatment regimens, consider performing a repeat kidney biopsy to distinguish active LN from scarring. (*Not Graded*)
- 12.9.2: Treat patients with worsening SCr and/or proteinuria who continue to have active LN on biopsy with one of the alternative initial treatment regimens (see Section 12.3). (*Not Graded*)
- 12.9.3: We suggest that nonresponders who have failed more than one of the recommended initial regimens (see Section 12.3) may be considered for treatment with rituximab, i.v. immunoglobulin, or CNIs. (*2D*)

Rationale

- Most patients are expected to show some evidence of response to treatment after a year of therapy, although complete remission may occur beyond a year.
- There are no prospective data on patients who fail to achieve at least partial response, it is reasonable, however, to repeat biopsy and determine if there has been a change in kidney pathology that could account for treatment failure.
- There are no prospective data on patients who fail initial therapy; however, it is reasonable to try a second course of initial therapy using an alternative regimen, as dictated by repeat biopsy.
- There have been small studies of 'rescue' therapies for patients who have been refractory despite multiple treatment attempts.

Comment

There is no consensus definition of refractory LN in the literature. However, to guide treatment decisions, the Dutch Working Party on SLE has defined refractory LN as persistent or worsening renal disease activity as manifested by progressive deterioration of renal function and/or proteinuria despite optimal immunosuppressive therapy and supportive treatment, and involving at least one of the following conditions:

- I) failure of the initial induction treatment at 3 months, for which a switch to another induction therapy regime has already been carried out,
- II) intolerance for cyclophosphamide and mycophenolate mofetil (MMF),
- III) exceeding a cumulative dose of 15 gram of cyclophosphamide,
- IV) a second relapse within two years after start of the initial induction therapy,
- V) a relative contraindication for high dose oral or intravenous (i.v.) prednisone, such as avascular osteonecrosis, previous psychosis on corticosteroids, osteoporosis and/or severe obesity (BMI \geq 35 kg/m²).

The evidence for any kind of immunosuppressive therapy in refractory LN is weak. Small observational studies provided evidence that rituximab seems to be an effective treatment for patients with active LN that is refractory to standard immunosuppressive therapy. However, the use of the different dosing schedules in these observational studies make an interpretation difficult. Adjunctive treatment with tacrolimus resulted in a significant clinical response in patients resistant to MMF. However, although these newly introduced immunosuppressive regimens have proven their efficacy in some cases of refractory LN, the

application of high-dose cyclophosphamide (NIH regimen) could still be a possibility. These (adjunctive) regimens are described in *Table III, blz 15*.

Both the KDIGO-guideline as also the EULAR/EDTA recommendations mention the use of immunoglobulins as rescue therapy in refractory LN.

12.10: Systemic lupus and thrombotic microangiopathy

- 12.10.1: We suggest that the antiphospholipid antibody syndrome (APS) involving the kidney in systemic lupus patients, with or without LN, be treated by anticoagulation (target international normalized ratio [INR] 2–3). (2D)
- 12.10.2: We suggest that patients with systemic lupus and thrombotic thrombocytopenic purpura (TTP) receive plasma exchange as for patients with TTP without systemic lupus. (2D)

Rationale

- APS occurs frequently in systemic lupus, and there is moderate-quality evidence that failure to treat it may lead to CKD and ESRD, despite adequate control of LN or other systemic lupus manifestations with immunosuppression.
- There are no specific studies of anticoagulation for APS with systemic lupus. There have been two RCTs of the intensity of warfarin therapy in APS. They provided moderate-quality evidence of no difference in thrombotic events if the INR was 2-3 or 3-4, but that bleeding complications were higher when INR was maintained greater than 3.
- TTP in lupus is associated with a high mortality. There are no RCTs to guide treatment of TTP in the setting of systemic lupus, but it seems appropriate to use regimens beneficial in TTP without lupus.

Comment

The treatment of APS involving the kidney in systemic lupus patients, with or without LN, does not arise in the Dutch guideline. However, both the ACR guideline and the EULAR-ERA-EDTA guideline underscore with the above mentioned suggestions.

12.11: Systemic lupus and pregnancy

- 12.11.1: We suggest that women be counseled to delay pregnancy until a complete remission of LN has been achieved. (2D)
- 12.11.2: We recommend that cyclophosphamide, MMF, ACE-I, and ARBs not be used during pregnancy. (1A)
- 12.11.3: We suggest that hydroxychloroquine be continued during pregnancy. (2B)
- 12.11.4: We recommend that LN patients who become pregnant while being treated with MMF be switched to azathioprine. (1B)
- 12.11.5: We recommend that, if LN patients relapse during pregnancy, they receive treatment with corticosteroids and, depending on the severity of the relapse, azathioprine. (1B)
- 12.11.6: If pregnant patients are receiving corticosteroids or azathioprine, we suggest that these drugs not be tapered during pregnancy or for at least 3 months after delivery. (2D)
- 12.11.7: We suggest administration of low-dose acetylsalicylic acid during pregnancy to decrease the risk of fetal loss. (2C)

Rationale

- Data suggest that active LN or LN in partial remission is associated with an increase in fetal loss and an increased rate of kidney relapse during pregnancy.
- Cyclophosphamide, MMF, ACE-I, and ARBs are teratogenic.
- Hydroxychloroquine, azathioprine, and corticosteroids have been used safely during pregnancy in patients with systemic lupus; low-dose acetylsalicylic acid may decrease fetal loss in systemic lupus.

Comment

Systemic lupus and pregnancy is not described in the Dutch guideline. In addition to the abovementioned KDIGO recommendations, the ACR guidelines suggest that the dose of azathioprine should not exceed 2 mg/kg during pregnancy. In contrast to the KDIGO and ACR guidelines, the EULAR-EDTA recommendations emphasize that MMF should not be given in the last three months prior to conception and biologicals for at least four months, dependent upon the agent used before conception. The Dutch Working Party suggests that if LN cannot be controlled by azathioprine, corticosteroids and hydroxychloroquine, calcineurin inhibitors are acceptable and a safe alternative. Moreover, bisfosfonates should be stopped a year before conception.

The Dutch Working Party agrees with the suggestion that low-dose acetylsalicylic acid during pregnancy can be considered to reduce the risk of fetal loss. However, it must be noticed that this suggestion is based on a single retrospective study of 113 pregnant patients with active lupus nephritis.

12.12: LN in children

12.12.1: We suggest that children with LN receive the same therapies as adults with LN, with dosing based on patient size and GFR. (2D)

Rationale

- LN shows the same range of clinical and pathological phenotypes as is seen in adults.
- There are no RCTs of LN therapy in children.

Comment

No additional comment.

Bijlagen

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as Level 1, Level 2, or Not Graded, and the quality of the supporting evidence is shown as A, B, C, or D.

Grade*	Implications		
	Patients	Clinicians	Policy
Level 1 “We recommend”	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 “We suggest”	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category “Not Graded” was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.

Conversion factors of metric units to SI units

Parameter	Metric units	Conversion factor	SI units
Albumin (serum)	g/dl	10	g/l
Creatinine (serum)	mg/dl	88.4	μmol/l
Creatinine clearance	ml/min	0.01667	ml/s
Cyclosporine (serum)	ng/ml	0.832	nmol/l
uPCR	mg/g	0.1	mg/mmol

Note: Metric unit x conversion factor = SI unit.

Tables**Table I: Induction treatment: Cyclophosphamide. #*****Cyclophosphamide***

A fixed dose of 500 mg intravenous, 6 times every two weeks

Corticosteroids

Methylprednisone pulse 750 mg intravenous at day 0,1 and 2, followed by prednisone 0.5-1.0 mg/kg/day

After 4 weeks prednisone tapered every 2 weeks with 2.5 mg to 5-7.5 mg at 30 months

Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis. The Euro-Lupus Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum.*2002;46:2121-31.

Table II: Induction treatment: MMF (= mycophenolate mofetil) ##***Mycophenolate mofetil***

Week 1: 1000 mg/day

Week 2: 2000 mg/day

Week 3: 3000 mg/day

Corticosteroids

Prednisone 1 mg/kg/day, maximum 60 mg/day

After 4 weeks prednisone tapered every 4 weeks with 10 mg to 20 mg, followed by prednisone tapered every 4 weeks with 5 mg to 10 mg

Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol.* 2009;20:1103-12.

Table III: Treatment of refractory Lupus Nephritis (LN)***Rituximab****

1000 mg intravenous at day 1 and 15 as add-on therapy

Tacrolimus*

0.1 mg/kg/day, through level 4-10 µg/l as add-on therapy

Cyclophosphamide*750 mg/m² intravenous, increased with 250 mg per dose to a maximum of 1500 mg
6 times monthly, then every 3 months for an additional 2 years***Prednisone 1 mg/kg/day, maximum 60 mg/day**

Appendix

Indications for a first renal biopsy in patients with SLE

[\(Neth J of Med 2012;70\(4\):199-206\)](#)

The occurrence of LN should be considered in any SLE patient with recent onset of impaired kidney function, proteinuria and/or microscopic haematuria (≥ 5 red cells per high-power field). However, as these clinical features do not permit a reliable prediction of the class of LN (see *Figure I*), the diagnosis must be confirmed by kidney biopsy, since this can have clinical consequences on treatment decisions.[1] Six classes of LN are distinguished in the current classification of the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) (see *Table IV*).[2] These histological findings provide the basis for treatment recommendations. Based on panel discussions, the Dutch Working Party formulated guidelines (as stated in *Figure II*), when to perform a first renal biopsy in patients with SLE.

Although clinically silent proliferative LN occurs in a substantial proportion of patients, it is generally accepted to decide not to perform a renal biopsy in SLE patients who have a normal renal function, no haematuria and less than 0.5 g/24h of proteinuria (Level C).[3] In such patients renal parameters should be monitored carefully. In SLE patients presenting with more than 0.5 g/24h of proteinuria after exclusion of other causes a renal biopsy is indicated, independent of the presence of microscopic haematuria and/or an increase in serum creatinine (Level C). These patients may have focal or diffuse proliferative glomerulonephritis, or membranous lupus.

In SLE patients with microscopic haematuria in the absence of an increase in serum creatinine or proteinuria it is not clear whether a renal biopsy should be performed. Although prompt diagnosis after the onset of LN and subsequent initiation of appropriate therapy are associated with improved outcomes, persistent isolated microscopic haematuria has not been associated with a negative outcome so far and warrants close monitoring of other renal parameters (Level C).[4,5]

An increase in serum creatinine may implicate a proliferative LN. However, is it possible that these patients present without microscopic haematuria or proteinuria? Since clinical features do not permit a reliable prediction of the class of LN, the Dutch Working Party came to an opinion based agreement that in this setting a biopsy should be considered when the observed increase in serum creatinine is persistent over several weeks and is more than 30%, together with the presence of either I) extra-renal lupus manifestations and/or serological activity and/or II) the presence of anti-phospholipid antibodies.[6-9] Moreover, in the absence of an obvious extra-renal explanation for deteriorating renal function a kidney biopsy may be warranted to exclude renal pathology other than LN, including a tubulo-interstitial nephritis, vascular disease (e.g. thrombotic microangiopathy or vasculitis), diabetes or drug-induced nephrotoxicity (Level C).

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4. Faurschou M, Starklint H, Halberg P, Jacobsen S. Prognostic factors in lupus nephritis: diagnostic and therapeutic delay increases the risk of terminal renal failure. *J Rheum* 2006;33:1563-9.
5. Contreras G, Pardo V, Cely C, et al. Factors associated with poor outcomes in patients with lupus nephritis. *Lupus* 2005;14:890-5.
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Table IV: Abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis 2003.

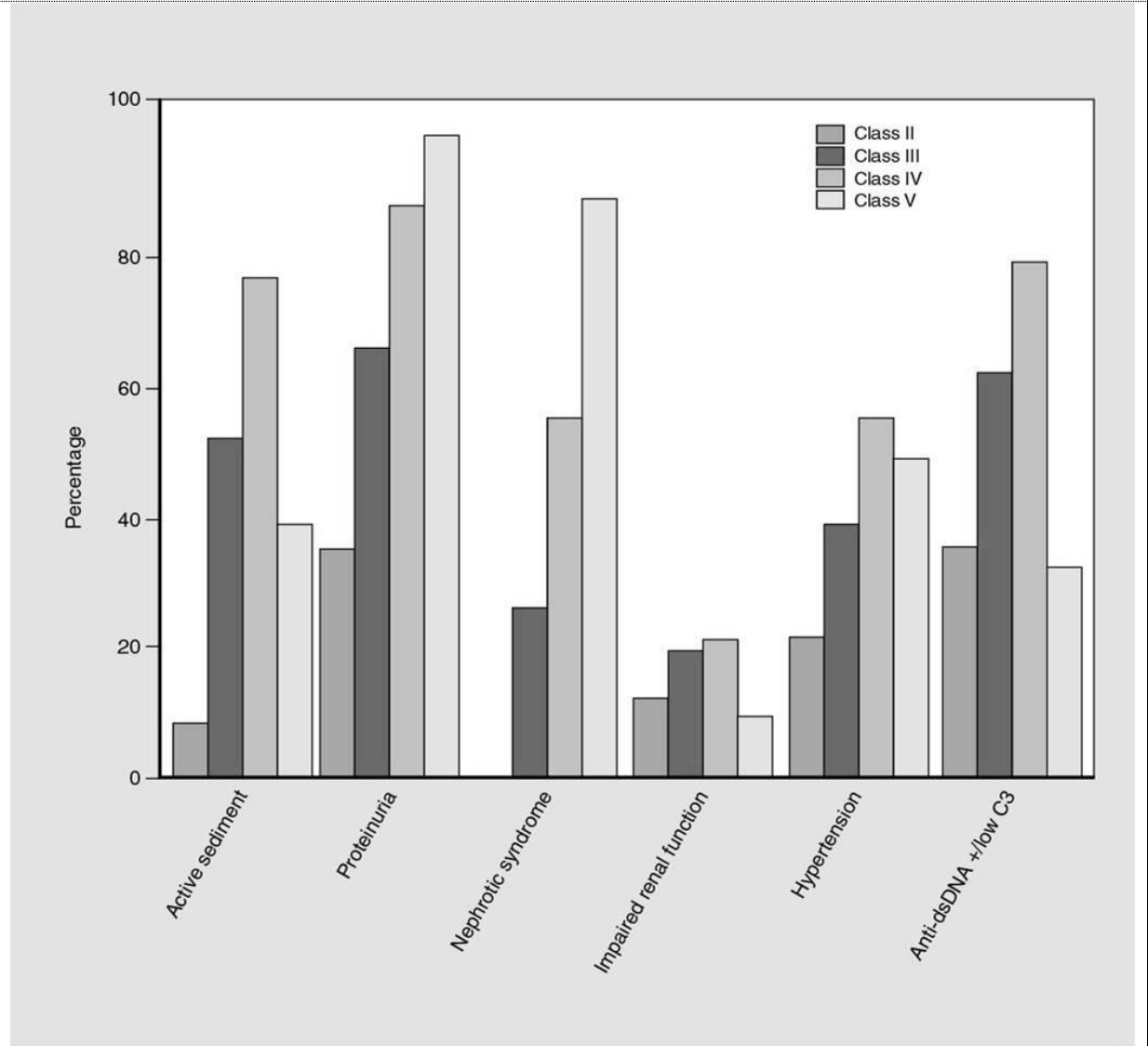
Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal proliferative lupus nephritis (involving < 50% of all glomeruli)
Class IV	Diffuse proliferative lupus nephritis ^{a,b} (involving ≥ 50% of all glomeruli) <ul style="list-style-type: none"> • Segmental lesions: IV-S (involving < 50% of the glomerular tuft) • Global lesions: IV-G (involving ≥ 50% of the glomerular tuft)
Class V	Membranous lupus nephritis ^c
Class VI	Advanced sclerosing lupus nephritis without active lesions

^aIndicate the presence of active (A), active and chronic (A/C) and chronic (C) lesions.

^bIndicate the proportion of glomeruli with fibrinoid necrosis and cellular crescents.

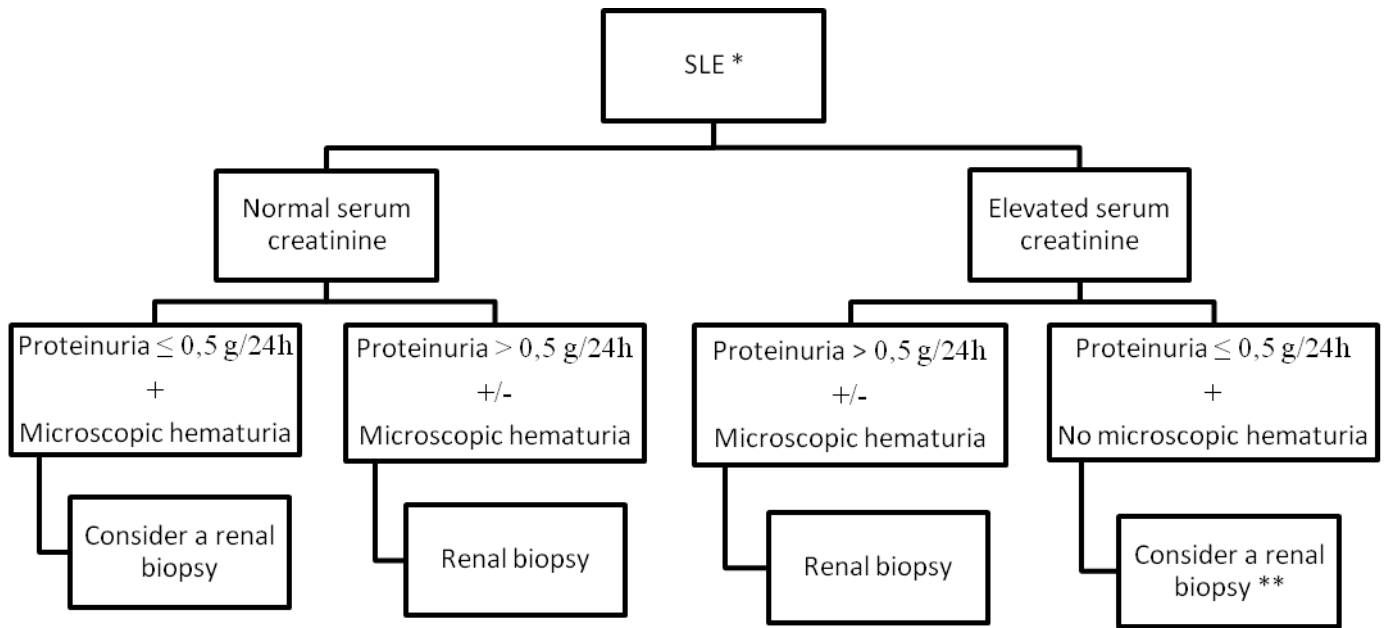
^cClass V may occur in combination with class III or IV, in which case both will be diagnosed.

Figure I: Incidence of clinical symptoms in various forms of lupus nephritis.



Lupus nephritis, based on the 1995 classification published under the auspices of the World Health Organization.

Figure II: Indications to perform a first renal biopsy in patients with Systemic Lupus Erythematosus.



*Systemic Lupus Erythematosus: at least 4 ACR criteria positive; **Consider a renal biopsy when either i) a persistent elevation of serum creatinine >30%, ii) other causes of renal impairment are excluded, iii) positive anti-phospholipid antibodies, iv) extra-renal involvement/presence of anti-dsDNA antibodies/hypocomplementemia