Managing lupus nephritis

This is the lay version of the 2019 update of the EULAR recommendations for the management of people with lupus nephritis. The original publication can be downloaded from the EULAR website: www.eular.org.

Fanouriakis A, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis 2020;79:713–723. doi:10.1136/annrheumdis-2020-216924

Introduction

EULAR recommendations give advice to doctors, nurses and patients about the best way to treat and manage diseases. EULAR has updated its recommendations on the management of people with lupus nephritis.

Doctors, nurses, other health professionals and patients worked together to develop this advice. The patients in the team ensured that the patient point of view was included.

What do we already know?

Up to 40% of people with systemic lupus erythematosus (often shortened to SLE) develop kidney disease. This form of the disease is known as *lupus nephritis.* Lupus nephritis can be difficult to treat and is linked to poor health and an increased risk of death.

EULAR and ERA-EDTA published joint recommendations in 2012. These have now been updated based on new evidence, and in order to include new treatments that have become available.

What do the recommendations say?

In total, there are 4 overarching principles and 10 groups of recommendations. The overarching principles highlight the burden of lupus nephritis, and the need to manage it in an interdisciplinary way. Looking out for symptoms and signs suggestive of kidney involvement helps to ensure optimal outcomes. Management of active phases includes an initial period of intense immunosuppressive therapy to control disease activity, followed by a longer period of less intensive therapy to try and prevent relapse.

Each recommendation is based on the best current knowledge and studies of scientific evidence or expert opinion. The more stars a recommendation has the stronger the evidence is. However, even recommendations with limited scientific evidence may be important, because the experts can have a strong opinion even when the published evidence may be lacking.

One star (*) means it is a recommendation with limited scientific evidence.

Two stars (**) means it is a recommendation with some scientific evidence.

Three stars (***) means it is a recommendation with quite a lot of scientific evidence.

Four stars (****) means it is a recommendation supported with a lot of scientific evidence.

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- **Kidney biopsy is valuable, and should be considered when there is evidence the kidneys are affected.*****
  If you have evidence of kidney involvement, such as persistent raised protein in your urine (proteinuria) or an unexplained decrease in your glomerular filtration rate (GFR, a marker of kidney function) then you should have a kidney biopsy. Other clinical or laboratory tests cannot substitute kidney biopsy.

- **Kidney biopsy results should be assessed using the International Society of Nephrology/Renal Pathology Society 2003 classification system.*****
  A classification system is a way of describing and defining your disease. The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system is considered the best for lupus nephritis. Overall, there are six classes, named with roman numerals I to VI. Class I is minimal disease, and classes move up in severity. Each assessment should consider the level of disease activity in the kidney and whether you have only *active* or a combination of *active* and *chronic* lesions; this adds A, C or A/C to the class number.

- **Indications for immunosuppressive treatment vary depending on the classification of nephritis.****/***
  Immunosuppressive drugs in combination with glucocorticoids are recommended if you have class III_A, III_{AC}, IV_A or IV_{AC}. Glucocorticoids and immunosuppression may also be recommended in some cases of pure class V nephritis.

- **Treatment aims to preserve or improve kidney function, and will depend on your nephritis class and response.*/**/***/****
  Initial treatment: If you have lupus nephritis, your treatment should aim for optimising your kidney function, accompanied by a reduction in proteinuria of at least 50% by 6 months. Initial treatment will vary depending on the nephritis class. If you are in class III or IV (±V), the recommendation is mycophenolate mofetil, or low-dose intravenous cyclophosphamide, in combination with glucocorticoids. Mycophenolate mofetil plus a calcineurin inhibitor (like tacrolimus) is an alternative. People at high risk for kidney failure can also be treated with mycophenolate mofetil or low-dose cyclophosphamide, but high-dose cyclophosphamide can also be considered. Methods to reduce cumulative glucocorticoid dose are recommended. If you have pure class V nephritis, mycophenolate mofetil in combination with lower doses of glucocorticoids is recommended as initial treatment. Alternative options for class V nephritis include intravenous cyclophosphamide, or calcineurin inhibitors (the latter alone or in combination with mycophenolate mofetil). Tailored doses of hydroxychloroquine should also be given.

  Subsequent treatment: After improvement with initial treatment, ongoing immunosuppression is recommended with either mycophenolate mofetil or azathioprine, in combination with low-dose prednisone when needed. Treatment can be gradually withdrawn after 3 to 5 years, but you should continue taking hydroxychloroquine for the long-term.

  Non-responding disease: If you do not achieve the treatment goals, it is important for the physician to work out why, including whether you have been taking your treatment as prescribed. To achieve

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a better response you might be switched to an alternative initial therapy or rituximab.

- **Other medicines may be needed alongside your nephritis treatment.*/****
  Angiotensin converting enzyme-inhibitors or angiotensin receptor blockers (drugs to treat hypertension) are recommended for all patients with proteinuria or arterial hypertension. Statins might be offered based on your lipid levels and estimated 10-year cardiovascular disease risk. Most people will be prescribed calcium or vitamin D supplementation to protect their bones, and immunisation with non-live vaccines may be recommended to protect you against infections. If you are positive for antiphospholipid antibodies, you may receive acetyl-salicylic acid. Some people might also need anticoagulant treatment. Finally, belimumab may be added to help reduce glucocorticoid use, control extra-renal lupus activity and decrease extra-renal flares.

- **In the first 2–4 months after diagnosis or flare you should be monitored every 2–4 weeks, and then according to response to treatment.*/**/*****
  Body weight, blood pressure, and blood tests should be done at every visit when your nephritis is active, and less frequently if it is stable. Your autoantibody levels may also be checked periodically. Some people may need another kidney biopsy at some point if their renal disease gets worse. If you have lupus nephritis, you will need to be monitored for the rest of your life.

- **All methods of kidney replacement treatment for end-stage renal disease can be used in people with lupus nephritis.*****
  Immunosuppression in people with end-stage kidney disease on dialysis should be guided by their particular extra-renal signs and symptoms. Transplantation may be preferred over other kidney replacement options (like dialysis) and should be considered when extra-renal lupus is inactive for at least 6 months. Antiphospholipid antibodies should be measured during transplant preparation.

- **In people with antiphospholipid syndrome-associated nephropathy, antiplatelet or anticoagulant treatment can be considered, in addition to hydroxychloroquine.****
  Kidney damage associated with antiphospholipid syndrome is a rare but distinct type of vascular nephropathy. Antiplatelet agents or anticoagulants are recommended, in addition to hydroxychloroquine.

- **Women with stable, inactive lupus nephritis can plan a pregnancy.*****
  If you are planning to have a baby, mycophenolate mofetil should be withdrawn at least 6 months before conception. There are some drugs you can continue taking throughout pregnancy and lactation, including hydroxychloroquine, prednisone, azathioprine or calcineurin inhibitors, and possible flares of lupus nephritis can also be treated. Additionally, acetylsalicylic acid is recommended to help reduce your chances of getting pre-eclampsia. During your pregnancy, you should be assessed at least every 4 weeks, preferably by a multidisciplinary team including an obstetrician with expertise in lupus nephritis.

- **Diagnosis, management and monitoring of lupus nephritis in children is similar to adults.*/****
  Children with lupus nephritis might have more severe disease, and build up more organ damage. They can be managed and treated the same as adult patients. As children get older, they will need

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a coordinated transition program from paediatric to adult care, to ensure they stick to their therapy in order to optimise their long-term outcomes.

Summary

Overall, the recommendations highlight that there are many different treatments for people with lupus nephritis. These recommendations should give you some guidance on what to expect from your doctor and what treatments you may be offered. Recommendations with just one or two stars are based mainly on expert opinion and not backed up by studies, but these may be as important as those with three or four stars.

There is a lot of information in this recommendation. We have summarized some of it in the table below, along with information about each of the classes from the 2003 classification system. The classes depend on the health of your *glomeruli* – a network of small blood vessels in your kidneys that filter your blood. Lupus nephritis causes inflammation in the kidney, which affects this network. As the glomeruli become more damaged, it is harder for the kidney to work. The treatment choices will depend not only on your class, but also on other elements of your disease, and how well it responds at each stage.

If you have any questions or concerns about your disease or your medication, you should speak to a health professional involved in your care.

Class of lupus nephritis	Description of this class	Treatment options recommended by EULAR
I (one)	**Minimal mesangial lupus nephritis** Your glomeruli might look normal, but special tests can reveal very small changes. You will only have mild or no symptoms.	• Hydroxychloroquine
II (two)	**Mesangial proliferative lupus nephritis** Too many cells accumulate in your glomeruli. There are still very few or no symptoms.	• Hydroxychloroquine
III (three)	**Focal lupus nephritis** There are lesions or scarring on less than half of your glomeruli. You may have blood in your urine, or it may look foamy.	• Hydroxychloroquine • Immunosuppressive agents (in combination with glucocorticoids), such as • Mycophenolate mofetil • Mycophenolate acid • Low-dose intravenous cyclophosphamide • Mycophenolate mofetil plus calcineurin inhibitors (tacrolimus or cyclosporine A)
IV (four)	**Diffuse lupus nephritis** At least half of your glomeruli have lesions or scarring. Your blood pressure might be raised.	• Hydroxychloroquine • Immunosuppressive agents (as above, possibly also rituximab), in combination with glucocorticoids
V (five)	**Membranous lupus nephritis** Deposits are found in the membranes of the	• Hydroxychloroquine • Immunosuppressive agents, in combination with glucocorticoids

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	glomeruli. You might be more at risk of blood clots.	• Mycophenolate mofetil • Mycophenolate acid • Cyclophosphamide • Calcineurin inhibitors • Rituximab
VI (six)	**Advanced sclerosing lupus nephritis** 90% or more of the glomeruli are affected.	• Hydroxychloroquine

Further reading

If you would like to find out more about the classes for lupus nephritis, you can read about them here:

Weening JJ, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004;15(2):241–50. https://jasn.asnjournals.org/content/15/2/241.long

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