Surveillance and management strategies for lupus nephritis: A practical summary guide for clinical settings lacking specialist care and expert histopathology

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Abstract

Lupus nephritis may be the presenting feature of Systemic Lupus Erythematosus (SLE) and is often an early complication of the disease affecting up to half of patients with SLE. It is a major cause of morbidity and mortality. It is typically heralded by the silent onset of proteinuria, then may progress to a clinically evident edematous state with hypertension and renal impairment. The overarching goals of treatment of lupus nephritis include patient survival, preservation of kidney function, prevention of disease flares and organ damage, management of comorbidities, and improvements in disease-related quality of life. Management of active lupus nephritis should include an initial period of intense immunosuppressive therapy (induction) followed by a longer period of maintenance therapy. In the English-speaking Caribbean, as in many developing states, the lack of specialists results in non-specialists having to manage cases of lupus nephritis often with limited resources and guidance. We proffer a 14-step approach which highlights key issues and allows the novice doctor to gain some level of comfort and confidence when faced with the daunting task of having to function as a combined nephrologist/ rheumatologist and assume responsibility for care of patients with this most challenging condition. It begins with case ascertainment by formal screening and home testing for proteinuria and continues with guides to the more widely available immunosuppressive therapy and addresses supportive care including a guide to effective blood pressure control.

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Introduction

Systemic Lupus Erythematosus (SLE) is the prototypic systemic autoimmune inflammatory disease predominantly affecting black women of child-bearing age. Lupus nephritis may be the presenting feature of SLE and is often an early complication of the disease affecting almost half of patients with SLE. Men are over 10 times less likely to develop SLE than women but when they do, they are then almost three times more likely to develop lupus nephritis. Younger patients tend to have more severe lupus nephritis.

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The aim in lupus nephritis management is for improved proteinuria levels by 3 months, and a 50% reduction in proteinuria (partial clinical response) by 6 months. By 12 months, therapy should aim for proteinuria <0.5 to 0.7g in 24 hours (complete clinical response). For patients with nephrotic-range proteinuria at baseline, an additional 6 to 12 months may be required to reach complete clinical response.

In the English-speaking Caribbean, as in many developing states, the lack of specialists results in non-specialists having to manage cases of lupus nephritis often with limited resources and guidance. For those settings we have developed what we consider a safe simplified approach which in our experience has been effective for the majority of cases and can help guide the novice in an isolated setting to make the necessary decisions.

The following strategies are recommended-:

1. On initial diagnosis of SLE all patients are to be screened for

lupus nephritis as follows-: urgent urinalysis by dipstick; spot urine protein/creatinine ratio (>0.5 is significant); microscopy of spun urine for cells/ casts; serum electrolytes/urea/creatinine/albumin. Abnormal results should prompt urgent nephrology/ rheumatology referral where these subspecialties exist. Thereafter monitoring for renal disease is to be a routine part of all clinic visits indefinitely. Any outstanding vaccines that can be safely given should be completed.

2. Patients with no significant proteinuria are advised on monthly home testing for proteinuria using the dipstick method. An early morning clean-catch mid-stream specimen is collected for testing (not done close to or at the time of the menstrual period). This is critical in the first 3 years of the disease - 98% of patients with SLE who develop nephritis do so within the first 3 years of diagnosis. Note that dipstick testing is a qualitative test only accurate for detecting proteinuria not quantifying it - any level of proteinuria should prompt urgent presentation for medical assessment before the routine scheduled clinic visit.
3. Other relevant investigations are as follows-:

(a) Antids DNA titre - a high antids DNA supports the presence of active lupus nephritis.
(b) Complement (C3/C4) – low complements support the presence of active lupus nephritis. Awaiting these results should not delay initiation of appropriate therapy.
(c) Antiphospholipid antibodies are associated with thrombotic microangiopathy in lupus nephritis (Appendix A).
(d) HIV, VDRL, Hepatitis B & C serology - these infectious conditions are important causes of renal disease with proteinuria and must be excluded prior to the administration of immunosuppressive treatment.

4. Patients with proteinuria greater than 0.5gram and/ or a fall in Glomerular Filtration Rate (GFR) > 5mls/ min in one month on two blood tests (if no other cause is evident) or microscopic haematuria or casts are candidates for ultrasound-guided renal biopsy and detailed histopathology where available. However, this should not delay initiation of therapy where lupus nephritis is deemed to be a good clinical diagnosis. Pregnancy should be ruled out by careful history.
5. Steroid therapy in lupus nephritis is recommended as follows: - Prednisone 1mg/kg (60mg) daily for 2 weeks aiming to wean to 10mg daily over a 12-week period (Appendix B). A lower starting dose of 0.5mg/kg may also be considered in less severe cases. For severe cases, oral prednisone may be preceded by pulse methylprednisolone 500mg IV daily for 3 days. Because of the risk of infection and the risk of Posterior Reversible Encephalopathy Syndrome (PRES) more conservative doses of methyl prednisolone are encouraged (<1gram).
6. Patients with severe lupus nephritis defined as the presence of any one or combination of the following parameters:

(a) Estimated Glomerular Filtration Rate (eGFR) < 30mls/min
(b) Serum creatinine > 265.2 umol/l (3mg/dl)
(c) Presence of crescenteric glomerulonephritis on biopsy. May be treated as follows-:
(i) Eurolupus Protocol-Cyclophosphamide (CTX) induction 500mg IV in 250mls normal saline infused over 1 hour every 2 weeks over a 12-week period (6 doses). Oral antiemetics are used to prevent nausea. Follow up therapy with mycophenolate mofetil maintenance 2-3 grams daily (preferably taken on an empty stomach).
Or
(ii) The National Institute of Health (NIH) induction protocol for severe proliferative SLE nephritis with CTX (0.5- 1.0g/m^2) given monthly over a 6-month period (6 doses) followed by administration every 3 months for 2 years - if the infection risk can be well managed. For the NIH protocol bladder toxicity is mitigated with Mesna (2-mercaptoethane sulphonate sodium) and for women in their latter childbearing years Lupron (Leuprorelin) administration in an attempt to preserve ovarian function is to be discussed. *Pneumocystis Jirovencii* prophylaxis is not universally required in settings with low or no occurrence of this condition in SLE patients (Appendix C). The advantage of intravenous CTX therapy is the assurance of demonstrable treatment adherence.

7. For patients with less severe disease, Mycophenolate Mofetil (MMF) 2-3g daily may be used for induction (Appendix D) followed by maintenance on a lower dose of MMF or on azathioprine 1-2.5mg/kg/day.
8. Alternative therapeutic options include rituximab 1gram IV infusion on Day 1/Day 15, calcineurin inhibitors e.g. Cyclosporine (2-5mg/kg/day) or tacrolimus (~2-4mg/day) either as monotherapy or in combination with mycophenolate mofetil. Newer and emerging therapies (Belimumab, Voclosporin) are considered as availability permits. Among patients with antiphospholipid syndrome-associated nephropathy, recommended treatment is with antiplatelet/anticoagulant agents.
9. Angiotensin Receptor Blockers (ARB) or Angiotensin Converting Enzyme (ACE) inhibitors reduce proteinuria and are prescribed once proteinuria surpasses 1gram.
10. Maintain blood pressure control 130/80mmHg or below. Treatment options for hypertension-:

(a) ACE inhibitor/ARB +/-
(b) Diuretic (depending on GFR, thiazide-like or loop) +/-
(c) Calcium Channel Blocker (CCB) - long acting dihydropyridine CCBs such as amlodipine are

very effective for blood pressure control, non-dihydropyridine CCBs such as diltiazem and verapamil have an additional property of modestly reducing proteinuria but caution due to potential interaction with concomitant beta blocker therapy

(d) Vasodilating beta blocker (Labetalol or carvedilol or nebivolol)

(e) For more refractory cases,

(i) Minoxidil may be added if no heart failure or

(ii) Add a Nitrate and Hydralazine if heart failure is present.

11. All patients should be prescribed Hydroxychloroquine (HCQ) (5mg/kg lean body weight) to a maximum of 400mg daily unless otherwise contraindicated. Where available documentation of a whole blood level of 700- 1000mg/ml is ideal. The dose of HCQ should be reduced in the presence of renal impairment. This drug reduced flares and improves the effectiveness of mycophenolate mofetil. Patients should have a baseline retinal screen (optical coherence tomography) then again at year 5 post initiation of treatment then annually thereafter.
12. Repeat renal biopsy may be recommended for patients with no response to immunosuppressive treatment to differentiate between ongoing activity versus irreversible damage, or to determine histologic class transition.
13. Recommendations for lupus nephritis and pregnancy - stable patients with inactive lupus nephritis and proteinuria < 500mg /24 hours off ACE inhibitor/ ARB for at least 6 months may consider pregnancy. Prednisone, azathioprine, calcineurin inhibitors, and hydroxychloroquine are compatible with pregnancy and lactation.
14. Attention must be paid to addressing potential comorbidities such as diabetes mellitus, hypercholesterolemia, osteoporosis, and depression. General healthy lifestyle- diet, exercise, weight control, sleep hygiene, stress management is to be encouraged. Involvement in support groups complements disease management and can help bolster treatment adherence. This 14-step approach highlights the key issues and allows the novice doctor to gain some level of comfort and confidence when faced with the daunting task of having to function as a combined nephrologist/rheumatologist and assume responsibility for care of patients with this most challenging condition of lupus nephritis.

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Appendix A

Testing for antiphospholipid antibody syndrome-:

This syndrome is classically characterized by recurrent arterial and venous thromboses along with pregnancy loss (after 10 weeks). It can occur as a primary phenomenon or secondary to SLE. The following tests are ordered for suspected cases-:

- Lupus anticoagulant (screening and confirmatory components)
- Anticardiolipin antibodies (IgG; IgM; IgA- the higher the titre the higher the risk of thrombosis)
- Anti-beta2- Glycoprotein 1 (IgG; IgM)

Testing is repeated in 12 weeks to confirm.
Some patients with anticardiolipin antibodies may have a false positive VDRL.

Appendix B

Proposed standard prednisone taper

(modify as needed) Prednisone 60mg PO daily × 14 days

Prednisone 40mg PO daily × 14 days Prednisone 35mg PO daily × 7 days Prednisone 30 mg PO daily × 7 days Prednisone 25 mg PO daily × 7 days Prednisone 20 mg PO daily × 7 days Prednisone 15 mg PO daily × 7 days

Prednisone 10mg PO daily × 7 days (by week 12) Prednisone 7.5mg PO daily × 7 days

Prednisone 5mg PO daily × 7 days (may need to hold long-term at this dose) Prednisone 2.5mg PO daily × 7 days then OFF

Appendix C

Sample cyclophosphamide infusion for NIH protocol
Cyclophosphamide (0.5- 1g/m^2) given monthly x 6 doses. Followed by 3-monthly doses for a duration of 2 years.

Monitoring - Complete Blood Count (CBC), serum creatinine, urinalysis prior to each infusion CBC 10 days after each infusion (used to adjust the dose for the next infusion)

1st infusion - Start 500mg/m^2 in patients over age 70 years, or where creatinine clearance (CrCl) < 40 mls/min. Reduce dose by 30% if CrCl < 30mls/min, and by 50% if on haemodialysis and the dose should be given after dialysis.

Subsequent doses - Based on nadir of white cell count (WBC)10 days from the preceding infusion.

WBC > 4000 – increase dose by 20-25% to maximum 1g/m^2. Between 3500 – 4000 – keep the same dose.
< 3500 or absolute neutrophil count (ANC) < 1500 - decrease dose by 20%
< 2500 or ANC < 1000 -hold, until WBC increases.
Evidence of active infection necessitates a deferral of infusions.

Pneumocystis Jirovencii prophylaxis - This is not universally necessary. Where it is deemed necessary options are Bactrim DS 1 tablet Monday, Wednesday, Friday. For patients with sulphur allergies, atovaquone 1500mg daily, dapsone 100 mg daily or monthly inhaled pentamidine infusions can be used.

Contraception and reproductive health - Women must have effective contraception during infusion period and up to 6 months after.

To reduce the risk of ovarian failure and preserve future fertility in women in their latter childbearing years, Leuprorelin (GnRH agonist) may be given to suppress ovarian function.

Post cyclophosphamide nausea - Ondansetron or granisetron. Alternatives include metaclopramide and dimenhydrinate.

Haemorrhagic cystitis prophylaxis - Mesna (2-mercaptoethane sulphonate sodium)- intravenous dose should be 20% that of the cyclophophosphamide dosage given 2 hours prior to the pulse and repeated 2 and 6 hours after the pulse of cyclophosphamide. Extra fluid intake as can be safely undertaken, and frequent bladder emptying are advised.

Appendix D

Dosing of mycophenolate mofetil for induction of lupus nephritis

Week 1 – 500mg bid
Week 2 – 750mg bid
Week 3 – 1g bid (maybe an appropriate maximum dose for Caucasian patients)
Week 4 – 1.5g bid

Disclosures – None