Title: Diagnosis, monitoring and treatment of systemic lupus erythematosus: a systematic review of clinical practice guidelines.

Authors' names, major degree and affiliations:

David J Tunnicliffe, MIPH[1,]2, Davinder Singh-Grewal, PhD[3,4,5], Siah Kim, MBBS[1,2], Jonathan C Craig, PhD[1,2], Allison Tong, PhD[1,2]

Institution where the work was done:

1. Sydney School of Public Health, The University of Sydney, Sydney, Australia
2. Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, Australia
3. Sydney Medical School, The University of Sydney, Sydney, Australia
4. Paediatric Rheumatology, The Sydney Children's Hospital's Network, Sydney, Australia
5. Faculty of Medicine, The University of New South Wales, Sydney, Australia

Corresponding author:

David Tunnicliffe

Centre for Kidney Research,

The Children's Hospital at Westmead,

Westmead, NSW 2145 Australia

Phone: +61 2 9845 1470

Fax: +61 2 9845 1491

Email: david.tunnicliffe@health.nsw.gov.au

Financial support:

DT is funded by a postgraduate scholarship from the Sydney Medical School, The University of Sydney.

Word count:

2939/3800 words

ABSTRACT

Objectives: Management of SLE is complex and variability in practices exists. Guidelines have been developed to help improve the management of SLE patients but there has been no formal evaluation of these guidelines. This study aims to compare the scope, quality and consistency of clinical practice guidelines on the diagnosis, monitoring and treatment of patients with systemic lupus erythematosus (SLE).

Methods: Electronic databases were searched up to April 2014. The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument and textual synthesis was used to appraise and compare recommendations.

Results: Nine clinical practice guidelines and five consensus statements were identified, which covered seven topics: diagnosis, monitoring, treatment, neuropsychiatric SLE, lupus nephritis, anti-phospholipid syndrome and other manifestations of lupus. The methodological quality of the guidelines was variable, with the overall mean AGREE II scores ranging from 31% to 75% out of a maximum 100%. Scores were consistently low for applicability, with only one guideline scoring above 50%. There was substantial variability in the treatments recommended for class II and V lupus nephritis, the recommended duration of maintenance therapy for class III/IV lupus nephritis (from 1 to 4 years), and timing of ophthalmological examination for patients on corticosteroids.

Conclusion: Published guidelines on SLE cover a complex area of clinical care but the methodological quality, scope and recommendations varied substantially. Collaborative and multidisciplinary efforts to develop comprehensive, high-quality evidence-based guidelines are needed to promote best treatment and health outcomes for patients with SLE.

Significance and Innovations:

- Multiple clinical practice guidelines have been developed in the area of systemic lupus erythematosus globally
- SLE Guidelines vary in scope, methodological rigor and recommendations based on poor quality evidence
- International collaborative multidisciplinary efforts are required for the development of high quality guidelines.

Introduction

Systemic lupus erythematosus (SLE) is a multi-system disease with a highly variable course. Management is complex and involves clinicians across many different specialties with important variation in practice apparent across and within specialties evident. For example, prescription of anti-malarial drugs and testing for anti-phospholipid antibodies are routine among rheumatologists but not among non-rheumatologists[1]. Prescribed doses for glucocorticoid regimens also differ across specialties[2]. Monitoring protocols and measures of disease activity in patients with nephritis varies among rheumatologists, with those with greater than 10 years experience more likely to use qualitative (dipstick) than quantitative measures of proteinuria to guide therapy[3]. Significant variation in practice is also seen within specialty groups such as paediatric rheumatology[4].

Clinical practice guidelines are “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances”[5]. They need to be rigorously developed, consistent with the scientific literature, accessible and implementable in practice[6, 7]. Given the complexity of and variation in SLE management, clinical practice guidelines may support clinical decision-making, improve care, and optimize outcomes. This review aims to compare the scope, quality and consistency of clinical practice guidelines on the diagnosis, monitoring and treatment of patients with SLE.

Materials and Methods:

Eligibility criteria

Evidence based clinical practice guidelines and consensus statements focused primarily on diagnosis, monitoring and management of SLE were included. Non-English language publications were excluded due to lack of resource for translation. Laboratory protocols, primary research, opinions, previous guideline versions and draft unpublished guidelines were excluded.

Search for guidelines and consensus statements

MEDLINE, Embase, PsycINFO and CINAHL were searched from inception to April 2014. The search strategies are provided in supplementary data (table S1). We also searched the websites of guideline organizations (Guidelines International Network and National Guideline Clearinghouse, Intercollegiate Guidelines Network [SIGN], National Institute of Health and Care Excellence [NICE]) and professional rheumatology and nephrology societies. The titles and abstracts were screened by DJT/AT and those which did not meet the inclusion criteria were discarded. Full texts of the remaining citations were obtained and examined for eligibility.

Appraisal of guidelines and consensus statements

The quality of the each guideline was appraised using the Appraisal of Guidelines and Research and Evaluation (AGREE) II instrument[8]. AGREE II is an internationally validated 23 item tool involving six domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability and editorial independence. Each guideline was independently appraised by two authors (DJT and SK) and each item within

the six domains was rated on a Likert scale ranging from 1 to 7 (1= ‘strongly disagree’; 7= ‘strongly agree’). Differences in scores were resolved through discussion until consensus was reached. Domain scores were calculated as per the AGREE II user’s manual, where a total quality score was obtained for each domain by summing the total items scores. The following formula was used to determine domain scores as a percentage of the total maximum score possible for that domain.

$$\text{domain score} = \left(\frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possble score} - \text{minimum possible score}} \right) x100$$

Maximum possible score= highest possible score (7) x number of items x number of appraisers (2)

Minimum possible score= lowest possible score (1) x number of items x number of appraisers (2)

Synthesis of guideline recommendations

Textual descriptive synthesis was performed to analyse the scope, content and consistency of recommendations across the guidelines. All text from guidelines were imported into HyperRESEARCH software for managing and retrieving textual data. DJT inductively identified topics addressed by the guidelines and coded the guideline recommendations into the corresponding topic. For each topic, the guideline recommendations were compared to identify similarities and differences.

Results:

Search and guideline characteristics

The search yielded 2399 citations. Fourteen were eligible and included (nine clinical practice guidelines and five consensus statements (figure 1). The articles were published between 1999 and 2014, nine from international groups and five from national groups. Eight guidelines were published by rheumatology societies or working groups, one guideline was published by a nephrology guideline organization, and five guidelines were published by multidisciplinary working groups. The characteristics of the guidelines are provided in table 1. Four (29%) guidelines conducted external peer review and 11 (79%) guidelines included a systematic literature review, although the methods of data extraction and synthesis varied (supplementary data table S2).

Methodological quality

Table 2 provides a summary of the results of the methodological quality appraisal. The domain scores of each guideline are displayed in the supplementary data (table S3). The highest scoring domain was scope and purpose 67% (44-89%), the lowest scoring domain was applicability 29% (4-67%).

Descriptive synthesis

The seven topics addressed by the guidelines were: diagnosis, monitoring, treatment, neuropsychiatric SLE, lupus nephritis, anti-phospholipid syndrome and other organ manifestations. The scope of the guidelines varied considerably (supplementary data table S4, S5).

Diagnosis

The American College of Rheumatology (ACR) criteria for classification of patients with SLE[9] are widely used as a diagnostic aid. In patients with four of the 11 criteria the diagnosis of SLE can be made with 95% specificity and 85% sensitivity[9]. One guideline specifically stated that SLE should be suspected in any patient with features affecting two or more organ systems listed in the ACR criteria[10].

Monitoring

Six guidelines provided recommendations on monitoring disease activity, disease damage, and quality of life[10-15].

Measuring disease activity with full blood count, serum creatinine and urinalysis[10-12], and other tests including : C3/C4, anti-dsDNA, anti-phospholipid, anti-RO/SSA, C-reactive protein, anti-C1q, serum albumin, estimated glomerular filtration rate (eGFR) and urinary protein/creatinine ratio were recommended[12, 13]. The SLE Disease Activity Index (SLEDAI) was the only tool specified for adults[13] and adolescents[15].

Annual assessment of organ damage was recommended[11, 13, 15], The Systemic Lupus International Collaborating Clinics/American College of Rheumatology/ Damage Index (SLICC/ACR/SDI) was specified for use in both the adult[13] and paediatric[15] populations.

Quality of life monitoring by clinical interview and/or Visual Analogue Scale [11] or Paediatric Quality of Life Inventory Generic Core Scale version 4.0 were suggested[15].

Monitoring of drug toxicity was mentioned but no thresholds were provided[10, 11]. The National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 was recommended for use to monitor treatment side effects in paediatric SLE[15].

Long term monitoring was recommended[10, 14], with 3-6 month assessment for mild disease and increased frequency for patients with severe active disease and in pregnancy[10]. Patients with non-active SLE and no damage or comorbidity could be assessed every 6 to12 months with additional evaluation prior to pregnancy, surgery, transplantation, use of oestrogen containing medication or occurrence of a new neurological or vascular event[11].

Recommendations for monitoring comorbidities were presented in three guidelines[11, 12, 16]. EULAR 2010 stated that all patients with SLE should be assessed for adequate calcium intake, vitamin D intake, regular exercise, smoking status and cardiovascular risk factors, blood cholesterol, glucose, BMI and blood pressure with no specific parameters provided[11]. Ophthalmological examination for patients taking anti-malarial medication varied; one guideline recommending annual[16] and another five yearly review[11] (table 3).

The ACR 1999 guideline advocated multidisciplinary monitoring of SLE, involving collaboration among primary care physicians, specialists, nurses, pharmacist, families and patients[10].

Treatment

Treatment was covered by five guidelines. Recommendations focused on ensuring long-term survival, preventing organ damage and improving quality of life by controlling disease activity, minimizing comorbidities and drug toxicity[14]. Treatment targets for SLE were

defined as remission and prevention of flares[14], with goals defined through a shared decision making process between the patient and clinician[14, 17].

Recommended treatment for constitutional SLE included anti-malarial[10, 12, 14], corticosteroids and non-steroidal anti-inflammatory drugs[10, 12]. Appropriate adjunct therapy included vitamin D and calcium supplements for preventing osteoporosis in patients using corticosteroids, antihypertensive and statins were also recommended[12]. One guideline recommended that all patients with SLE should receive education, counselling and support, particularly in terms of managing the complexity and unpredictability of the disease[10]. Multidisciplinary care involving nephrologists, rheumatologists and other appropriate specialists was recommended by two guidelines[12, 14].

Neuropsychiatric SLE

The diagnostic work-up to identify neuropsychiatric disease for patients with SLE should be the same as the general population[12, 18]. The EULAR guideline[18] provided in-depth recommendations regarding diagnosis with a diagnostic work-up for acute confusional state (cerebrospinal fluid analysis and MRI) and optic neuritis (complete ophthalmological evaluation, MRI and visual evoked potentials). One guideline addressed recommended evaluating attention, concentration and memory for cognitive impairment[11].

Treatment was discussed in four guidelines[12, 13, 17, 18]. The use of corticosteroids and immunosuppressive therapy in neuropsychiatric SLE of inflammatory origin was recommended in both EULAR guidelines[12, 18]. For severe disease such as acute confusional state, movement disorders, myelitis, psychosis or peripheral nephropathy induction therapy (high dose corticosteroids and IV cyclophosphamide) followed with maintenance therapy with less intensive immunosuppression was recommended[18]. Manifestations, including cerebrovascular, cognitive dysfunction, seizures and major

depression should be managed the same as for the general population with anti-coagulation recommended for patients with anti-phospholipid syndrome. Methylprednisone alone or in combination with immunosuppression was recommended for optic neuritis[18]. Other suggestions included Rituximab for cognitive deficits, psychosis or seizures[13] and intravenous immunoglobulin, immunoadsorption or plasmapheresis for refractory disease not caused by anti-phospholipid syndrome or atherosclerosis[17].

Lupus Nephritis

Twelve guidelines provided recommendations on lupus nephritis in four main areas -

1) Indications for renal biopsy and monitoring*:* Four guidelines specified indications for first renal biopsy (table 3). There was variability in proteinuria thresholds for first renal biopsy, some guidelines recommended biopsy when proteinuria was 0.5g/24hr with active urine sediment[19-21], in addition another guideline recommended biopsy when proteinuria was 1g/24hr alone[21]. Monitoring C3/C4, anti-dsDNA, full blood cell count and serum creatinine were recommended for nephritis; while other recommendations varied (table 3).

2) Treatment: Recommendations are summarized in Table 4. Class II recommendations were classified by range of proteinuria by three guidelines,[16, 19, 22] but not classified by one guideline[23]. One guideline did not separate class V by non-nephrotic and nephrotic proteinuria and recommended that all class V be treated the same as class III and IV[16], unlike four other guidelines[19, 20, 22, 23] which recommended only class V with persistent nephrotic proteinuria be treated the same as class III and IV.

There were inconsistencies in recommendations for class III and IV induction and maintenance therapy. Three guidelines suggested a change of induction agent if there was a failure to respond by six months[12, 16, 20] and two recommended this at three months[21, 22]. The duration of maintenance therapy varied from one to four years[14, 16, 19, 21, 22].

Hydroxychloroquine use in all lupus nephritis patients was recommended by five guidelines[16, 19-22], though one guideline recommended its use only in mild to moderate disease[23]. Seven guidelines[10, 15, 16, 19-22] dealt with adjunct therapy for comorbidities for lupus nephritis patients, which included antihypertensives, statins, vitamin D and calcium supplementation for bone protection and vaccination recommendations (supplementary data table S6).

Four guidelines[15, 16, 19, 21] provided definitions of partial and complete remission of lupus nephritis where serum creatinine reduction for complete remission was defined as <1.2mg/dl[16] or within 125% of baseline at 6-12 months after induction therapy[21], (supplementary data table S7).

3) Reproductive health: Seven guidelines addressed this issue (table 5). EULAR EDTA/ERA recommended that pregnancy should be planned in patients with inactive lupus nephritis and urinary protein creatinine ratio <50 mg/mmol for the preceding 6 months and preferably a glomerular filtration rate (GFR) >50 ml/min[19]. Other guidelines indicated that pregnancy should not occur until complete remission of lupus nephritis[20, 22].

4) Paediatric lupus nephritis*:* Three guidelines addressed this issue[15, 19, 22]. Two guidelines recommended that it should be managed similar to adults[19, 22], with drug dosages based on patient size and GFR[22]. Coordinated transition from paediatric to adult care recommended[19]. One guideline discussed induction therapy for proliferative lupus nephritis, with in-depth corticosteroid and immunosuppressant regimens provided; drug toxicity thresholds and monitoring tests for mycophenolate mofetil and mycophenolate sodium/acid were also provided[15].

Anti-phospholipid syndrome

The therapeutic goal was prevention of thromboembolic events[14, 17]. Low-dose aspirin was recommended as primary prevention for thrombosis[12, 19], preeclampsia and pregnancy loss[12, 19, 21, 22] and associated nephropathy[19, 21], while in nephropathy anti-malarial and/or antiplatelet/anticoagulation therapy could be considered[19], with INR of 2-3[22].

Long-term anticoagulation for secondary prevention of recurrent stroke,[19] or thrombosis was recommended[12, 16]. Intensive immunomodulatory therapy (high dose glucocorticoids, IV immungloublins, plasmapheresis) or B cell depletion (rituximab or apheresis) were suggested for catastrophic anti-phospholipid syndrome[17].

Other manifestations of SLE

Three guidelines provided recommendations regarding other organ manifestations of SLE[13, 16, 22]. Lupus arthritis standard of care included corticosteroids, anti-malarial drugs, azathioprine and methotrexate[13, 17]. For refractory disease, mycophenolate mofetil as well as rituximab were suggested[13, 17]. Anti-IL-1 and anti-TNF antagonists were not recommended in these patients[17].

The standard of care for haematological manifestations of SLE included corticosteroids and azathioprine, mycophenolate or cyclophosphamide[17], with rituximab in refractory disease[13, 17]. Plasma exchange[18, 23] or immunoadsorption were mentioned[17]. as was splenectomy in disease refractory to drug therapy.[17]

Discussion

The variability in published guidelines for SLE was substantial, particularly in terms of scope and methodological rigor. Many recommendations were consistent but major discrepancies were observed for specific clinical situations, particularly proteinuria thresholds indicating renal biopsy, treatment of class II and V nephritis and duration of maintenance therapy.

Guideline scope varied broadly, ranging from the complete management of SLE to off label medication use. Diagnosis of SLE was sparsely covered by guidelines and perhaps this is because it remains a challenging area due to the wide differential diagnoses, lack of evidence on the signs, symptoms and biomarkers for SLE and a lack of consensus[24-26]. Guidelines rarely discussed the treatment goal of complete and/or partial remission, which are frequently reported in randomized control trials of treatment for lupus nephritis despite there being no standardized criteria[27].

Although most guideline recommendations were formed on the basis of a systematic literature review, there were important differences in the approach to evidence appraisal and grading of recommendations. Guideline applicability was generally poor using the AGREE II instrument. For example the target clinical context and patient population were often not specified. Also, potential barriers to guideline implementation were not identified in most guidelines. To assess barriers, we suggest using the National Institute for Clinical Studies barrier tool[28], or Barriers identification and Mitigation tool[29]. Furthermore, criteria and frequency for auditing should be provided, for example, lupus nephritis guidelines could suggest collecting data on the indication for renal biopsy for on-going audit. Well-designed, focused guideline implementation projects with active involvement from guideline organizations are widely advocated[30]. Mold et al. 2007 explored adherence to national guidelines on asthma using multifaceted interventions in a cluster randomized trial, which showed facilitation of the guideline by an independent source improved adherence to

recommendations compared to passive facilitation, by the provision of education and performance feedback alone[31].

Improving guideline applicability could also be achieved by the active involvement of patient and caregivers in their development, which has been widely advocated[32-34], yet only one guideline addressed stakeholder involvement by specifically involving patients in guideline development. Active consumer engagement can be facilitated by involving more than one consumer in working groups or conducting stakeholder input exercises to elicit consumers' preferences and priorities[35], and this has been successfully conducted for developing guidelines addressing other specialties including chronic kidney disease[36].

The recommendations on the diagnosis, monitoring and treatment for lupus nephritis varied across guidelines and this could be due to the different populations included. For example, one guideline focused on the treatment of paediatric patients[15], and another guideline focused on treatment of adult Asian patients[23]. These discrepancies were more apparent in areas with low quality evidence and were thus based on expert opinion and consensus, for example treatment of class II and V lupus nephritis. In some areas evidence was not included in guideline recommendations, for example intravenous cyclophosphamide use in induction therapy. A recent Cochrane review suggested that mycophenolate mofetil and corticosteroids have the same efficacy at inducing remission and a better side effect profile compared to cyclophosphamide and corticosteroids[37]. Two guidelines were published after this review[15, 23] but specific therapies for lupus nephritis induction was not covered by one[14], while the other recommended corticosteroid and either mycophenolate mofetil or cyclophosphamide induction therapy[23].

Some important areas of treatment were not covered in guidelines, such as non-adherence. Rates of non-adherence in SLE have been reported as high as 76%[38] and are associated with a higher risk of flare, morbidity, hospitalization and poor renal outcome[39]. Non-

adherence to therapy as a cause of treatment failure is commonly seen in clinical practice[28] and may affect therapeutic decisions. Addressing the issue of adherence is likely to be an important part of optimizing outcomes and a number of trials are underway examining a mean of measuring adherence and will help inform future guidelines[40], while further studies are required to identify appropriate interventions for adherence in chronic disease[41].

This study is the first to systematically review the quality of clinical practice guidelines on SLE diagnosis, monitoring and treatment. However, our study has limitations. The assessment of the guidelines is based on the reporting by guideline developers and the exclusion of non-English guidelines may limit the generalizability of the findings to other settings. Overall there is significant variability in existing guidelines for the management of SLE. Some of the variation is explained by the paucity of evidence in areas such as biomarkers, signs and symptoms for the monitoring and diagnosis of SLE, studies to identify the lowest ‘safe’ dose of corticosteroid and the duration of maintenance therapy for patients with nephritis. Furthermore evidence-based criterion for diagnosis, SLE flare, SLE remission need to be better defined and means of monitoring adherence would be a beneficial addition to guidelines.

Clearly a great deal of work has been done in developing the identified guidelines but to avoid duplication of effort in the future we recommend that international collaborative multidisciplinary efforts are undertaken to ensure the development of comprehensive, high quality evidence-based guidelines and improve the treatment and health of patients with SLE.

References:

1. Bernatsky S, Boivin JF, Joseph L*, et al.* Mortality in systemic lupus erythematosus. Arthritis Rheum. 2006;54:2550-7.

2. Lerang K, Gilboe I-M, Gran JT. Differences between rheumatologists and other internists regarding diagnosis and treatment of systemic lupus erythematosus. Rheumatology. 2012;51:663-9.

3. Walsh M, Jayne D, Moist L*, et al.* Practice pattern variation in oral glucocorticoid therapy after the induction of response in proliferative lupus nephritis. Lupus. 2010;19:628-33.

4. Siedner MJ, Christopher-Stine L, Astor BC, Gelber AC, Fine DM. Screening for proteinuria in patients with lupus: a survey of practice preferences among American rheumatologists. J Rheumatol. 2007;34:973-7.

5. Brunner H, Klein-Gitelman M, Ying J, Tucker L, Silverman E. Corticosteroid use in childhood-onset systemic lupus erythematosus-practice patterns at four pediatric rheumatology centers. Clin Exp Rheumatol. 2009;27:155-62.

6. Grimshaw J, Russell I. Achieving health gain through clinical guidelines. I: Developing scientifically valid guidelines. Quality in health care. 1993;2:243.

7. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet. 1993;342:1317-22.

8. Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. BMJ. 1999;318:527.

9. Hochberg M. for the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40:1725.

10. Guidelines for referral and management of systemic lupus erythematosus in adults. Arthritis Rheum. 1999;42:1785-96.

11. Mosca M, Tani C, Aringer M*, et al.* European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis. 2010;69:1269-74.

12. Bertsias G, Ioannidis JPA, Boletis J*, et al.* EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis. 2008;67:195-205.

13. Calvo-Alén J, Silva-Fernández L, Úcar-Angulo E*, et al.* SER Consensus Statement on the Use of Biologic Therapy for Systemic Lupus Erythematosus. Reumatología Clínica. 2013;09:281-96.

14. van Vollenhoven RF, Mosca M, Bertsias G*, et al.* Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. Ann Rheum Dis. 2014;73:958-67.

15. Mina R, von Scheven E, Ardoin SP*, et al.* Consensus treatment plans for induction therapy of newly diagnosed proliferative lupus nephritis in juvenile systemic lupus erythematosus. Arthritis Care Res. 2012;64:375-83.

16. Ruiz IG, Espinosa G, Frutos M*, et al.* Diagnosis and treatment of lupus nephritis. Consensus document from the systemic auto-immune disease group (GEAS) of the Spanish Society of Internal Medicine (SEMI) and Spanish Society of Nephrology (SEN). Nefrología: publicación oficial de la Sociedad Española Nefrologia. 2012;32:1.

17. Aringer M, Burkhardt H, Burmester GR*, et al.* Current state of evidence on “off label” therapeutic options for systemic lupus erythematosus, including biological immunosuppressive agents, in Germany, Austria, and Switzerland – a consensus report. Lupus. 2011.

18. Bertsias GK, Ioannidis JPA, Aringer M*, et al.* EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis. 2010;69:2074-82.

19. Bertsias GK, Tektonidou M, Amoura Z*, et al.* Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012;71:1771-82.

20. Hahn BH, McMahon MA, Wilkinson A*, et al.* American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res. 2012;64:797-808.

21. Van Tellingen A, Voskuyl A, Vervloet M*, et al.* Dutch guidelines for diagnosis and therapy of proliferative lupus nephritis. Neth J Med. 2012;70:199-207.

22. KDIGO G. Work Group. KDIGO clinical practice guideline for glomerulonephritis. Kidney inter, Suppl. 2012;2:139-274.

23. Mok CC, Yap DY, Navarra SV*, et al.* Overview of lupus nephritis management guidelines and perspective from Asia. Int J Rheum Dis. 2013;16:625-36.

24. Bertsias GK, Pamfil C, Fanouriakis A, Boumpas DT. Diagnostic criteria for systemic lupus erythematosus: has the time come? Nat Rev Rheumatol. 2013;9:687-94.

25. Doria A, Zen M, Canova M*, et al.* SLE diagnosis and treatment: when early is early. Autoimmun Rev. 2010;10:55-60.

26. Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: A critical review. Journal of autoimmunity. 2014;48:10-3.

27. Boumpas D, Balow J. Outcome criteria for lupus nephritis trials: a critical overview. Lupus. 1998;7:622-9.

28. Bose B, Silverman ED, Bargman JM. Ten Common Mistakes in the Management of Lupus Nephritis. Am J Kidney Dis. 2013.

29. Gurses AP, Murphy DJ, Martinez EA, Berenholtz SM, Pronovost PJ. A practical tool to identify and eliminate barriers to compliance with evidence-based guidelines. Jt Comm J Qual Patient Saf. 2009;35:526-32.

30. Grol R. Successes and failures in the implementation of evidence-based guidelines for clinical practice. Medical care. 2001;39:II-46-II-54.

31. Mold JW, Fox C, Wisniewski A*, et al.* Implementing Asthma Guidelines Using Practice Facilitation and Local Learning Collaboratives: A Randomized Controlled Trial. Ann Fam Med. 2014;12:233-40.

32. Krahn M, Naglie G. The next step in guideline development: incorporating patient preferences. Jama. 2008;300:436-8.

33. Nilsen E, Myrhaug H, Johansen M, Oliver S, Oxman A. Methods of consumer involvement in developing healthcare policy and research, clinical practice guidelines and patient information material. Cochrane Database Syst Rev. 2006;3.

34. Schünemann H, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 10. Integrating values and consumer involvement. Health Res Policy Syst. 2006;4:22.

35. Eccles MP, Grimshaw JM, Shekelle P, Schünemann HJ, Woolf S. Developing clinical practice guidelines: target audiences, identifying topics for guidelines, guideline group composition and functioning and conflicts of interest. Implementation Science. 2012;7:60.

36. Tong A, Lopez-Vargas P, Howell M*, et al.* Consumer involvement in topic and outcome selection in the development of clinical practice guidelines. Health Expect. 2012;15:410-23.

37. Henderson L, Masson P, Craig JC*, et al.* Treatment for lupus nephritis. Cochrane Database of Systematic Reviews. 2012.

38. Costedoat-Chalumeau N, Pouchot J, Guettrot-Imbert G*, et al.* Adherence to treatment in systemic lupus erythematosus patients. Best Practice & Research Clinical Rheumatology. 2013;27:329-40.

39. Bruce IN, Gladman DD, Urowitz MB. Factors associated with refractory renal disease in patients with systemic lupus erythematosus: the role of patient nonadherence. Arthritis Care & Research. 2000;13:406-8.

40. Costedoat-Chalumeau N. International prospective study on adherence to treatment in patients with active systemic lupus erythematosus (TPASLE) 2011 [cited 2014 15th July]; Available from: http://clinicaltrials.gov/show/NCT01509989.

41. Nieuwlaat R, Wilczynski N, Navarro T*, et al.* Interventions for enhancing medication adherence. The Cochrane Library. 2014.

Table 1: Characteristics of included guidelines

Guideline Organization/ Society	Guideline Name/s	Year of Publication	Target Users	Work Group Specialties	Guideline Review	Methods Support	Evidence Base	Level of Evidence *	Grade of recommendation †
EULAR [12]	EULAR recommendations for the management of SLE	2008	Not stated	Rheumatology Immunology Nephrology Epidemiology	Review (unclear if external)	Editorial Team	Systematic review and expert opinion	+	+
EULAR [18]	EULAR recommendations for the management of neuropsychiatric SLE	2010	Not clear	Rheumatology Neurology Radiology Immunology Epidemiology	External peer review	Editorial Team	Systematic review	+	+
EULAR [11]	EULAR recommendations for monitoring patients with SLE	2010	Not clear	Rheumatology General Medicine Dermatology Nephrology Immunology	External peer review	Editorial Team	Systematic review	+	+
EULAR/ERA-EDTA [19]	(EULAR/ERA-EDTA) recommendations for the management of lupus nephritis	2012	Not clear	Rheumatology Nephrology Pathology General medicine Neurology	External peer review	Editorial Team	Systematic review	+	+
ACR [10]	Guidelines for referral and management of SLE in adults	1999	Primary care physicians	Rheumatology	Reviewed by primary care physicians	Not stated	Available evidence‡ and expert opinion	—	—
ACR [20]	ACR Guidelines for screening, treatment and management of lupus nephritis	2012	Physicians managing lupus nephritis patients	Rheumatology Nephrology	Internal Review	Working group	Systematic review and expert opinion	+	—
KDIGO [22]	KDIGO Guideline for Glomerulonephritis. Chapter 12: Lupus Nephritis	2012	Nephrologists	Nephrology	External peer review	Evidence Review Team	Systematic review	+	+
SER [13]	SER consensus statement on the use of Biologic Therapy for SLE	2013	Clinicians involved in treatment of SLE patients	Rheumatology	Not stated	SER Research Unit	Systematic review	+	+
SEMI and SEN [16]	Diagnosis and treatment of lupus nephritis. Consensus document	2012	Not clear	Rheumatology Nephrology	Not stated	Not stated	Systematic review and expert opinion	+	+

Guideline Organization/ Society	Guideline Name/s	Year of Publication	Target Users	Work Group Specialties	Guideline Review	Methods Support	Evidence Base	Level of Evidence *	Grade of recommendation †
Dutch Working Group on SLE [21]	Dutch Guidelines for diagnosis and therapy of proliferative lupus nephritis	2012	Not clear	Rheumatology Nephrology Immunology	Not stated	Not stated	Systematic review and expert opinion	+	—
Working group of experts on SLE/ Aringer et al. [17]	'off-label' therapeutic options for SLE.	2012	Clinicians involved in treatment of difficult SLE	Rheumatology	Not stated	Not stated	Systematic review and expert opinion	+	—
T-2-T international task force [14]	Treat-to-target in systemic lupus erythematosus: recommendations from an international task force	2014	Those involved in care of patients with SLE	Rheumatology Nephrology Immunology Dermatology Internal medicine Patient representative	External peer review	Not stated	Systematic review and expert opinion	+	+
ALNN [23] §	Lupus nephritis management guidelines, perspective from Asia	2013	Not clear	Nephrology Rheumatology	Not stated	Not stated	Available evidence‡ and expert opinion	+	+
CARRA [15]	Consensus treatment plans for induction therapy of proliferative lupus nephritis in juvenile SLE	2012	Paediatric rheumatologists	Rheumatology	Not stated	Not stated	Systematic review and expert opinion	—	+

EULAR- European League Against Rheumatism; **ERA-** European Renal Association; **EDTA-** European Dialysis and Transplant Association; **ACR-** American College of Rheumatology; **KDIGO-** Kidney Disease Improving Global Outcomes; **SER-** Spanish Society of Rheumatology; **SEMI-** The Spanish Society of Internal Medicine; **SEN-** Spanish Society of Nephrology; **T-2-T**- Treat-to-target; **ALNN-** Asian Lupus Nephritis Network **CARRA**- Childhood Arthritis and Rheumatology Research Alliance

+ = used in guideline recommendations — = not used in guideline recommendations
***,** † Detailed explanation of level of evidence and grade of recommendation in supplementary data (table S2).

‡ Available evidence- Unclear if systematic review completed.

§ ALLN 2013 is also published in Nephrology. Mok, CC, Yap DYH, Navara SV, Liu ZH, Zhao MH, Lu L, Takeuchi T, Avihingsanon Y, Yu XQ, Lapid EA, Lugue-Lizardo LR, Sumethkul V, Shen Nm Chen SL, Chan TM. Overview of lupus nephritis management guidelines and perspective from Asia. Nephrology 2014;19(1):11-20.

Table 2: Guideline assessment, mean domain scores using AGREE II instrument (n=14).

Domain	Mean domain score (range)%	Number of guidelines that scored ≥50%
Scope and purpose	67 (44-89)	12
Stakeholder involvement	42 (28-78)	4
Rigor of development	44 (17-83)	7
Clarity and presentation	64 (33-100)	11
Applicability	29 (4-67)	1
Editorial independence	55 (8-92)	8
Overall mean	50 (31-75)	8

Table 3: Guideline recommendations for first renal biopsy and monitoring lupus nephritis

Guideline Recommendations	EULAR [11, 12]	EULAR/ERA-EDTA [19]	ACR [10, 20]	KDIGO [22]	SEMI and SEN [16]	Dutch Group [21]
Indications for first renal biopsy						
Proteinuria	○	● 0.5g/24hr	● 1g/24hr	—	○	● 0.5g/24hr
Active urine sediment (haematuria and/or cellular casts)	○	● + proteinuria	● + proteinuria 0.5g/24 hr.	—	○	● + proteinuria
Serum creatinine (inexplicable elevation)	○	—	○	—	—	● >30% elevation
Kidney function (abnormal renal function)	—	●	—	—	●	●
Histological classification system (ISN/RPS* 2003)	—	●	●	—	●	●
Monitoring						
Frequency of visits (3-6 monthly monitoring & increased for active disease)	—	●	●	—	●	—
Blood pressure (mmHg)	○	○	○	—	○	●<130/80
Body weight (BMI or waist circumference)	○	○	—	—	—	● 25
Kidney function (eGFR)	●	●	—	—	●	—
Proteinuria	●	●	●	—	●	—
Urinalysis	●	●	●	—	●	—
Immunological tests (C3/C4 Anti-dsDNA)	●	● +anti-phospholipid	●	—	● + yearly anti-Ro/La/RNP/SM/C_{1q}	—
Other blood tests (full blood count, serum creatinine)	—	● + serum albumin	● + alkaline phosphatase, Na^{2+}, K^{+} $Ca^{2+}P^{3-}$, cholesterol	—	● +blood glucose, serum urea/albumin anticoagulant PTH, 25(OH)D_3	—
Lipid profile	—	●	—	—	●	—
Initial renal ultrasound	—	—	—	—	●	—
Ophthalmological examination (patients on anti-malaria therapy)	● 5 yearly	—	—	—	● Yearly	—
Indications for repeat renal biopsy						
Proteinuria	—	● <50% reduction	—	● <50% reduction	○	—
Serum Creatinine (rising creatinine)	—	—	—	●	—	—
Worsening GFR	—	●	●	—	—	—
Relapse of disease (if change in disease suspected)	—	●	—	●	—	—
Other	—	No response to treatment	No response to treatment or/and deteriorating renal function	Worsening disease or no remission after 12 months	No response to treatment	Only if it will have a therapeutic benefit

○= recommended without dosage/criteria ●= recommended — = no recommendation

*(ISN/RPS)= International Society of Nephrology/Renal Pathology Society

Table 4: Guideline recommendations for treatment of lupus nephritis

Guideline Treatment Recommendations	EULAR [11, 12]	EULAR/ ERA-EDTA [19]	ACR [10, 20]	KDIGO [22]	SEMI and SEN [16]	Dutch Group [21]	Aringer et al [17]	ALNN* [23]	CARRA† [15]
Class I lupus nephritis									
Treat to extra renal	—	—	—	●	●	—	—	—	—
Class II lupus nephritis									
Treat to proteinuria	—	● Yes	—	● Yes	● Yes	—	—	● No	—
Proteinuria <1g/d									
Treat to extra renal	—	—	—	●	●	—	—	—	—
Proteinuria>1-2g/d									
CS (mg/kg/d)	—	● 0.25-0.5	—	—	● 0.5	—	—	○	—
AZA (mg/kg/d) or	—	● 1-2	—	—	○	—	—	○	—
MMF (mg/kg/d)	—	—	—	—	○	—	—	○	—
Proteinuria >3g/d									
CS(mg/kg/d) for 1-4 months	—	—	—	● 1	—	—	—	○	—
CNI	—	—	—	●	—	—	—	—	—
Class III and IV lupus nephritis									
Induction therapy									
Pulsed MPD (g/d) &	—	● 0.5-0.75	● 0.5-1.0	—	● 0.25-1.0	● 0.75	—	● 0.5-1	● 0.3-1
CS(mg/kg/d) &	○	● 0.5	● 0.5-1	○	● 0.5-1 <60mg/d	● 0.5-1 <60mg/d	● 0.5	● 0.5-0.6‡	●§
IV CYC (dose) or	○	● 3g over 3 months	● 'Euro lupus'‖ or 'NIH'¶	○	● 'Euro Lupus'‖	● 'Euro lupus'‖	● 'Euro lupus'‖	○	● 'NIH'¶
MMF(g/d) or	○	● 3	● 2-3	○	● 1 to 2-2.5 in 2 wks.	● 1 to 3 in 2 wks.	○	● 1.5-2	● <3
MPA (g/d) or	—	● equivalent to MMF	● 1.44-2.16	—	● 0.72 to 1.44-1.88 in 2 wks.	—	—	—	● <1.08
AZA(mg/kg/d)	—	● 2	—	—	—	—	—	—	—
Tapering of CS (mg/d)	—	● ≤10 by 4-6 months	○	—	—	● 5-7.5 by 30 months	—	● < 20 by 3 months, ≤7.5 by 6 months	● 10-20 by 6 months
IV CYC for adverse prognosis (IV g/m^2 , Oral mg/kg/d)	—	● 0.75-1, 2-2.5	—	—	● 0.75, —	—	—	○	—
CNI when MMF and CYC contraindicated	—	—	—	—	—	—	—	○	—
Review treatment (months)	● 6	—	● 6	● 3	● 6	● 3	—	—	● 3
Maintenance therapy									
CS (mg/d) &	—	● 5-7.5	—	● <10	● <10	○	—	—	—
MMF (g/d) or	—	○	○	● 1-2	● 1.5-2	○	—	—	—
MPA (g/d) or	—	—	—	—	● 1.1 -1.4	—	—	—	—

Guideline Treatment Recommendations	EULAR [11, 12]	EULAR/ ERA-EDTA [19]	ACR [10, 20]	KDIGO [22]	SEMI and SEN [16]	Dutch Group [21]	Aringer et al. [17]	ALNN* [23]	CARRA† [15]
AZA (mg/kg/d) or	—	● 2	○	● 1.5- 2.5	● 1.5-2	○	○	—	—
Duration of therapy (years)	—	● 3	—	● 1	● 2	● 4	—	—	—
Class V lupus nephritis									
+ non-nephrotic proteinuria									
Treat to extra renal	—	—	—	●	—	—	—	—	—
Same as class III & IV	—	—	—	—	●	—	—	—	—
+ CNI or AZA	—	—	—	—	●	—	—	—	—
+ persistent nephrotic proteinuria									
Induction therapy									
Same as class III & IV	—	●	●	●	●	—	—	●	—
+ CNI or AZA	—	—	—	●	●	—	—	●	—
Maintenance therapy									
Same as class III & IV	—	●	●	—	●	—	—	●	—
CNI	—	—	—	—	—	—	—	●	—
Class VI lupus nephritis									
Treat to extra renal	—	—	—	●	●	—	—	—	—
Stage 5 CKD (<30ml/min GFR) prepare for RRT	—	—	—	—	●	—	—	—	—
Difficult disease									
Relapsing lupus nephritis									
Same induction/ maintenance therapy	—	—	—	●	●	—	—	—	—
CYC toxicity, switch immunosuppressant	—	—	—	●	●	—	—	—	—
Non-responders									
Switch immunosuppressant &	—	●	●	●	●	●	—	—	—
Pulsed MPDs (same as induction therapy) &	—	—	●	—	—	●	—	—	—
CS (1mg/kg/d max 60mg/d)	—	—	—	—	—	●	—	—	—
Alternative treatments									
rituximab	—	●	●	●	●	●	●	—	—
CNI	—	—	—	●	●	●	●	—	—
Immunoglobulin	—	—	—	●	●	—	—	—	—
Immunoadsorption	—	—	—	—	—	—	●	—	—
TNF blockade	—	—	—	—	—	—	●	—	—
All classes of lupus nephritis									
hydroxychloroquine (dose)	—	○	○	● ≤6-6.5 mg/kg/d ideal wt.	○	● 200-400mg	—	● Only class II	—
Ethnicity dependent dosing	—	—	● MMF, CYC	—	● MMF, CYC	—	—	● All	—

○= recommended without dosage/criteria ●= recommended — = no recommendation
CS= corticosteroid, AZA= azathioprine, MMF= mycophenolate mofetil, CNI= calcineurin inhibitors, MPD= methylprednisolone
CYC=cyclophosphamide, MPA= mycophenplolic acid/ sodium

* ALNN recommendations are for adult Asian lupus nephritis patients
† CARRA recommendations on paediatric lupus nephritis
‡ 0.8 mg/kg/day prednisone when not used with IV MPD
§ See reference for CS dosages, CS regimen can be primarily oral, primarily IV or mixed oral/IV
‖ Euro lupus IV CYC dose= 0.5 g/m^2 fortnightly for a total of 6 doses (3 months)
¶ NIH IV CYC dose= 0.5-1 g/m^2 monthly for 6 months

Table 5: Guideline recommendations for pregnancy and lupus nephritis

Guideline Recommendations	EULAR [11, 13]	EULAR/ ERA-EDTA [19]	ACR [10, 20]	KDIGO [22]	SEMI and SEN [16]	Dutch Group [21]	CARRA* [15]
Reproductive health & lupus nephritis (LN)							
Fertility							
MMF/MPA recommended over CYC	—	—	●	—	—	—	—
Oestrogen based contraceptives not recommended in active LN	—	—	—	●	●	—	—
Delaying pregnancy until LN remission	—	—	●	●	—	—	—
Gonadotropin for ovarian protection	—	—	—	—	—	—	●
Pregnancy and SLE							
Monitoring							
Multi-disciplinary monitoring	—	—	—	—	●	—	—
Close/monthly monitoring	●	—	—	—	●	—	—
Pregnancy avoidance in ESKD	—	—	—	—	●	—	—
Recommended treatments							
CS (low dose)	●	●	●	●	—	—	—
AZA	●	●	●	●	—	—	—
Hydroxychloroquine	●	●	●	●	—	—	—
CNI	—	●	—	—	—	—	—
Low dose aspirin	●	—	—	●	●	●	—
Treatments not recommended							
MMF/MPA	●	—	●	●	—	—	—
CYC	●	—	●	—	—	—	—
ACEs/ARBs	—	—	—	●	●	—	—
Methotrexate	●	●	●	—	—	—	—

●= recommended — = no recommendation
* CARRA recommendations on paediatric lupus nephritis

Figure legends:

Figure 1: Search results

* Guideline organizations; SIGN, NICE and professional rheumatology and nephrology society websites.