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Egyptian evidence-based consensus on clinical practice recommendations for the management of lupus nephritis

Yasser El Miedany¹ , Nadia Salah Kamel² , Mohammed Hassan Abu-Zaid^{3*} , Khaled El Hadidi⁴, Geilan Abdelmoneim Mahmoud⁴ , Eman Sarhan⁵, Maha El Gaafary⁶ , Ahmed Abdel-Nasser⁷ , Esam M. Abualfadl⁸ , Atef Abdel Azim^{9,10}, Nihal Ahmed Fathi¹¹, Abir Mokbel⁴, Waleed Hassan¹² , Samar Abd Alhamed Tabra³ , Mervat Eissa⁴ , Mohamed Mortada¹³ , Nermeen Ahmed Fouad¹⁴ , Rehab Elnemr¹⁵ , Ahmed Ezzat Mansour¹⁶ , Ismail Elaraby^{17,18}, Basma M. Medhat⁴ , Sally S. Mohamed⁴ , Eman Ragab Abdelradi¹⁹ , Rehab Ali Ibrahim² and Sally Saber² 

Abstract

Background: Lupus nephritis (LN) affects a substantial number of the patients living with Systemic lupus erythematosus (SLE), representing a major cause of morbidity and mortality. Patients with lupus nephritis should be referred to a lupus nephritis expert who can confirm the diagnosis, assess the level of disease activity, and offer guidance on treatment and monitoring of the disease, as well as its consequences and side effects. The aim of this guideline was to develop recommendations for the management of adult lupus patients, including lupus nephritis diagnosis, assessment, and monitoring.

Nineteen key clinical questions were identified by scientific committee according to the Patient/Population, Intervention, Comparison, Outcomes and Timing (PICOT) approach. Literature review team performed a systematic review to summarize evidence advocating the benefits and harms of available pharmacologic and nonpharmacologic therapies for LN. Subsequently, recommendations were formulated. The level of evidence was determined for each section using the Oxford Centre for Evidence-based Medicine (CEBM) system. A 2-round Delphi process was conducted with 24 experts. All rounds were conducted online. A consensus was achieved on the direction and the strength of the recommendations.

Results: An online questionnaire was sent to an expert panel who participated in the two rounds (response rate 100%). At the end of round 2, a total of 19 recommendation items, categorized into 11 sections to address the main LN categories, were obtained. The percentage of those who agreed with the recommendations (ranks 7–9) ranged from 90.5 to 100%. The phrasing of all 19 clinical standards identified by the scientific committee was agreed upon (i.e., 75% of respondents strongly agreed or agreed).

Conclusion: These recommendations provide an updated consensus on the pharmacological treatment of lupus nephritis and strategies to reach optimal treat to target outcomes in common clinical scenarios, based on a combination of evidence and expert opinion. Best treatment decisions should be tailored to each individual patient situation.

*Correspondence: Drmhassan113@yahoo.com; drmhassan113@yahoo.com

³ Rheumatology and Rehabilitation, Tanta University, Tanta, Egypt
Full list of author information is available at the end of the article

Keywords: Systemic lupus erythematosus, Lupus nephritis, Treat-to-target approach, Renal biopsy, Prognosis, Activity index

Background

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of autoantibodies and the deposition of immune complexes, affecting a broad range of systemic affection and causing variable degrees of organ damage. Consequently, progressive accumulation of irreversible organ damage remains the predominant cause of mortality in SLE patients [1, 2]. Lupus nephritis (LN) affects a substantial number of the patients living with SLE, representing a major cause of morbidity and mortality. Up to 40% of SLE patients develop kidney disease [3]. Overall survival in patients with SLE is approximately 95% at 5 years after diagnosis and 92% at 10 years. The presence of lupus nephritis significantly reduces survival, to approximately 88% at 10 years [4, 5]. In spite of treatment, 10% of persons with LN develop end-stage kidney disease (ESKD) [6]. These findings have been endorsed by the outcomes of earlier studies which clearly indicated that once irreversible damage ensues in SLE, especially early in the course of the disease, it has a direct impact on the prognosis [7, 8].

The treat-to-target (T2T) strategy has proven its efficacy in the management of several chronic medical illnesses including rheumatoid and spondylo-arthritis. However, in SLE with its multi-organ affection, the possibility of implementing the T2T principle has become a topic of discussion. A European panel of rheumatologists [9] was in favor of implementing the concept of treat to target for SLE treatment of SLE which should target at several goals including control of disease activity, prevention of disease flares, minimization of disease or treatment-related comorbidity, and improvement of quality of life. However, implementing the T2T concept specifically in LN remains another challenge in this cohort of patients. Several features of this condition influence the decision to use a treat-to-target (T2T) strategy. Furthermore, until recently, outcomes of targeted treatment strategies were unsatisfactory in terms of complete renal response, prevention of relapses, chronic kidney disease (CKD), and progression to end-stage kidney disease. To improve the LN prognosis, recent data [10] suggested that treatment approaches should be modified to (1) adapt the current treat-to-target approach to include, in addition to a clinical target, a pathological target and (2) switch from the conventional sequential therapeutic approach to combination therapy policy.

As Egypt has launched a nationwide universal health coverage in 2020, setting up guidelines for management

of patients is vital to the process. Therefore, there was a real need to update the treatment recommendations for LN management. Treatment recommendations are developed aiming at several goals: optimize the standards of clinical care, minimize inadequate management variance, and establish quality control parameters and also, to update clinicians, principally in a landscape of changing therapeutics, highlighting where there is evidence to guide treatment decisions, promoting resource efficiency, and highlighting the research that needs to be done to improve future care [11]. This consensus main objective is to provide updated, evidence-based recommendations for treat-to-target management of lupus nephritis and its associated clinical manifestations. Although these guidelines were developed for Egyptian patients with LN, we hope that they would be helpful to rheumatologists all over the world.

Methods

Design

A multistep procedure was used to create evidence-based, consensus therapy recommendations for lupus nephritis. The study was designed utilising the “Clinical, Evidence-based, Guidelines” (CEG) guideline creation process methodology, which involves a scientific data and consensus approach based on established scientific evidence and clinical experience. The publication adhered to the required reporting elements for systematic reviews and meta-analyses criterion [12].

Development stages

Core team

This team included of two rheumatologists and two nephrologists with deep experience of LN management. The core team oversaw and organized the team's efforts, aided in the development of the project's scope and initial Population, Intervention, Comparison, Outcomes (PICO) clinical questions, and came to an agreement on the essential questions to be included in the recommendations. The core team identified outcomes as critical for each PICO question's systematic literature review. The group was also in responsible of choosing the expert panel and putting together the manuscript.

Key questions used to develop the guideline

The suggestions were based on a series of structured key questions that identified the target audience, treatment, enquiry, comparison(s), and outcomes that

were used to measure efficacy, effectiveness, or risk. To acquire evidence to answer the clinical questions, researchers employed the following methods: formulation of clinical questions, question structure, evidence search, critically selection and evaluation of evidence, presentation of the results, and suggestions. The questions guiding the systematic literature search and, as a results, the clinical treatment guidelines are shown in Table 1.

Literature review team The literature study was carried out with the help of a methodology specialist, under the supervision of experienced literature review consultant, and was based on the study questions selected to focus on the management of LN. A systematic literature search was conducted utilising the PubMed/MEDLINE, EMBASE, and Cochrane databases to get sufficient evidence-based baseline knowledge for considerations. Following data abstraction, evaluation of published recommendations, and quality of evidence grading [13, 14], the specialists in charge of the literature review revised the list of propositions for the management of LN based on available research evidence and their own clinical competence. The Oxford Centre for Evidence-based Medicine (CEBM) approach was used to establish the degree of evidence for each section [14].

Data sources and search strategies The search approach was designed to find all studies having adults living with LN as the study population. The literature search was conducted using the PICO questions. Randomized clinical studies testing the diagnosis and efficacy of LN management, as well as quality improvement outcomes/approaches, were found using literature search methodologies.

The keywords used were determined by the PICO elements utilized in various combinations. Namely, clinical (search terms: diagnosis, clinical manifestations, classification, clinical features, presentation), Lab (search terms: immunology/Immunological, antibody/auto-antibody/serological, anti-nuclear antibodies, ANA, anti-dsDNA, anti-Ro, anti-Sm, C3, C4, antiphospholipid, anticardiolipin, lupus anticoagulant), LN features (assessment, disease activity, monitoring, damage, prognosis, quality indicators, recommendations), and LN treatment (treatment or therapy). PubMed and Cochrane Database of systematic reviews databases were being searched on January 14, 2022, and Embase was being searched on January 16, 2022. Electronically, duplicate screening of literature search results was performed. Additional studies that satisfied the inclusion requirements were found by looking through the reference lists of research indicate using database search tools.

Table 1 Key Clinical Questions for Treat to Target management approach for lupus nephritis

Domains	Key questions
Targeted patients	Who are the targeted patients? What is the classification system for lupus nephritis?
Treatment target	What are the targets of lupus nephritis treatment?
Renal biopsy	What are the indications for a renal biopsy in an SLE patient? What is the importance of evaluating biopsies for the extent of activity or chronicity?
Lab tests	Which serologic tests are most useful when following a patient with lupus nephritis?
Treatment of lupus nephritis	What is the first line of therapy for patients with severe lupus nephritis? Describe a protocol for using CYC in management of lupus nephritis Describe a protocol for using MMF in management of lupus nephritis Which cytotoxic agents are most frequently used for maintenance therapy in the treatment of lupus nephritis? What is the role of B cell depletion therapy in managing lupus nephritis? What is the role of B cell depletion therapy in managing lupus nephritis? What is the adjunctive therapy used in management of lupus nephritis?
Management outcome	Who are the patients with lupus nephritis more likely to progress to end-stage renal disease?
Management of refractory lupus nephritis	What is the strategy for management of refractory Lupus nephritis?
Pregnancy and lupus nephritis	What is the approach toward management of lupus nephritis during pregnancy?
Patient's education and lifestyle advice	What are the main points to be included in the patients' education program for Lupus nephritis patients?
Comorbidities screening	Should people with gout be screened for comorbidities?
Novel treatments facilitating T2T of lupus nephritis	What are the targeted novel biologic agents that are likely to boost the T2T approach to LN?

SLE systemic lupus erythematosus, LN lupus nephritis, T2T treat to target, CYC cyclophosphamide, MMF mycophenolate mofetil

Study selection

Relevant studies were chosen using inclusion and exclusion criteria applied to the literature found using the search methodologies.

Inclusion criteria Articles included were systematic reviews, randomized controlled trials (RCTs), uncontrolled trials, observational studies including cohort, case-control and cross-sectional studies, or those where economic evaluation was made. Trials were eligible if they included people with LN regardless of age or sex, from any health care setting receiving any therapy. The included studies should have the criteria of classification evidence and recommendations used identified. Also, the formal process for establishing recommendations (Delphi exercise, panel conference) outlined.

Exclusion criteria Editorials, commentaries, conference abstracts, and non-evidence-based narrative/personal reviews, manuscripts lacking of English version, were excluded.

Ethical aspects The Helsinki Declaration was followed when doing this research. The local ethical committee approved the Clinical, Evidence-based, Guidelines (CEG) initiative protocol: ethical approval code: 34842/8/21, ethical board Tanta University. All study participants were required to provide informed consent. All individuals were kept anonymous in compliance with data protection regulations.

Expert panel Twenty-four people were nominated by the core leadership team (20 rheumatologists, 3 nephrologists, one internist with special interest in rheumatology). Professional skill and experience (at least 8 years) in the area of rheumatology, management of inflammatory arthritis, notably SLE and LN, and active participation in rheumatic illness scientific research were among the criteria for their selection. The expert panel endorsed the project's scope as well as the preparation of the PICO questions. The PICO questions were transformed into recommendation sentences and delivered to the expert panel for voting along with the evidence report.

Target audience The guideline was created to assist health care providers who manage LN patients. The guideline should also be useful to patients and those responsible for managing SLE care in the National Health Service.

Developing the clinical care standard framework

Based on responses to the structural key questions and the literature review, a structured template was created

to aid in the consistent identification of guideline components. The format in which the recommendations/information will be delivered and extracted has been identified for each guideline component.

Delphi process The Delphi method [15] is a systematic method for acquiring critical information on a certain topic. It is based on the assumption that group forecasts are more precise than individual estimates. The Delphi method's purpose is to generate structured iterative consensus forecasts from a group of experts. Its method is based on a set of "rounds" of expert questions. The stages of the Delphi technique are usually as follows: (1) a group of experts is put together. (2) Forecasting tasks/challenges are assigned to professionals and spread. (3) Experts provide preliminary predictions and justifications. In order to provide input, these are collated and summarized. (4) The experts receive comments, which they consider when revising their forecasts. This process can be repeated until there is a reasonable degree of agreement. (5) The final forecasts are created by combining the forecasts of the experts. The anonymity of participants and the controlled feedback are two key features of this strategy [15–17].

Consensus process To reach consensus on the T2T technique in LN, three Delphi rounds were conducted. The structured Delphi method ensures that all participants' opinions are taken into account equally. Online surveys were used to conduct the Delphi method. The computerized questionnaire's initial round contained 11 domains related to LN T2T strategy.

Voting process There were two rounds of live online voting, each with a stringent time limit. All task force members were invited to vote, and the beginning and finish timings of each round were publicized in advance. Votes were collected and processed anonymously, and special access links were sent forth. For each statement, comments on rephrasing, potential confusion, and unidentified overlaps were received at the same time as the voting process. Only the task force members were allowed to vote on the statements.

Rating Each statement was assessed on a scale of 1 to 9, with 1 representing "total disagreement" and 9 representing "complete agreement." 1–3, 4–6, and 7–9, respectively, signify disagreement, uncertainty, and agreement. It was not necessary for members to vote on all statements, and they were encouraged to do so if they felt a statement was outside their area of competence. "Inconvenience concerning the veracity of the recommendation" is represented by an "uncertainty" vote. All

statements allowed for the submission of comments, which the scientific committee assessed following each round of voting. Members were encouraged to offer comments during all rounds of voting, especially when there was a disagreement. This allowed the panel to spot a case of statement misinterpretation and invalidate the vote on that statement.

Definition of consensus Prior to data analysis, a consensus definition was established. Consensus was attained, and this guideline became a suggestion if at least 80% of respondents obtained agreement (scores 7–9) or disagreement (scores 1–3). A statement was retired if it earned a mean vote of less than 3 or a “bad” degree of agreement. Statements having an ambiguity score of 4–6 were altered as a result of the input. If all votes on a statement dropped into the agreement bracket after the second round of voting (7–9), the levels of agreement on that statement were considered “strong” [17–19].

Chronogram of Delphi rounds The first round took place on January 29 and February 1, 2022 (4 days). In view of the feedback, the aspects on which respondents could not agree in the first round were updated and included in the second round. The second round began on February 4, 2022, 3 days after the first round, and lasted 9 days (till 12 Feb 2022).

Results

Literature research and evidence selection

By using a search strategy, we identified 3174 possibly relevant studies during the research selection phase. 3013 were excluded: 406 duplicates and 2607 by title and abstract screening (studies did not examine population or intervention of interest, did not match study design of interest, or did not report outcome measures of interest). As a result, 161 studies were selected for full-article evaluation. Due to the fact that 133 research did not provide evidence that matched a PICO, only 28 studies were considered in this study (Fig. 1).

Expert panel characteristics

The Delphi form was sent to expert panel ($n=24$), of whom 24 (100%) completed in the two rounds. The participants were from governorates and health centres throughout Egypt: Ain Shams University ($n=4$, 16.6%), Cairo University ($n=7$, 29.2%), Tanta University ($n=2$, 8.3%), Benha University ($n=2$, 8.3%), South Valley University ($n=1$, 4.15%), Alexandria University ($n=1$, 4.15%), Fayoum University ($n=1$, 4.15%), Sohag University ($n=1$, 4.15%), Zagazig University ($n=1$, 4.15%), Assiut University ($n=1$, 4.15%), Minia University ($n=1$, 4.15%),

Ministry of Health ($n=1$, 4.15%), in addition to ($n=1$, 4.15%) international expert from the UK. 83.4% of the experts' panel (20) were rheumatologists and 16.6% (4) were nephrologists.

Delphi round 1

The clinical question round was made up of 19 questions divided into 11 categories (Table 1) including targeted patients, treatment target, renal biopsy, lab tests, treatment of lupus nephritis, management outcome, management of refractory lupus nephritis, pregnancy and lupus nephritis, patient's education and lifestyle advice, comorbidities screening, and novel treatments facilitating T2T of lupus nephritis. Each domain entails one or more elements. Participants were asked to evaluate the overall principles considered in LN T2T management decision-making in this round. The experts' panel responded 100% (24/24) in round one. All domains and questions were agreed upon (with 80% of respondents strongly agreeing or agreeing), and no questions were retired.

Delphi round 2

Based on the literature research, a list of 11 domains with 19 recommended suggestions was generated using the input from round 1, 2 for targeted patients and 1 for the treatment target, 2 for the renal biopsy, 1 for the lab tests, 7 for treatment of lupus nephritis, 1 for management outcome, 1 for management of refractory lupus nephritis, 1 for pregnancy and lupus nephritis, 1 for patient's education and lifestyle advice, 1 for comorbidities screening, and 1 for novel treatments facilitating T2T of lupus nephritis. The response rate for round 2 was 100% from the experts' panel (24/24). Modifications of the words were suggested for 4 statements (1 in the investigations, 2 in the treatment, and 1 in the outcomes). The statements were modified and amended. For all statements, the consensus was reached (as $\geq 80\%$ of respondents strongly agreed or agreed).

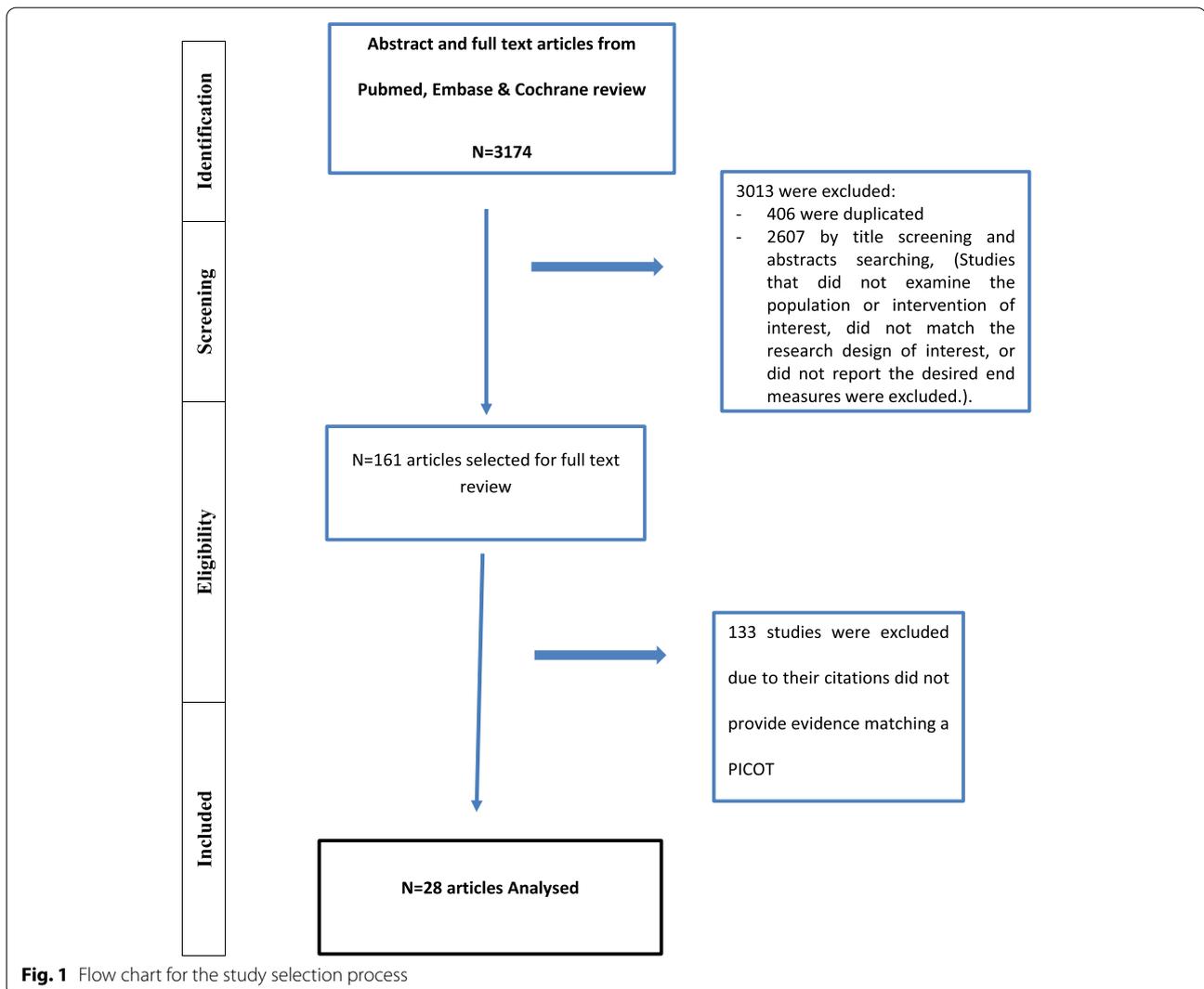
Based on those results, this document was written, containing the answers to the key clinical questions which entails recommendations for the management of lupus nephritis, as follows:

General principles

Level of evidence: 1, grades of recommendations (GoR): A, mean+SD: 8.9+0.5, percentage of agreement: 100%

Level of agreement: High

- Management of lupus nephritis should adopt a multidisciplinary approach, in specialized centers. The team should include both rheumatologists and nephrologists, adopting a shared decision-making process with the patients.



- Because of slower proteinuria recovery in these patients, prompt switching of therapies is not necessary as long as proteinuria is improving.
 - It is fairly straightforward to establish the target in a T2T management approach for lupus nephritis. Lupus nephritis management is based on both clinical (e.g., hypertension, lower limb oedema, fluid overload symptoms and signs) and laboratory measures (e.g., proteinuria, erythrocyturia, RBC casts, and serum creatinine). Reappearance of glomerular hematuria or cellular casts can be a predictor of impending kidney flare [20].
1. Establishment of target(s) tailored to the patient condition and prospects (individual patient's clinical condition/patient's requirements and expectations)
 2. Identify the management plan to achieve the target (medications/dose adjustments)
 3. Monitor case progression till target achievement
 4. Optimization of the management strategy (response to therapy, dose adjustment, side effects, comorbidities)

Treat to target management strategy for lupus nephritis

- The use of combined immunosuppressive ("multi-target") therapy and reducing the dosages of concomitant glucocorticoids have been suggested in some cases to increase efficacy, lower toxicity, or both

Who are the targeted patient?

Level of evidence: 1, GoR: A, mean+SD: 8.77+1.7, percentage of agreement: 95.2%,

Level of agreement: High

- SLE patients who develop nephritis
- SLE patients, with poor prognostic markers for LN (at high risk of developing lupus nephritis:
- The presence of hypertension, hypercreatininemia/renal failure, massive proteinuria, and high activity index score of LN.

What is the classification system for lupus nephritis?

Level of evidence:1, GoR: A, mean+SD:8.8+0.5, percentage of agreement: 100%,

Level of agreement: High

According to the World Health Organization (WHO) and subsequent clinicopathologic data [21],

- Class I and II are used for purely mesangial involvement:
- I: mesangial immune deposits without mesangial hypercellularity.
- II: mesangial immune deposits with mesangial hypercellularity).
- Class III for focal glomerulonephritis (involving <50% of total number of glomeruli) with subdivisions for active and sclerotic lesions.
- Class IV for diffuse glomerulonephritis (involving $\geq 50\%$ of total number of glomeruli) either with segmental (class IV-S) or global (class IV-G) involvement and also with subdivisions for active and sclerotic lesions.
- Class V for membranous lupus nephritis.
- Class VI for advanced sclerosing lesions. Combinations of membranous and proliferative glomerulonephritis (i.e., classes III and V or classes IV and V) should be reported individually in the diagnostic line.

What are the targets of lupus nephritis treatment?

Level of evidence: 1, GoR: B, mean+SD: 8.67+0.82, percentage of agreement: 100%

Level of agreement: High

Short term

- 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 g per 24 h, normal or stable renal function and an inactive urinary sediment (complete clinical response).
- Nephrotic-range proteinuria at baseline: an additional 6 to 12 months may be required to reach complete clinical response.

Long term

- Inducing and maintaining remission of the kidney inflammation so as to preserve renal function and improve survival in the long term.
- Prevent chronic kidney disease and end-stage renal disease.
- Minimize LN flares.
- Improve disease-related quality of life [22].

What are the indications for a renal biopsy in an SLE patient?

Level of evidence: 1, GoR: A, mean+SD: 8.3+2.28, percentage of agreement: 95.2%

Level of agreement: High

- Increasing serum creatinine levels without a compelling reason (e.g., hypovolemia and medication)
- Confirmed proteinuria of ≥ 1 g/24 h
- Proteinuria ≥ 0.5 g/day plus hematuria or cellular casts

What is the importance of evaluating biopsies for the extent of activity or chronicity?

Level of evidence: 2, GoR: B, mean+SD: 8.5+1.25, percentage of agreement: 90.5%

Level of agreement: H

Pathologists used to generate a calculated score to signify disease activity and chronicity on a kidney biopsy report [23]. Though these formulas are no longer widely used, identifying histologic changes that signify chronicity and activity can help with the overall description of the renal biopsy. Fibrosis indicates a chronic scarring illness that is less likely to respond to treatment.

When following a patient with lupus nephritis, which serologic tests are most useful?

Level of evidence: 1, GoR: A, mean+SD: 8.5+0.82, percentage of agreement: 100%

Level of agreement: High

- Anti-dsDNA can be elevated with disease flare.

- Complement component levels decreased complement component levels (e.g., C3 and C4) as well as total hemolytic complement (CH50), correlate also with the renal disease activity. (Many lupus patients have partial C4 deficiency so may have a low C4 level. In those patients, only C3 levels can be followed) [24].
- Glomerulonephritis can develop in a patient with SLE who has no anti-dsDNA antibodies and normal complement levels (especially in membranous lupus nephritis).
- High-dose IV regimen (500–1000 mg/m² monthly × 6 doses)
- Low-dose IV regimen (Euro-lupus: 500 mg IV every 2 weeks × 6 doses)

- Patients who fail improving on MMF, switching to CYC is considered. Patients who fail to respond to CYC consider switching to MMF.
- In patients who fail responding to both, they are candidates for rituximab, calcineurin inhibitors (cyclosporine, tacrolimus), or a combination of calcineurin inhibitors and low-dose MMF.
- The combination of MMF with a calcineurin inhibitors (CNI) (especially tacrolimus (TAC) might be a therapeutic option, especially in nephrotic-range proteinuria
- **Anticoagulant therapy:** Anticoagulant therapy should be considered in nephrotic syndrome with heavy proteinuria and serum albumin less than 20 g/L.

Which patients with severe lupus nephritis are more likely to progress to end-stage renal disease (ESRD)?

Level of evidence: 2, GoR: A, mean+SD: 8.67+1.12, percentage of agreement: 95.2%

Level of agreement: High

- Lower socioeconomic status
- Poor medication compliance
- Comorbidities such as diabetes and hypertension
- Failure to normalize serum creatinine or serum creatinine of >2mg/dL on therapy
- Failure to decrease proteinuria to <1 g/day within 6 months of starting treatment
- Renal biopsy evidence of high disease activity (cellular crescents) and chronicity (interstitial fibrosis) [25]

Management strategy for LN

What is the first line of therapy for patients with severe lupus nephritis?

Level of evidence: 1, GoR: A, mean+SD: 8.43+1.48, percentage of agreement: 95.2%

Level of agreement: High

A) Induction therapy

- **Class III/IV lupus nephritis**
 - Intravenous (IV) pulse methylprednisolone (500 mg to 1 g) daily for 3 days followed by prednisone 1 mg/kg/day (crescents on biopsy) or 0.5 mg/kg/day (no crescents). Taper after few weeks to lowest effective dose

Plus

- Mycophenolate mofetil (MMF) 2–3 g/day for 6 months **or** cyclophosphamide (CYC) in 2 different regimens:

Class V lupus nephritis

- Oral prednisone 0.5 mg/kg/day for 6 months; **plus** MMF 2–3 g/day for 6 months
- Calcineurin inhibitors (cyclosporine/tacrolimus) can be added to MMF: use caution in patients with renal insufficiency or hypertension.
- IV CYC if other therapies fail

B) Adjunctive therapies

- Hydroxychloroquine
- Angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) if proteinuria ≥ 0.5 g/24 h
- Control blood pressure (BP): should be $\leq 130/80$
- Statin therapy if low-density lipoprotein (LDL) cholesterol >100 mg/dL
- Stop smoking
- Counsel against pregnancy while nephritis is active or creatinine >2mg/dL

Which cytotoxic agents are most frequently used for maintenance therapy in the treatment of lupus nephritis?

Level of evidence: 1, GoR: A, mean+SD: 8.67+0.82, percentage of agreement: 100%

Level of agreement: High

- After induction therapy, maintenance therapy is provided to ensure a long-term response.
- Hydroxychloroquine 200–400 mg/day
- oral AZA (up to 2 mg/kg/day) or MMF; which is generally preferred (1–3 g/day)
- Patients on allopurinol (gout) or warfarin should avoid azathioprine (AZA) (warfarin resistance)
- Patients who cannot tolerate AZA or MMF can get CYC IV every 3 months after induction.
- Prednisone is tapered over time if renal and extra-renal manifestations are in control.
- Maintenance therapy is recommended for at least 1–2 years (or longer)
- Other maintenance therapies
 - Rituximab or Blimumab
 - Calcineurin inhibitors (cyclosporine, vocosporin, or tacrolimus): alone or combined with low-dose MMF.

Drugs used in LN

I. Cyclophosphamide

Is there an optimal dosing regimen for CYC?

Level of evidence: 1, GoR: A, mean+SD: 8.7+0.82, percentage of agreement: 100%
Level of agreement: High

- The two commonly recommended IV regimens are as follows:
- **High dose:** Monthly boluses of 0.5–1.0 g/m² IV × 6 months
- **Low dose** (Euro-Lupus protocol): 500 mg IV every 2 weeks × 6 doses
- Low-dose therapy is associated with fewer serious infections and less risk of infertility, but some patients may fail to respond to lower doses
- IV dosing regimens (compared with oral) result in a lower total CYC exposure, which is important when considering effects on fertility and bladder toxicity.
- Premature ovarian failure risks correlate with the cumulative dose of CYC (>10–15 g total dose) and the age of the patient (>30 years) [26].
- Anti-Mullerian hormone measurement can be used to determine ovarian reserve, but its clinical value is unclear.

Consider rituximab 1 g IV plus CYC 500–750 mg IV for resistant disease, followed by the same 14 days later.

Describe a protocol for using monthly IV CYC

Level of evidence: 1, GoR: A, mean+SD: 8.57+1.12, percentage of agreement: 100%
Level of agreement: High

a) Prior to CYC

- Premedication 15–30 min prior to CYC: dexamethasone 10 mg, and ondansetron (Zofran) 8 mg or ganisetron (Kytril) 1 mg in 100 cc normal saline IV
- Mesna (25% of CYC dose in milligrams) in 250 cc normal saline

b) CYC infusion

- CYC 0.5–1.0 g/m² of a body surface area in 1000 cc normal saline for initial dose. If creatinine clearance is less than 35–40 cc/minute, then start initial dose at 0.5 g/m² of bovine serum albumin. If on dialysis, give 0.4–0.5 g/m² 8–10 h before or after dialysis.

c) Post CYC infusion

- Mesna (25% of CYC dose in mg) in 250 cc normal saline

d) Follow-up patients for hematuria and cancer bladder whenever feasible.

- e) To prevent premature gonadal failure from long-term therapy, consider using gonadotropin-releasing hormone (Leuprolide) 3.75 mg intramuscularly (IM) 10 days prior to each monthly CYC dose or testosterone supplementation (200 mg IM every 2 weeks) for men (data is limited) [20].

e) Maintenance after the CYC course

- Maintenance with AZA or MMF

II. B cell therapy in lupus nephritis

Role of B cell depletion therapy

Lupus nephritis is characterized by a complicated interplay of immunologic disturbances and renal damage caused by the development of pathogenic autoantibodies and immune complexes, which activate complement and cause inflammatory cell infiltration in the kidney. B lymphocytes are key players in this process because they are the progenitors of plasma cells,

which create pathogenic autoantibodies, and they also serve as antigen presenters for T lymphocytes [27].

Rituximab (anti-CD20)

Loading: 1 g on days 1 and 15

Maintenance dose: 500 mg IV every 6 months

Ocrelizumab (anti-CD20)

The first dose is a 300-mg intravenous infusion given over 2.5 h, followed by another 300 mg intravenous infusion 14 days later.

Then, every 6 months, a 600-mg intravenous infusion is given over 3.5 h.

Obinutuzumab (anti-CD20) [28]

Obinutuzumab is a humanized type II anti-CD20 monoclonal antibody that binds to the CD20 antigen in a different way than type I anti-CD20 antibodies (1000mg/40ml).

Epratuzumab (anti-CD22)

- Epratuzumab is a recombinant humanized monoclonal IgG antibody to CD22 that promotes antibody-dependent cellular cytotoxicity and depletes B cells. Epratuzumab is thought to alter B cell function without killing them; however, the exact mechanism of action is unknown.
- **Targeting B cell survival factors**

Belimumab

Indicated for active lupus nephritis in patients who are receiving standard therapy.

IV

Initial: 10 mg/kg IV q 2 weeks x 3 doses, THEN

Maintenance: 10 mg/kg IV q 4 weeks

SC

Initial: 400-mg dose (two 200-mg injections) sc q week x 4 doses, THEN

Maintenance: 200 mg sc q week thereafter. Transitioning from IV to SC dosing at any time after completing the first 2 IV doses.

If transitioning, administer first sc dose of 200 mg 1–2 weeks after the last IV dose [29].

Ataccept

Ataccept inhibits B cell stimulation by binding to both BLy5 and a proliferation-inducing ligand (APRIL). Ataccept is thought to impair mature B cells and plasma cells while having little effect on progenitor and memory B cells.

What is the strategy for management of refractory Lupus nephritis?

Patients with refractory LN are those who do not obtain a partial response after 6–12 months, or whose LN worsens after 3 months, or who have treatment failure as determined by the treating physician after 6 months [30].

- Several therapeutic options are available, including the following:
 - Switching from CYC to MMF or vice versa

For patients with refractory LN, switching to a different first-line induction therapy is the suggested first step, according to both the EULAR/ERA-EDTA and the American College of Rheumatology guidelines. CYC-resistant patients are usually treated with MMF, while MMF-resistant patients are treated with CYC. Some patients combine switching immunosuppressive medications with three days of intravenous glucocorticoids pulses [31].

- Prolonged courses of cyclophosphamide

Patients who do not satisfy remission criteria after 6 months may be eligible for extended CYC therapy. The severe treatment toxicities of CYC, including as infertility, urotoxicity, and oncogenicity, which are especially relevant because the majority of patients are of reproductive age, constitute a major limitation [32].

- B cell therapies

B cells play a principal role in the pathogenesis of LN and are therefore attractive therapeutic targets as Rituximab (RTX) and Belimumab [33, 34].

- Calcineurin inhibitors

The CNIs cyclosporine A (CSA) and tacrolimus have been widely researched in LN, with rising evidence for their efficacy in refractory LN. CSA binds to cyclophilin, its cytoplasmic receptor, and the resulting drug-receptor complex binds to calcineurin and inhibits IL-2 synthesis, resulting in a selective and reversible suppression of T cell-mediated immune response. CSA has been demonstrated to have direct antiproteinuric effects in addition to its immunosuppressive effects. The mechanism is linked to actin stabilization in podocytes. Tacrolimus binds to the FK-binding protein-12, a distinct cytoplasmic receptor that interacts with calcineurin [35].

Volcospirin This is indicated in combination with a background immunosuppressive therapy regimen for active lupus nephritis (LN) 23.7 mg PO BID initially; modify dose based on eGFR—used in combination with mycophenolate mofetil (MMF) and corticosteroids. Consider discontinuation if no therapeutic benefit by 24 weeks [36].

Table 2 shows the list of medication and their advised doses which are recommended for induction therapy (class III/IV) lupus nephritis.

- Plasma exchange and immunoadsorption

Plasma exchange and immunoadsorption have little evidence in refractory LN. Patients with contraindications to traditional therapy, such as severe infection risk and substantial leucopenia, as well as additional indications including pulmonary hemorrhage, may benefit from extracorporeal therapies [37].

Figure 2 presented an algorithm for management of lupus nephritis.

Discussion

In SLE, an international panel of experts recently proposed the notion of “treat-to-target” (T2T), which is a therapeutic strategy aimed at improving illness outcomes by achieving predetermined treatment targets [38]. The T2T approach has been applied to a variety of chronic medical conditions, including diabetes and hypertension, as well as rheumatology, where the current therapeutic paradigm in rheumatoid arthritis (RA) focuses on disease remission to avoid long-term structural damage [39].

Unlike other SLE signs, LN is managed mostly through lab testing (primarily proteinuria, serum creatinine/eGFR, and erythrocyturia). Essentially, this would make the monitoring procedure for identifying the treatment goal in a T2T plan simple and fair, albeit

problems remain. Complete renal remission, defined as normal or stable renal function, low proteinuria, and, in some studies, inactive urinary sediment [40, 41], is the ultimate goal of therapy. Proteinuria of 0.5 to 0.7 g per 24 h was found to be the strongest positive individual predictor of long-term renal outcomes, despite the lack of consensus on the ideal target level. This agrees with the results of published research which identified <0.7 g daily as the expected treatment target [42, 43]. Otherwise, the use of other clinical measures to distinguish between ongoing disease activity and renal damage in those patients with persistent urinary aberrations remains challenging without carrying out and assessing a renal biopsy [44, 45].

The present treatment approach for LN is composed of 2 steps: (1) Induction phase where rigorous management with immunosuppressive therapies in combination with glucocorticoids is advised aiming to minimize the likelihood of early damage of the kidney glomeruli and preserve the kidney functions on the long term. (2) Maintenance phase: which follows the induction phase and involves the continuation of immunosuppressive management. This phase aims at attaining a complete renal response and minimizing or preventing renal flares [46, 47]. Sequential immunosuppressive treatments, such as cyclophosphamide followed by azathioprine, or monotherapy, such as MMF, can be used in both the induction and maintenance stages. This two-phase technique has drawbacks, such as a lower likelihood of reaching total effectiveness and the possibility of medication-induced adverse effects, which are mostly associated to the administration of large dosages of glucocorticoids and their known role in long-term damage in SLE [48]. In line with previous research [49–52], this advice proposed using “multitarget” combination immunosuppressive therapy and lowering concomitant glucocorticoids dosage in a study to improve efficacy and reduce toxicity or both.

Safety concerns have been raised particularly for increased prevalence of infectious complications among

Table 2 List of medication and their advised doses which are recommended for induction therapy (class III/IV) lupus nephritis

Medication	Advised dose
Cyclophosphamide	<u>High dose</u> : Monthly boluses of 0.5–1.0 g/m ² IV × 6 months <u>Low dose</u> (Euro-Lupus protocol): 500 mg IV every 2 weeks × 6 doses
Rituximab	1000 mg on days 0 and 14
Cyclosporine	50–200 mg/day
Mycophenolate mofetil (MMF)	2–3 g/day, reduced dose: 1 to 2 g/day [use MMF or mycophenolic acid in equivalent dose]
Tacrolimus	0.1 mg/kg/day
Voclosporine	23.7 mg oral, twice daily

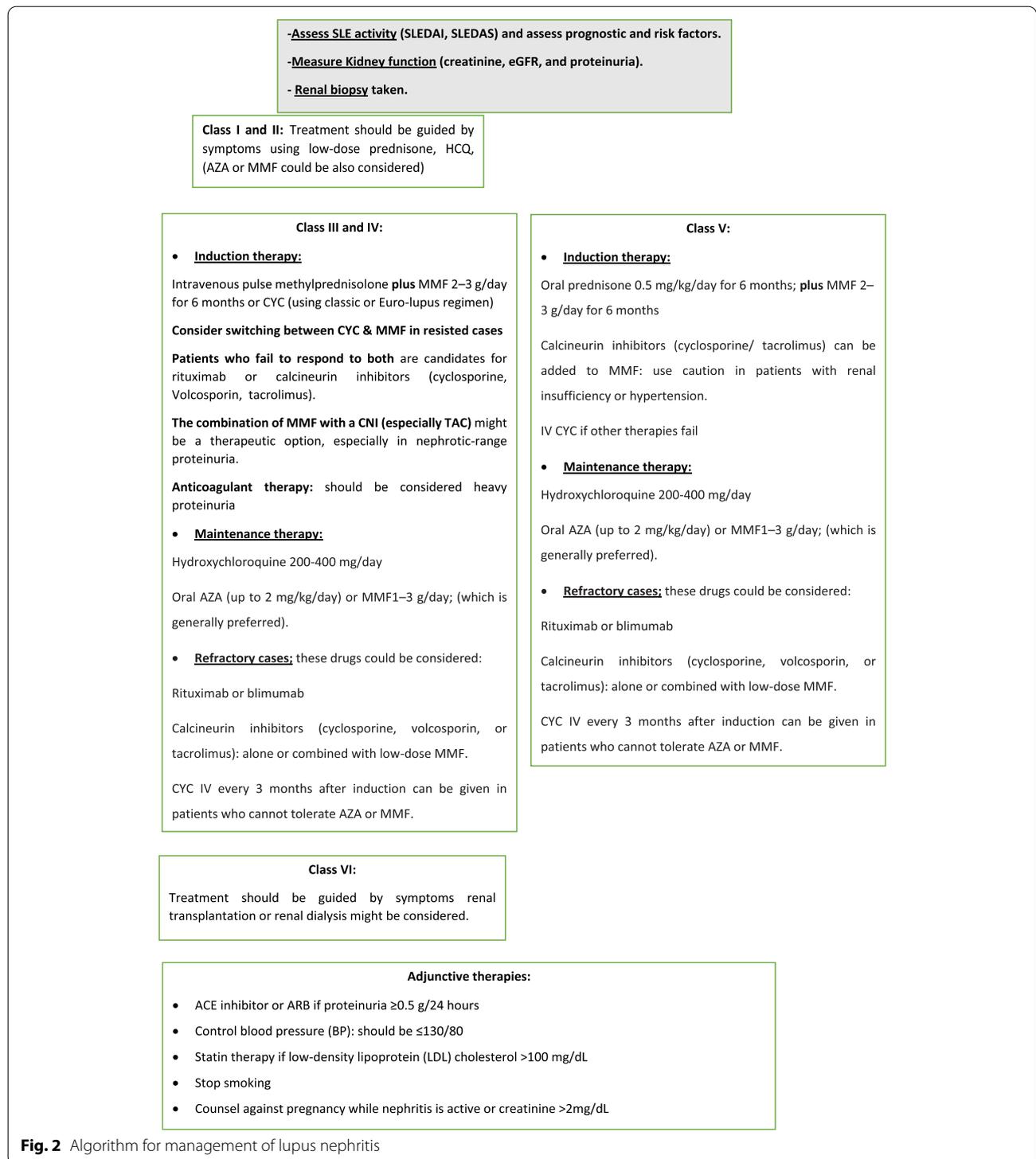


Fig. 2 Algorithm for management of lupus nephritis

LN patients [53]. These have been attributed to the limited current management options, the tight control management approach (T2T), and the use of aggressive/high-dose immunosuppressive therapy. This recommendation included a variety of recently approved therapies for LN. These novel biologic therapies are likely to boost

the T2T approach to LN. Such approach would pave the way to develop and validate better complete renal remission assessment tools.

The study's main strengths include the diversity and experience of the participants, the high levels of consensus attained, and conformity with the most recent

publication recommendations. The PICO methodology technique, as well as the treat-to-target outcome, were chosen as the work's main pillars.

Limitations of the guideline

Though the guideline reflects the best data available at the time the report was prepared, one of its limitations is the limited comparative evidence to inform selection of therapies. While these recommendations were developed using rigorous methodology, guidelines do have inherent limitations in informing individual patient care; hence the selection of the term “recommendations.” While they should not supplant clinical judgment or limit clinical judgment, they do provide expert advice to the practicing physician managing patients with lupus nephritis.

In conclusion, this evidence/consensus-based recommendation has endorsed an individualized treatment approach tailored to the patient's predominant clinical manifestation and associated morbidity. The main objective is to help health care professionals as well as patients in making challenging disease management decisions and achieve remission of their lupus nephritis.

Abbreviations

ACE: Angiotensin-converting enzyme; aPL: Anti-phospholipid antibodies; ARB: Angiotensin receptor blockers; APRIL: A proliferation-inducing ligand; AZA: Azathioprine; BMI: Body mass index; BP: Blood pressure; CNIs: Calcineurin inhibitors; CEBM: Centre for Evidence-based Medicine; CEG: Consensus, Evidence-based, Guidelines; CKD: Chronic kidney disease; CYC: Cyclophosphamide; CSA: Cyclosporine A; ESRD: End-stage renal disease; GFR: Glomerular filtration rate; GoR: Grade of recommendation; HCQ: Hydroxychloroquine; LN: Lupus nephritis; MMF: Mycophenolate Mofetil; PICOT: Patient/Population, Intervention, Comparison, Outcomes and Time; RCT: Randomized control trial; RTX: Rituximab; SC: Subcutaneous; SLE: Systemic lupus erythematosus; TAC: Tacrolimus; T2T: Treat to target; WHO: World Health Organization.

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Authors' contributions

Conceptualization and design: Yasser El Miedany, Mohammed Hassan Abu-Zaid, and Sally Saber; Acquisition of data: Yasser El Miedany and Mohammed Hassan Abu-Zaid; Formal analysis: Maha El Gaafary; Investigation: Ahmed Ezzat and Abeer Mokbel; Methodology: all authors; Writing—original draft: Yasser El Miedany, Mohammed Hassan Abu-Zaid, and Samar Tabra. The authors read and approved the final manuscript.

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Availability of data and materials

The data will be available upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Helsinki Declaration. This was a multistep process which followed the “Clinical, Evidence-based, Guidelines” (CEG) initiative protocol (ethical approval code: 34842/8/21, ethical board Tanta University) aiming at setting up an actionable clinical gold

standard for treat-to-target management of rheumatic and bone diseases. As per the Egyptian National Ethical Committee regulations, verbal informed consent was required from all the participants included in the study. All the participants included in the study gave their verbal informed consent. All the participants were kept anonymous, in compliance with data protection regulations.

Consent for publication

Not applicable

Competing interests

The authors declare that the corresponding author and Rehab Ali are associate editors in the *Egyptian Rheumatology and Rehabilitation*, and Mohammed Mortada and Yasser El Miedany are from the editorial board of the journal.

Author details

¹Canterbury Christ Church University, Canterbury, England. ²Physical Medicine, Rheumatology & Rehabilitation, Faculty of Medicine Ain Shams University, Cairo, Egypt. ³Rheumatology and Rehabilitation, Tanta University, Tanta, Egypt. ⁴Rheumatology, Cairo University, Cairo, Egypt. ⁵Nephrology, Ain Shams University, Cairo, Egypt. ⁶Community and Public Health, Ain Shams University, Cairo, Egypt. ⁷Rheumatology and Rehabilitation, Minia University, Minia, Egypt. ⁸Rheumatology, Sohag University, Sohag, Egypt. ⁹Rheumatology Unit, Dr. Erfan Hospital, Jeddah, Saudi Arabia. ¹⁰Internal Medicine & Rheumatology, Cairo University, Cairo, Egypt. ¹¹Rheumatology and Rehabilitation, Assiut University, Assiut, Egypt. ¹²Rheumatology and Rehabilitation, Benha University, Benha, Egypt. ¹³Rheumatology and Rehabilitation, Zagazig University, Zagazig, Egypt. ¹⁴Rheumatology and Rehabilitation, Fayoum University, Fayoum, Egypt. ¹⁵Physical Medicine, Rheumatology and Rehabilitation, Alexandria University, Alexandria, Egypt. ¹⁶Internal Medicine and Nephrology, Benha University, Benha, Egypt. ¹⁷Nephrology, Ministry of Health Egypt, Cairo, Egypt. ¹⁸Ministry of Health, Red Sea Government, Cairo, Egypt. ¹⁹Rheumatology and Rehabilitation, South Valley University, Qena, Egypt.

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