General

Guideline Title

American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis.

Bibliographic Source(s)


Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The levels of evidence supporting the recommendations (A-C) are defined at the end of the "Major Recommendations" field.

Renal Biopsy and Histology

The Task Force Panel recommended that all patients with clinical evidence of active lupus nephritis (LN), previously untreated, undergo renal biopsy (unless strongly contraindicated) so that glomerular disease can be classified by current International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification (level C evidence) (see Table 1 in the original guideline document for ISN/RPS classification of LN). In addition, disease can be evaluated for activity and chronicity and for tubular and vascular changes. Finally, biopsies may identify additional or alternative causes of renal disease, such as tubular necrosis related to medications, hypovolemia, or hypotension. Biopsy is most highly recommended in patients with the characteristics indicated in the following table.

Table. Indications for Renal Biopsy in Patients with Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Indication</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing serum creatinine without compelling alternative causes (such as sepsis, hypovolemia, or medication)</td>
<td>C</td>
</tr>
<tr>
<td>Confirmed proteinuria of ≥1.0 gm per 24 hours (either 24-hour urine specimens or spot protein/creatinine ratios are acceptable)</td>
<td>C</td>
</tr>
<tr>
<td>Combinations of the following, assuming the findings are confirmed in at least two tests done within a short period of time and in the absence of alternative causes:</td>
<td>C</td>
</tr>
</tbody>
</table>
The Task Force Panel recommended that treatment be based in large part on the classification of type of LN by these ISN/RPS criteria. As a result, the following recommendations are presented according to the histologic classification of nephritis. The Task Force Panel agreed that class I (minimal mesangial immune deposits on immunofluorescence with normal light microscopy) and class II (mesangial hypercellularity or matrix expansion on light microscopy with immune deposits confined to mesangium on immunofluorescence) generally do not require immunosuppressive treatment (level C evidence). In general, patients with class III (subendothelial immune deposits and proliferative changes in <50% of glomeruli) and class IV (subendothelial deposits and proliferative glomerular changes involving ≥50% of glomeruli) require aggressive therapy with glucocorticoids and immunosuppressive agents. Class V (subepithelial immune deposits and membranous thickening of glomerular capillaries) when combined with class III or IV should be treated in the same manner as class III or IV. Class V alone ("pure membranous LN") may be approached somewhat differently, as indicated below under "Recommendations for Induction of Improvement in Patients with Class V 'Pure Membranous' LN". Histologic class VI (sclerosis of ≥90% of glomeruli) generally requires preparation for renal replacement therapy rather than immunosuppression. The designations "A" and "C" indicate whether active or chronic changes are present; the higher the chronicity the less likely that the nephritis will respond to immunosuppression. However, A or C classifications were not included in the entry criteria for clinical trials in LN published to date, and therefore they are not considered in the recommendations.

Adjunctive Treatments

The Task Force Panel recommended that all systemic lupus erythematosus (SLE) patients with nephritis be treated with a background of hydroxychloroquine (HCQ; level C evidence), unless there is a contraindication.

All LN patients with proteinuria ≥0.5 gm per 24 hours (or equivalent by protein/creatinine ratios on spot urine samples) should have blockade of the renin–angiotensin system, which drives intraglomerular pressure (level A evidence for nondiabetic chronic renal disease). Treatment with either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) reduces proteinuria by approximately 30%, and significantly delays doubling of serum creatinine and progression to end-stage renal disease in patients with nondiabetic chronic renal disease. These classes of medications are contraindicated in pregnancy. The use of combination ACE inhibitors/ARB therapies is controversial. ACE inhibitors or ARB treatments are superior to calcium-channel blockers and diuretics alone in preserving renal function in chronic kidney disease.

The Task Force Panel recommended that careful attention be paid to control of hypertension, with a target of ≤130/80 mm Hg (level A evidence for nondiabetic chronic renal disease). The Task Force Panel also recommended that statin therapy be introduced in patients with low-density lipoprotein cholesterol >100 mg/dl (level C evidence). Note that a glomerular filtration rate <60 ml/minute/1.73 m² (equivalent to a serum creatinine level >1.5 mg/dl or 133 µmoles/liter) is a risk factor for accelerated atherosclerosis. SLE itself is also an independent risk factor for accelerated atherosclerosis.

Finally, the Task Force Panel recommended that women of child-bearing potential with active or prior LN receive counseling regarding pregnancy risks conferred by the disease and its treatments (level C evidence).

Recommendations for Induction of Improvement in Patients with ISN Class III/IV Lupus Glomerulonephritis

The Task Force Panel recommended mycophenolate mofetil (MMF) (2–3 gm total daily orally) or intravenous (IV) cyclophosphamide (CYC) along with glucocorticoids (level A evidence) (see Figure 2 in the original guideline document). MMF and CYC are considered equivalent based on recent high-quality studies, a meta-analysis, and expert opinion. Long-term studies with MMF are not as abundant as those with CYC; data show good results for induction therapy with MMF of 3 gm total dose daily for 6 months, followed by maintenance with lower doses of MMF for 3 years. MMF has been similar in efficacy in all races studied to date (whites, Asians, African Americans, and Latin/Hispanic Americans). The Aspreva Lupus Management Study (ALMS) trial comparing response rates of LN to MMF plus glucocorticoids showed similar improvement in whites, Asians, and other races (primarily African Americans and Hispanics). However, the Task Force Panel voted that Asians compared to non-Asians might require lower doses of MMF for similar efficacy (level C evidence). Therefore, the physician might aim for 3 gm per day total daily highest dose in non-Asians and 2 gm per day in Asians. There is evidence that African Americans and Hispanics with LN respond less well to IV CYC than do patients of white or Asian races. MMF/mycophenolic acid (MPA) may be an initial choice more likely to induce improvement in patients who are African American or Hispanic.

The exact suggested dose of MMF varied based on the clinical scenario: for those with class III/IV without cellular crescents and for those with...
proteinuria and a stable creatinine for whom a renal biopsy sample cannot be obtained, both 2 gm and 3 gm total daily doses were acceptable to the Task Force Panel, while a dose of 3 gm daily was favored for those with class III/IV and crescents and for those with proteinuria and a recent significant rise in creatinine.

Some evidence suggests that MPA and enteric-coated mycophenolate sodium are less likely than MMF to cause nausea and diarrhea, but this is controversial, and the exact equivalency of the preparations is not firmly established. The Core Expert Panel recommended that MMF and MPA are likely to be equivalent in inducing improvement of LN, with 1,440–2,160 mg total daily dose of MPA roughly equivalent to 2,000–3,000 mg total daily dose of MMF. Some investigators have suggested that serum levels of MPA, the active metabolite of MMF, should be measured at the trough or peak (1 hour after a dose), and treatment of SLE should be guided by these levels. However, there are not enough data at this time to make recommendations for monitoring of drug levels.

There are two regimens of IV CYC recommended by the Task Force Panel: 1) low-dose "Euro-Lupus" CYC (500 mg IV once every 2 weeks for a total of 6 doses), followed by maintenance therapy with daily oral azathioprine (AZA) or daily oral MMF (level B evidence), and 2) high-dose CYC (500–1,000 mg/m² IV once a month for 6 doses), followed by maintenance treatment with MMF or AZA (level A evidence) (see Figure 2 in the original guideline document). If CYC is being considered for treatment, the Core Expert Panel recommended IV CYC at the low "Euro-Lupus" dose for white patients with Western European or Southern European racial/ethnic backgrounds (level B evidence). In European study patients, the low- and high-dose regimens were equivalent in efficacy, and serious infections were less frequent with the lower doses. The low- and high-dose regimens have not been compared in nonwhite racial groups. Ten years of followup comparing low- and high-dose regimens showed similar rates of LN flares, end-stage renal disease, and doubling of the serum creatinine.

Pulse IV glucocorticoids (500–1,000 mg methylprednisolone daily for 3 doses) in combination with immunosuppressive therapy is recommended by the Task Force Panel, followed by daily oral glucocorticoids (0.5–1 mg/kg/day), followed by a taper to the minimal amount necessary to control disease (level C evidence). There are insufficient data to recommend a specific steroid taper because the nephritis and extrarenal manifestations vary from patient to patient. There was no consensus reached regarding the use of monthly IV methylprednisolone with monthly IV CYC.

Although AZA has been used to treat LN, the Task Force Panel did not recommend it as one of the first choices for induction therapy.

The panel recommends that most patients be followed for 6 months after initiation of induction treatment with either CYC or MMF before making major changes in treatment other than alteration of glucocorticoid doses, unless there is clear evidence of worsening at 3 months (50% or more worsening of proteinuria or serum creatinine; level A evidence).

Fertility issues are often a concern for young SLE patients with nephritis. In a discussion, the Task Force Panel recommended that MMF was preferable to CYC for patients who express a major concern with fertility preservation, since high-dose CYC can cause permanent infertility in both women and men (level A evidence of gonadal toxicity). Six months of high-dose IV CYC was associated with approximately 10% sustained infertility in young women, and higher rates in older women. If 6 months of CYC were followed by quarterly doses, there was a higher rate of infertility. The Task Force Panel did not reach a consensus on the use of leuprolide in patients with SLE receiving CYC as a means to preserve fertility. They also noted that MMF is teratogenic (class D in US Food and Drug Administration [FDA] ranking). Therefore, the physician should be sure that a patient is not pregnant before prescribing MMF or MPA, and the medications should be stopped for at least 6 weeks before pregnancy is attempted.

Recommendations for Induction of Improvement in Patients with Class IV or IV/V Plus Cellular Crescents

The Task Force Panel recommended either CYC or MMF for induction of improvement in this type of LN (level C evidence), along with IV pulses of high-dose glucocorticoid and initiation of oral glucocorticoids at the higher-range dosage, 1 mg/kg/day orally (see Figure 2 in the original guideline document). For the purpose of these recommendations statements, the presence of any crescents on a renal biopsy sample was considered crescentic LN. Until recently, experts have favored high-dose IV CYC for treatment of LN with cellular crescents. In general, the presence of crescents indicates a poorer prognosis, even with appropriate treatment. Further recommendations for a pregnant patient with crescentic glomerulonephritis are provided in the section on "Treatment of LN in Patients Who Are Pregnant," below.

Recommendations for Induction of Improvement in Patients with Class V "Pure Membranous" LN

The Task Force Panel recommends that patients with pure class V LN and with nephrotic range proteinuria be started on prednisone (0.5 mg/kg/day) plus MMF 2–3 gm total daily dose (level A evidence) (see Figure 3 in the original guideline document).

Other therapies for membranous LN have been reported; however, the Task Force Panel did not reach consensus on a recommendation regarding those therapies.

Recommendations for Maintaining Improvement in Patients Who Respond to Induction Therapy
The Task Force Panel recommended that either AZA or MMF be used for maintenance therapy (level A evidence) (see Figure 2 in the original guideline document). The Task Force Panel did not vote on the rate of medication taper during the maintenance phase; to date, there are no adequate data to inform the physician regarding how rapidly AZA or MMF can be tapered or withdrawn.

Recommendations for Changing Therapies in Patients Who Do Not Respond Adequately to Induction Therapy

In patients who fail to respond after 6 months of treatment (based on the treating physician's clinical impression) with glucocorticoids plus MMF or CYC, the Task Force Panel recommends a switch of the immunosuppressive agent from either CYC to MMF, or from MMF to CYC, with these changes accompanied by IV pulses of glucocorticoids for 3 days (level C evidence) (see Figure 2 in the original guideline document). For CYC, either low dose or high dose can be used in white individuals, as discussed above in the section on "Recommendations for Induction of Improvement in Patients with ISN Class III/IV Lupus Glomerulonephritis," above. Evidence to support these opinions is not as strong as evidence for the efficacy of initial induction therapy. The panel also voted that in some cases rituximab can be used in patients whose nephritis fails to improve or worsens after 6 months of one induction therapy, or after the patient has failed both CYC and MMF treatments (level C evidence). The Task Force Panel did not reach consensus regarding the use of calcineurin inhibitors in this setting; however, there is evidence for their efficacy as an induction agent and in refractory disease.

There is evidence in open-label trials that LN may respond to rituximab treatment. Prospective, randomized, placebo-controlled trials did not show a significant difference between rituximab and placebo (on a background of MMF and glucocorticoids) after 1 year of treatment.

Evidence to support the use of cyclosporine or tacrolimus in LN is from open trials and recent prospective clinical trials; additional prospective trials are in progress. In a recent prospective trial, tacrolimus was equivalent to high-dose IV CYC in inducing complete and partial remissions of LN over a 6-month period. In another 4-year-long prospective trial, cyclosporine was similar to AZA in preventing renal flares in patients receiving maintenance therapy.

If nephritis is worsening in patients treated for 3 months with glucocorticoids plus CYC or MMF, the Task Force Panel recommended that the clinician can choose any of the alternative treatments discussed (level C evidence). Although combinations of MMF and calcineurin inhibitors and of rituximab and MMF are being studied and might be considered for those who have failed the recommended induction therapies, data are not robust enough at this time to include them for voting scenarios.

The FDA has approved belimumab for use in seropositive patients with SLE who have active disease in spite of prior therapies.

Identification of Vascular Disease in Patients with SLE and Renal Abnormalities

Several types of vascular involvement can occur in renal tissue of SLE, including vasculitis, fibrinoid necrosis with narrowing of small arteries/arterioles ("blunt" vasculopathy), thrombotic microangiopathy, and renal vein thrombosis. In general, vasculitis is treated similarly to the more common forms of LN discussed above. Blunt vasculopathy is highly associated with hypertension; it is not clear which comes first, SLE or hypertension. Thrombotic microangiopathy can be associated with a thrombotic thrombocytopenia–like picture. The Task Force Panel recommended that thrombotic microangiopathy be treated primarily with plasma exchange therapy (level C evidence).

Treatment of LN in Patients Who Are Pregnant

The Task Force Panel recommended several approaches for management of LN in women who are pregnant (all level C evidence) (see Figure 4 in the original guideline document). In patients with prior LN but no current evidence of systemic or renal disease activity, no nephritis medications are necessary. Patients with mild systemic activity may be treated with HCQ; this probably reduces activity of SLE during pregnancy. If clinically active nephritis is present, or there is substantial extrarenal disease activity, the clinician may prescribe glucocorticoids at doses necessary to control disease activity, and if necessary AZA can be added. High-dose glucocorticoid therapy in patients with SLE is associated with a high risk of maternal complications such as hypertension and diabetes mellitus. MMF, CYC, and methotrexate should be avoided because they are teratogenic in humans. Although AZA is listed as pregnancy category D in Micromedex, cross-sectional studies have shown that the risk of fetal abnormalities is low. The dose of AZA should not exceed 2 mg/kg in a pregnant woman. For patients with a persistently active nephritis with documented or suspected class III or IV with crescents, consideration of delivery after 28 weeks for a viable fetus is recommended.

Monitoring Activity of LN

Recommendations for monitoring LN are shown in the following table, and result from votes of the Task Force Panel (level C evidence).

Table. Recommended Monitoring of Lupus Nephritis*
<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>Urinalysis</th>
<th>Protein/Creatinine Ratio</th>
<th>Serum Creatinine</th>
<th>C3/C4 Levels</th>
<th>Anti-DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active nephritis at onset of treatment</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2†</td>
</tr>
<tr>
<td>Previous active nephritis, none currently</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Pregnant with active GN at onset of treatment</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pregnant with previous nephritis, none currently</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>No prior or current nephritis</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

*Values are the monthly intervals suggested as the minimum frequency at which the indicated laboratory tests should be measured in the systemic lupus erythematosus scenarios shown in the left-hand column. GN = glomerulonephritis.
†Opinion of authors based on a study published after the Task Force Panel had voted.

Definitions:

- **Level of Evidence**
  - Level of Evidence A: Data derived from multiple randomized clinical trials
  - Level of Evidence B: Data derived from a single randomized trial, or nonrandomized studies
  - Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care

Clinical Algorithm(s)

The original guideline document contains clinical algorithms for:

- Class III/IV induction therapy for lupus nephritis (LN)
- Treatment of class V LN without proliferative changes and with nephrotic range proteinuria (>3 gm/24 hours)
- Treatment of class III, IV, and V LN in patients who are pregnant

Scope

Disease/Condition(s)

Lupus nephritis

Guideline Category

Counseling
Diagnosis
Evaluation
Management
Screening
Treatment

Clinical Specialty
Intended Users
Physicians

Guideline Objective(s)
To provide a new set of management recommendations for lupus nephritis (LN)

Target Population
Adults with lupus nephritis (LN), particularly to those receiving care in the United States

Interventions and Practices Considered

Diagnosis/Evaluation
1. Renal biopsy, unless contraindicated
   - Serum creatinine
   - Proteinuria based on 24-hour urine or spot protein/creatinine ratio
   - Proteinuria plus either hematuria or cellular casts
2. Histologic classification based on the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification scheme

Management/Treatment
1. Adjunctive treatment
   - Background treatment with hydroxychloroquine (HCQ)
   - Renin-angiotensin blockade with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)
   - Control of hypertension
   - Statin therapy for hypercholesterolemia
2. Treatment for LN by ISN class
   - Oral mycophenolate mofetil (MMF) or mycophenolic acid (MPA)
   - Orally glucocorticoids
   - Intravenous (IV) cyclophosphamide (CYC)
   - Dosing based on race
   - Pulse schedule and tapering for IV glucocorticoids
   - Followup and dose adjustments
   - Leuprolide to preserve fertility (no consensus for recommendation reached)
   - Alternative schedules and therapies (e.g., cyclosporine) (no consensus for recommendation reached)
3. Maintenance therapy
   - Azathioprine (AZA) (not recommended for initial therapy, but recommended for maintenance therapy)
   - MMF
4. Changing therapy
   - Switching from MMF to CYC or from CYC to MMF
Continuing pulses of IV glucocorticoids
Alternative therapies (rituximab, tacrolimus, belimumab; calcineurin inhibitors were considered but no consensus for recommendation was reached)

5. Plasma exchange therapy for thrombotic microangiopathy

6. Treatment of pregnant women
- Counseling of pregnant women on pregnancy risks from lupus nephritis (LN) and its treatment
- No treatment for inactive disease
- HCQ for mild systemic disease activity
- Glucocorticoids alone or with AZA for systemic active disease at the lowest effective dose
- MMF, CYC, and methotrexate considered but not recommended
- Early delivery in cases of women with suspected class III or IV disease with crescents

7. Frequency of monitoring

Major Outcomes Considered
- Survival/mortality
- Rates of disease flares
- Changes in serum creatinine/proteinuria
- Rates of disease progression/development of end-stage renal disease
- Rates of remission
- Change in Systemic Lupus Erythematosus Disease Activity Index score
- Toxicity/adverse effects of treatments
- Percent of patients requiring treatment change

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A systematic review was performed with the assistance of a University of California at Los Angeles (UCLA) research librarian. The search strategy is outlined in the Evidence Report (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658), and briefly, the working group used Medline (through PubMed) by applying medical subject headings and relevant keywords with references from January 1, 1966, through January 22, 2010, for all literature with the term “lupus kidney diseases” published in English. The search was updated on August 8, 2010, and clinical trials and meta-analyses published after that date were reviewed by the corresponding author in April 2011 and February 2012. The articles were divided among review teams, each comprised of a junior fellow and a senior mentor.

Articles were screened to eliminate reviews, opinion articles, cohort studies that did not include patients 18 years of age or older, cohorts or prospective trials containing fewer than 29 patients, studies not requiring patients to meet a preestablished definition of systemic lupus erythematosus (SLE) or lupus nephritis (LN), or studies with less than 6 months of followup data. The authors examined each publication, and only the most recent or complete report of a clinical trial was incorporated when duplicate reports were found. The remaining cohort articles and all prospective randomized clinical trials were reviewed in full.

Number of Source Documents

Not stated
Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence
- Level of Evidence A: Data derived from multiple randomized clinical trials
- Level of Evidence B: Data derived from a single randomized trial, or nonrandomized studies
- Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Of the studies selected for full review, the two reviewers independently reviewed the articles, and then conferred to reach agreement on the description of each study assigned to them. Tables were composed, including summaries of results, descriptions of patients studied (cohorts in one table and prospective clinical trials in another), therapeutic interventions, and outcomes for each study selected. The Working Group met weekly to review progress; the Core Executive Panel met monthly by teleconference.

The 2 committees wrote an Evidence Report (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658) to summarize the literature review.

The strength of the evidence was graded using the method reported by the American College of Cardiology and used in the previous American College of Rheumatology (ACR) recommendations articles.

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)
Expert Consensus (Nominal Group Technique)

Description of Methods Used to Formulate the Recommendations

A modified RAND/University of California at Los Angeles (UCLA) Appropriateness Method, summarized in Figure 1 in the original guideline document, was used to develop these recommendations. The RAND/UCLA methodology incorporates elements of the nominal and Delphi methods. This method uses a combination of a systematic literature review and expert opinion. A Core Executive Panel, in conjunction with the Working Group, reviewed the existing guidelines, refined the domains of the project, performed a systematic literature review, and developed clinical scenarios. Votes of the Task Force Panel on the appropriateness of interventions in the various scenarios determined the recommendations.

Using the Evidence Report and expertise of the Core Executive Panel members, clinical scenarios were constructed. These scenarios (provided in detail in the Evidence Report, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658) were voted on by the Task Force Panel to elicit opinions on the appropriateness regarding decisions involving case definition, renal biopsy and histology, treatments, outcomes, and monitoring. The scenarios included indications for a renal biopsy; laboratory monitoring of lupus nephritis (LN); induction treatment options for International Society of Nephrology/Renal Pathology Society (ISN/RPS) class II, class III/IV with and without crescents, and class V membranous LN; and thrombotic thrombocytopenic purpura. Maintenance therapy, treatment for refractory disease, management of nephritis during pregnancy, and management of comorbid conditions associated with nephritis.
itself and immunosuppression from treatments (i.e., hypertension, hypercholesterolemia, and pneumocystis prophylaxis) were also incorporated into scenarios. While steroid dosing and tapering were recognized to be important aspects of LN management, the Core Expert Panel could not reach a consensus on a regimen given the variability inherent in LN; therefore, precise steroid-tapering schedules were not included in the scenarios. Likewise, definitions of response, degree of response, flare, severity of flare, and remission vary significantly in the literature and depend on the starting point in each individual patient; therefore, an exact definition of these terms was not included in the scenarios. Identification of response, flare, and failure to respond were based on the experienced clinician’s opinion, and it is intended that the treating clinician make similar judgments in employment of the recommendations outlined here. The Core Expert Panel agreed that specific therapy was not indicated for class I or class II renal biopsies; therefore, scenarios and recommendations were not created for these histologic classifications.

The Evidence Report, including search strategies, abstraction tools, and case scenarios, as well as summaries of the literature for randomized controlled trials (RCTs) and cohort studies, was submitted to members of the Task Force Panel prior to their face-to-face meeting, which was held in November 2010 in Atlanta, Georgia. (These reports are available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658.) Each member of the Task Force Panel voted on each scenario using a 9-point Likert scale, where a vote of 1 meant not valid and 9 meant extremely valid. The results of the first round of voting were presented anonymously and discussed at the face-to-face meeting. At the conclusion of the meeting, a second round of voting occurred, with the results of this round informing the development of the final recommendations. After the meeting, members of the Core Executive Panel tallied the votes. Agreement was defined as not more than two votes outside of the 3-point range in which the median vote falls. A recommendation was made both when there was agreement and when the median vote fell in the 7–9 range. Members of the Core Executive Panel reviewed the tally and identified areas of agreement or disagreement that were not compatible with current therapeutic recommendations or opinions in the recent literature. New scenarios to clarify such issues were constructed, and members of the Task Force Panel voted on the new scenarios. The results of the voting are shown in Figures 2-4 in the original guideline document. They are also shown by italicized lettering in the text of the recommendations.

Based on those results, this document was written, containing recommendations for treatment and monitoring of LN, and distributed to all members of each panel for comments and editing.

See the Evidence Report for (see the "Availability of Companion Documents" field) additional details on the RAND/UCLA methodology.

Rating Scheme for the Strength of the Recommendations
Not applicable

Cost Analysis

Cost Effectiveness Analyses of Specific Treatments

Intravenous Cyclophosphamide vs. Steroids Alone

In a 1994 National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) funded study, the authors reported that cyclophosphamide plus steroids was cost-savings compared to steroids alone, attributable to the significant costs of higher rates of ESRD for patients treated with steroids alone. All costs were reported in 1998 dollars. When looking at costs projected over 10 years for a hypothetical cohort of 1130 SLE nephritis patients (annual estimate of incident nephritis), the expected total costs of patients treated with steroids alone would be $65 million (more than 99% of that cost coming from the care for the 50% of patients projected with ESRD). In contrast, the cost of providing care for patients treated with cyclophosphamide was $14 million with only 5% of patients progressing to ESRD. Even though the analysis was over-simplified the magnitude of the cost-savings is clear. (As an example, they have all of the 5% of patients treated with cyclophosphamide progressing to ESRD in year 3.)

Mycophenolate Mofetil (MMF) vs. Intravenous Cyclophosphamide

In a study funded and co-authored by Aspreva, the authors analyzed quality adjusted life-years (QALYs) by treatment type. Based on 2.7 g of MMF vs. 750 mg/m² of cyclophosphamide costs and quality of life were derived for a hypothetical cohort of 10,000 simulated patients. Algorithms were detailed to include crossover patients, expected outcomes, as well as major and some minor adverse infections. The expected cost in 2005 £ for MMF vs. cyclophosphamide over 24-weeks was £1,388 vs. £2,994. MMF also had superior quality of life scores with 0.26 QALYs vs. 0.22 QALYs therefore resulting in cost-saving (dominance) of MMF yielding a cost-savings of £41,205 per QALY. The typical willingness to pay for a QALY is £25,000–£35,000 (equivalent to $50,000–$70,000). Using sensitivity analyses to vary outcomes the confidence
interval around the £41,205 per QALY even with poorer outcomes, there was 81% probability that the cost per QALY would be less than the willingness to pay for QALY.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

The completed documents were submitted to the American College of Rheumatology (ACR) for review and approval by the ACR Guidelines Subcommittee, ACR Quality of Care Committee, and ACR Board of Directors.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is specifically stated for most recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate screening, treatment, and management of lupus nephritis (LN), which may further improve outcomes and decrease morbidity and mortality in systemic lupus erythematosus (SLE)

Potential Harms

- Adverse effects of drugs, including nausea, diarrhea, increased risk of infection, and infertility
- Teratogenesis (see the "Contraindications" field)

Contraindications

Contraindications

- The Task Force noted that mycophenolate mofetil (MMF) is teratogenic (class D in US Food and Drug Administration [FDA] ranking). Therefore, the physician should be sure that a patient is not pregnant before prescribing MMF or mycophenolic acid (MPA), and the medications should be stopped for at least 6 weeks before pregnancy is attempted.
- MMF, cyclophosphamide (CYC), and methotrexate should be avoided because they are teratogenic in humans.
- High-dose CYC can cause permanent infertility in both women and men.
- High-dose glucocorticoid therapy in patients with systemic lupus erythematosus (SLE) is associated with a high risk of maternal complications such as hypertension and diabetes mellitus.
- Although azathioprine (AZA) is listed as pregnancy category D in Micromedex, cross-sectional studies have shown that the risk of fetal abnormalities is low. The dose of AZA should not exceed 2 mg/kg in a pregnant woman.
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated in pregnancy.

Qualifying Statements
Qualifying Statements

- Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome.

- 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 (LN).

- Limitations of this report include the absence of an agreement on definitions of terms such as remission, flare, and response.

- Therapies that were approved after the original literature review are not included in these recommendations.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Patient Resources

For information about availability, see the Availability of Companion Documents and Patient Resources fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Adaptation
Not applicable: The guideline was not adapted from another source.

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Guideline Developer(s)
American College of Rheumatology - Medical Specialty Society

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American College of Rheumatology

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Core Expert Panel/Task Force Panel

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Financial Disclosures/Conflicts of Interest

Dr. Hahn has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from UCB and Abbott, and has served on the Data and Safety Monitoring Board for Anthera. Dr. McMahon has received speaking fees (more than $10,000) from HGS/GSK. Dr. Merrill has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from UCB, Amgen, Pfizer, Lilly, Bristol-Myers Squibb, Genentech/Roche, EMD Serono, Neovacs, Cephalon, MedImmune, Questcor, Argos, Abbott, Ono, Astellas, Baxter, RPS, and Takeda, and (more than $10,000 each) from Human Genome Sciences/GlaxoSmithKline and Parexel, and has served on the Data and Safety Monitoring Board and/or Adjudication for Industry Trials for Amgen, Celgene, and Pfizer. Dr. Rastogi has received consultant fees, speaking fees, and/or honoraria (more than $10,000 each) from ViiV, Novartis, Genzyme, and Cubist.

Guideline Status
This is the current release of the guideline.

Guideline Availability
Availability of Companion Documents

The following is available:


In addition, the evidence tables in Appendices A and B are available from the Arthritis Care and Research Journal Web site.

Patient Resources

The following are available:

- Mycophenolate mofetil (CellCept) and mycophenolate sodium (Myfortic). 2012 May. 3 p. Available in PDF from the ACR Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline’s content.

NGC Status

This NGC summary was completed by ECRI Institute on July 31, 2012. The information was verified by the guideline developer on August 24, 2012. This summary was updated by ECRI Institute on November 21, 2013 following the U.S. Food and Drug Administration advisory on Arzerra (ofatumumab) and Rituxan (rituximab).

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