

# Systemic Lupus Erythematosus

## A Review

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**IMPORTANCE** Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by inflammation and immune-mediated injury to multiple organ systems, including the mucocutaneous, musculoskeletal, hematologic, and kidney systems. Approximately 3.4 million people worldwide have received a diagnosis of SLE.

**OBSERVATIONS** Approximately 90% of people with SLE are female. Although there are no uniformly accepted diagnostic criteria for SLE, the 2019 European Alliance of Associations for Rheumatology (formerly the European League Against Rheumatism)/American College of Rheumatology classification criteria developed for scientific study are an estimated 96.1% sensitive and 93.4% specific for SLE. These classification criteria include both clinical factors, such as fever, cytopenia, rash, arthritis, and proteinuria, which may be indicative of lupus nephritis; and immunologic measures, such as SLE-specific autoantibodies and low complement levels. Approximately 40% of people with SLE develop lupus nephritis, and an estimated 10% of people with lupus nephritis develop end-stage kidney disease after 10 years. The primary goal of treatment is to achieve disease remission or quiescence, defined by minimal symptoms, low levels of autoimmune inflammatory markers, and minimal systemic glucocorticoid requirement while the patient is treated with maintenance doses of immunomodulatory or immunosuppressive medications. Treatment goals include reducing disease exacerbations, hospitalizations, and organ damage due to the disease or treatment toxicity. Hydroxychloroquine is standard of care for SLE and has been associated with a significant reduction in mortality. Treatments in addition to hydroxychloroquine are individualized, with immunosuppressive agents, such as azathioprine, mycophenolate mofetil, and cyclophosphamide, typically used for treating moderate to severe disease. Three SLE medications were recently approved by the Food and Drug Administration: belimumab (for active SLE in 2011 and for lupus nephritis in 2020), voclosporin (for lupus nephritis), and anifrolumab (for active SLE).

**CONCLUSIONS AND RELEVANCE** Systemic lupus erythematosus is associated with immune-mediated damage to multiple organs and increased mortality. Hydroxychloroquine is first-line therapy and reduces disease activity, morbidity, and mortality. When needed, additional immunosuppressive and biologic therapies include azathioprine, mycophenolate mofetil, cyclophosphamide, belimumab, voclosporin, and anifrolumab.

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**S**ystemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by inflammation and immune-mediated injury to multiple organ systems, including the mucocutaneous, musculoskeletal, hematologic, and kidney systems. It affects approximately 3.4 million people worldwide. Of these individuals, an estimated 3 million are female.<sup>1</sup>

Systemic lupus erythematosus is newly diagnosed in 400 000 people each year worldwide.<sup>1,2</sup> According to a 2023 systematic review and modeling study that included 112 studies, Poland, the US, Barbados, and China had the highest incidence of SLE.<sup>1</sup> The estimated incidence of SLE in the US in 2018 was approximately 5 to 12 per 100 000 person-years.<sup>1,3</sup> The US incidence among females compared with males was 8.7 vs 1.2 per 100 000 person-years, and the prevalence among

females vs males was 128.7 vs 14.6 per 100 000 person-years.<sup>3,4</sup> The annual incidence of SLE in the US was higher in Black females compared with White females (15.9 vs 5.7 per 100 000 person-years).<sup>3</sup> The prevalence was 230.9 per 100 000 person-years in Black females compared with 84.7 per 100 000 person-years in White females.<sup>3,4</sup>

This review summarizes current evidence regarding diagnosis and treatment of SLE.

## Methods

We conducted a PubMed search on January 19, 2024, of English-language articles published since 2013, using keywords *systemic lupus*

Figure 1. Guide to Systemic Lupus Erythematosus Diagnostic Classification Adapted From 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology Classification Criteria

Initial criterion required for systemic lupus erythematosus (SLE) classification			
Antinuclear antibodies $\geq 1:80$			
Summation of criteria points from clinical and immunologic domains			
<b><math>\geq 10</math> total points indicates SLE classification</b> At least 1 clinical criterion is required. Only the highest point value criterion from each domain is counted.			
CLINICAL DOMAINS	<b>Constitutional</b> Points Fever Temperature $>38.3^{\circ}\text{C}$ 2	<b>Mucocutaneous<sup>a</sup></b> Points Nonscarring alopecia 2 Oral ulcers 2 Subacute cutaneous lupus Annular or papulosquamous eruption, usually photodistributed or Discoid lupus Erythematous-violaceous cutaneous lesion 4 Acute cutaneous lupus Malar or generalized maculopapular rash 6 <sup>a</sup> Observed by a clinician	<b>Serosal</b> Points Pleural or pericardial effusion Requires imaging evidence 5 Acute pericarditis $\geq 2$ of pericardial chest pain, pericardial rub, electrocardiogram with new widespread ST-segment elevation or PR depression, new or worsened pericardial effusion on imaging 6
	<b>Renal</b> Points Proteinuria $>0.5\text{ g/24 h}$ 4 Class II lupus nephritis Mesangial proliferative lupus nephritis or Class V lupus nephritis Membranous lupus nephritis 8 Class III lupus nephritis Focal proliferative lupus nephritis or Class IV lupus nephritis Diffuse proliferative lupus nephritis 10		<b>Musculoskeletal</b> Points Joint involvement $\geq 2$ joints involved with either swelling or effusion, or tenderness and morning stiffness 6
		<b>Hematologic</b> Points Leukopenia WBC count $<4 \times 10^9/\text{L}$ 3 Thrombocytopenia Platelets $<100 \times 10^9/\text{L}$ 4 Autoimmune hemolysis Defined by laboratory findings (eg, reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated lactate dehydrogenase, and positive Coomb test result) 4	<b>Neuropsychiatric</b> Points Delirium Acute, fluctuating change in consciousness and either acute or subacute change in cognition, or change in behavior, mood, or affect 2 Psychosis Delusions and/or hallucinations 3 Seizure Primary generalized or partial or focal 5
	<b>Immunologic Domains</b> <b>Complement proteins</b> Points Low C3 or low C4 3 Low C3 and low C4 4	<b>SLE-specific antibodies</b> Points Anti-double-stranded DNA antibody or Anti-Smith antibody 6	<b>Antiphospholipid antibodies</b> Points Anticardiolipin IgA, IgG, or IgM, medium or high titer ( $>40$ units or $>99$ th percentile) or Anti- $\beta_2$ -glycoprotein I IgA, IgG, or IgM or Lupus anticoagulant 2

Adapted from Aringer et al.<sup>9</sup>

erythematosus and lupus nephritis. We prioritized meta-analyses, systematic reviews, practice guidelines, and randomized clinical trials (RCTs). References of articles were manually reviewed to identify additional sources. We also performed PubMed searches for specific subtopics. Narrative reviews and large observational studies were included when higher-quality evidence was lacking. Articles of higher quality and greater relevance to general medical practice were prioritized for inclusion. Of 950 articles retrieved, 90 were included, consisting of 32 meta-analyses, 10 systematic reviews, 15 practice guidelines or society statements, 9 RCTs, 10 observational studies (5 cross-sectional, 5 longitudinal), and 14 narrative reviews.

## Discussion and Observations

### Pathophysiology

The pathogenesis of SLE involves systemic inflammation associated with elevated levels of type I interferon and autoantibodies against nuclear antigens, such as double-stranded DNA and nucleic acid-binding proteins.<sup>5</sup> Development of clinical disease is thought to require exposure to environmental risk factors, such as UV light, cigarette smoking, Epstein-Barr virus, or silica from occupational ex-

posures such as painting, foundry work, or sandblasting, in an individual with a genetic predisposition.<sup>5-8</sup>

### Clinical Presentation

Systemic lupus erythematosus affects multiple organs. Although there are no formal diagnostic criteria for clinical practice, the 2019 European Alliance of Associations for Rheumatology (formerly the European League Against Rheumatism)/American College of Rheumatology (EULAR/ACR) classification criteria, designed for scientific investigation, had 96.1% sensitivity and 93.4% specificity for an SLE diagnosis by expert rheumatologists (Figure 1).<sup>9,10</sup> A positive antinuclear antibody test result at a titer of greater than or equal to 1:80 is required for SLE classification, according to the 2019 EULAR/ACR criteria. These criteria may aid in diagnosis because they identify most patients with SLE. However, given the heterogeneity of SLE, the diagnosis of SLE should not be excluded and treatment should not be withheld for patients thought to have SLE if the 2019 EULAR/ACR classification criteria are not met.<sup>9</sup> Typical clinical manifestations of SLE include fever (defined in the classification criteria as a temperature  $>38.3^{\circ}\text{C}$ ), alopecia, skin exanthem, oral ulcers, and joint pain and swelling. Laboratory abnormalities include anemia; thrombocytopenia; leukopenia; hypocomplementemia; serum and urine

Table 1. Autoantibodies Associated With Systemic Lupus Erythematosus

Antibody	Clinical associations	Sensitivity, % (95% CI)	Specificity, % (95% CI)
ANA	Entry criterion (at titer ≥1:80) for 2019 EULAR/ACR SLE classification criteria. Typically used as the initial screening test for SLE in clinical practice	By titer: 1:40, 98.4 (97.6-99.0) 1:80, 97.8 (96.8-98.5) 1:160, 95.8 (94.1-97.1) 1:320, 86.0 (77.0-91.9)	By titer: 1:40, 66.9 (57.8-74.9) 1:80, 74.7 (66.7-81.3) 1:160, 86.2 (80.4-90.5) 1:320, 96.6 (93.9-98.1)
aPL: aCL antibodies, aβ2GPI antibodies, or LAC	Associated with thrombosis, thrombocytopenia, autoimmune hemolytic anemia, pulmonary hypertension, nonbacterial thrombotic endocarditis, adverse pregnancy outcomes	Not available	Not available
Anti-dsDNA	Associated with lupus nephritis. Elevated titers may be indicative of increased SLE disease activity, and specifically of lupus nephritis flares	57	97
Anti-Smith	Associated with lupus nephritis	24	98
Anti-Ro/SSA	Not included in 2019 EULAR/ACR SLE classification criteria. Associated with Sjögren syndrome (as an independent diagnosis and overlapping with SLE), neonatal lupus, cutaneous lupus (especially SCLE)	61	80
Anti-La/SSB	Not included in 2019 EULAR/ACR SLE classification criteria. Associated with Sjögren syndrome (as an independent diagnosis or overlapping with SLE). Most often occurs concomitantly with anti-Ro/SSA	35	88
Anti-RNP	Not included in 2019 EULAR/ACR SLE classification criteria. Characteristic of mixed connective tissue disease, an overlap syndrome defined by symptoms of ≥2 diseases, including SLE, systemic sclerosis, inflammatory myopathy, and rheumatoid arthritis	39	84

Abbreviations: aCL, anticardiolipin; ANA, antinuclear antibody; aPL, antiphospholipid antibodies; aβ2GPI, anti-β<sub>2</sub>-glycoprotein I; dsDNA, double-stranded DNA; EULAR/ACR, European Alliance of Associations for Rheumatology/American College of Rheumatology; LAC, lupus anticoagulant; RNP, ribonucleoprotein; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; SSA, Sjögren syndrome A; SSB, Sjögren syndrome B.

markers of lupus nephritis such as proteinuria, hematuria, and elevated serum creatinine level; and characteristic autoantibodies. Specific autoantibodies (such as antiphospholipid antibodies, anti-double-stranded DNA antibody, and anti-Smith antibody) and other autoantibodies (such as antiribonucleoprotein, anti-Ro/Sjögren syndrome A, and anti-La/Sjögren syndrome B antibodies) may be associated with specific clinical manifestations (Table 1).

Mucocutaneous Manifestations

Systemic lupus erythematosus is associated with characteristic skin exanthems, including acute, subacute, and chronic cutaneous lupus exanthems with differing clinical and histologic features (Figure 2). Acute cutaneous lupus erythematosus is defined as a maculopapular rash in a generalized or malar distribution (Figure 2A). Up to 50% of patients with SLE will have acute cutaneous lupus erythematosus sometime in their disease course.<sup>9,11</sup> Subacute cutaneous lupus erythematosus is a photosensitive annular or papulosquamous rash that affects 10% to 15% of people with SLE (Figure 2B). The most common chronic cutaneous lupus erythematosus, discoid lupus, is defined by well-demarcated, scaly, erythematous macules or papules that evolve into indurated circular plaques, often affecting the head and neck. Discoid lupus may be associated with permanent hair loss due to scarring (Figure 2C).<sup>11</sup> Nonscarring alopecia occurs in 40% to 70% of patients with SLE.<sup>9,11</sup> Although acute cutaneous lupus erythematosus occurs almost exclusively in association with SLE, subacute cutaneous lupus erythematosus and discoid lupus can also occur independently.<sup>11</sup> Of patients who present with discoid lupus, up to 30% progress to SLE.<sup>12</sup> In a Swedish nationwide prospective cohort study including 868 patients with discoid lupus, the probability of SLE diagnosis after 3 years was 16.7% (95% CI, 12.1%-21.3%).<sup>13</sup> Anti-Ro/Sjögren syndrome A antibody is as-

sociated with cutaneous lupus: in one multicenter study, anti-Ro/Sjögren syndrome A antibodies were detected in 47.4% of 272 patients with acute cutaneous lupus erythematosus, 72.1% of 226 patients with subacute cutaneous lupus erythematosus, and 22.0% of 345 patients with chronic cutaneous lupus erythematosus.<sup>14</sup> In a meta-analysis of 113 studies that included 53 307 patients with SLE, approximately 30% of patients had oral ulcers.<sup>15</sup>

Joint Involvement

Many patients with SLE report joint pain (most commonly in the hands) with or without inflammatory arthritis. Radiographic joint erosions are not typical for SLE and suggest an alternative etiology such as rheumatoid arthritis.<sup>16</sup> Jaccoud arthropathy, long-standing periarticular inflammation that causes reducible joint deformity, affects approximately 3% to 13% of patients with SLE.<sup>16</sup>

Hematologic Abnormalities

Patients with SLE may have leukopenia, thrombocytopenia, or anemia. In the EULAR/ACR classification criteria, leukopenia was defined by a white blood cell count less than 4 ×10<sup>9</sup>/L, thrombocytopenia by a platelet count less than 100 ×10<sup>9</sup>/L, and autoimmune hemolytic anemia by laboratory evidence of hemolysis.<sup>9</sup> In a systematic review with 5 studies and 1253 participants, approximately 22% to 42% of patients with lupus had leukopenia (primarily lymphopenia).<sup>17</sup> A meta-analysis that included 53 studies reported that 1815 of 9019 patients (20.1%) with SLE had thrombocytopenia.<sup>18</sup> A meta-analysis including 38 studies reported that 977 of 8286 patients (11.8%) with SLE had autoimmune hemolytic anemia.<sup>19</sup> Thrombocytopenia and autoimmune hemolytic anemia each occurred more frequently for patients with SLE who had antiphospholipid antibodies (thrombocytopenia: 29.0%



Figure 2. Cutaneous Rashes in Systemic Lupus Erythematosus



in antiphospholipid-positive patients vs 15.1% in antiphospholipid-negative patients with SLE [odds ratio {OR}, 2.48; 95% CI, 2.10-2.93]; autoimmune hemolytic anemia: 20.5% in antiphospholipid-positive patients vs 8.7% in antiphospholipid-negative patients with SLE [OR, 2.83; 95% CI, 2.12-3.79].<sup>18,19</sup> Macrophage activation syndrome, the phrase designating the presence of hemophagocytic lymphohistiocytosis when it develops in the context of a rheumatologic condition, affects approximately 0.9% to 4.6% of patients with SLE. Macrophage activation syndrome is a life-threatening systemic inflammatory disorder that may present with fever, lymphadenopathy, hepatosplenomegaly, and coagulopathy and may lead to multiorgan system failure.<sup>20</sup>

#### Vascular Complications and Pregnancy Risk

*Antiphospholipid antibodies* refers to a set of antibodies that include anticardiolipin IgA, IgG, or IgM; anti- $\beta_2$ -glycoprotein I IgA, IgG, or IgM; and lupus anticoagulant. Patients with SLE and antiphospholipid antibodies have an increased risk of vascular complica-

tions such as thrombosis and adverse pregnancy outcomes such as preeclampsia and fetal loss compared with those without antiphospholipid antibodies.<sup>18,19,21-27</sup> In a meta-analysis of 35 studies that included 3505 individuals with SLE, 31.3% of patients who were antiphospholipid antibody-positive compared with 18.2% of those who were antiphospholipid antibody-negative had microvascular kidney disease (OR, 3.03; 95% CI, 2.25-4.09).<sup>23</sup> In a meta-analysis of 31 studies that included 4480 patients with SLE, 12.3% of individuals with antiphospholipid antibodies compared with 7.3% without them had pulmonary hypertension (OR, 2.28; 95% CI, 1.65-3.15).<sup>27</sup> *Antiphospholipid syndrome* refers to patients with antiphospholipid antibodies who have had thrombotic events, adverse pregnancy outcomes, or both in association with presence of these antibodies.<sup>22</sup> A meta-analysis of 10 studies including 941 pregnant patients with SLE alone, antiphospholipid syndrome alone (primary antiphospholipid syndrome), or SLE with antiphospholipid syndrome (secondary antiphospholipid syndrome) showed that people with SLE and antiphospholipid syndrome had a higher risk of arterial or venous thrombosis, fetal loss, and stillbirth pregnancies compared with those with SLE alone (thrombosis: 79 of 178 [44.4%] vs 29 of 177 [16.4%] [relative risk {RR}, 7.73; 95% CI, 2.22-26.89]; fetal loss: 37 of 137 [27.0%] vs 12 of 178 [6.7%] [RR, 4.49; 95% CI, 2.09-9.64]; stillbirth: 4 of 15 [26.7%] vs 6 of 69 [8.7%] [RR, 8.07; 95% CI, 2.81-23.15]).<sup>25</sup> Additional characteristics associated with adverse pregnancy outcomes in SLE include active disease at conception, kidney disease, and presence of maternal anti-Ro/Sjögren syndrome A antibodies, anti-La/Sjögren syndrome B antibodies, or both (associated with risk of neonatal lupus).<sup>28,29</sup>

#### Cardiopulmonary Manifestations

Pericarditis affects up to 25% of patients with SLE.<sup>30</sup> One meta-analysis of 39 studies and 12 619 people with SLE reported that 16.5% had pleuritis.<sup>31</sup> Rare cardiopulmonary manifestations of SLE include valve thickening, valvular regurgitation and vegetations, myocarditis, pulmonary hypertension, pneumonitis, interstitial lung disease, diffuse alveolar hemorrhage, and shrinking lung syndrome, defined by a progressive decline in lung volumes. Nonbacterial thrombotic endocarditis affecting the mitral valve is the most common valvular manifestation and is associated with the presence of antiphospholipid antibodies.<sup>30,32</sup> Clinically significant valvular dysfunction due to nonbacterial thrombotic endocarditis occurs in approximately 1% to 2% of patients with SLE.<sup>30</sup>

#### Lupus Nephritis

Lupus nephritis may present with asymptomatic proteinuria (defined as >0.5 g protein per 24 hours or >0.5 g protein per gram of creatinine on random urine sample testing<sup>9</sup>), nephrotic syndrome, or acute kidney injury. Elevated titers of anti-double-stranded DNA antibodies and decreased complement levels are associated with greater SLE disease activity and with the occurrence of lupus nephritis flares.<sup>33,34</sup> In the 1827-participant Systemic Lupus International Collaborating Clinics inception cohort study, lupus nephritis occurred in 38.3% of people and was an early or initial manifestation of SLE in 80.9% of patients with SLE who had lupus nephritis.<sup>35</sup>

#### Neuropsychiatric Manifestations

Neuropsychiatric symptoms consist of central and peripheral nervous system conditions, including headache, mood disorders,

cognitive impairment, seizures, psychosis, and polyneuropathy. In a meta-analysis of 22 studies that included 6055 patients with SLE, the pooled prevalence of neuropsychiatric SLE was 52.2% (range, 10.6%-96.4%).<sup>36</sup> Nonspecific, variably defined manifestations, including headache, mood disorder, and cognitive dysfunction, were the most common neuropsychiatric symptoms.<sup>36</sup> In the Swiss SLE cohort study that included 688 participants, 28.1% had a neuropsychiatric manifestation; 7.1% had stroke or transient ischemic attack, 6.5% had psychosis, and 5.4% had seizures. Peripheral neuropathy, which occurred in 3.6% of participants, was the most common peripheral nervous system manifestation.<sup>36</sup>

### Gastrointestinal Manifestations

Gastrointestinal manifestations of SLE include protein-losing enteropathy, hepatitis, pancreatitis, and intestinal pseudo-obstruction, which presents with clinical features of intestinal obstruction without an identifiable obstructive lesion.<sup>37,38</sup> Each of these conditions affects less than 10% of patients with SLE.

### Assessment and Diagnosis

Patients with SLE nearly always have a positive antinuclear antibody test result. However, the antinuclear antibody result may be positive in other rheumatic autoimmune conditions, such as Sjögren syndrome, systemic sclerosis, and idiopathic inflammatory myopathy; in nonrheumatic autoimmune conditions, such as autoimmune hepatitis and autoimmune thyroiditis; and in up to one-third of healthy individuals typically with titers less than or equal to 1:80.<sup>39,40</sup> The specificity of a positive antinuclear antibody result for SLE increases with higher antinuclear antibody titers. For patients with signs or symptoms of SLE, a 1:80 titer was 74.7% specific for SLE and a 1:320 titer was 96.6% specific (Box).<sup>40</sup>

Included in the classification criteria,<sup>9</sup> anti-double-stranded DNA antibody is approximately 57% sensitive and 97% specific, whereas anti-Smith antibody is approximately 24% sensitive and 98% specific.<sup>33,41</sup> For patients with established SLE, anti-double-stranded DNA antibody titers and complement C3 and C4 levels are routinely assessed in clinical practice to monitor disease activity.<sup>33,34</sup> Approximately 20% to 40% of patients with SLE have antiphospholipid antibodies.<sup>21,26</sup> The presence of antiphospholipid antibodies is associated with increased risk for thrombosis and adverse pregnancy outcomes (Table 1). Higher-titer antibodies (ie, >40 units or >99th percentile) or the presence of lupus anticoagulant that meets criteria for persistence, defined as 2 positive test results separated by at least a 12-week interval, is associated with the highest risk.<sup>21,22</sup>

Although sensitivity and specificity of anti-Ro/Sjögren syndrome A, anti-La/Sjögren syndrome B, or antiribonucleoprotein antibodies for SLE are not sufficiently high for inclusion in the 2019 EULAR/ACR classification criteria,<sup>9,41</sup> their presence can assist with diagnosis and characterization of SLE.<sup>42</sup> Anti-Ro/Sjögren syndrome A antibodies, anti-La/Sjögren syndrome B antibodies, or both are associated with overlapping Sjögren disease and with neonatal lupus, and anti-Ro/Sjögren syndrome A is associated with cutaneous lupus. Antiribonucleoprotein antibody is characteristic of mixed connective tissue disease, an overlap syndrome defined by symptoms of at least 2 diseases, including SLE, systemic sclerosis, inflammatory myopathy, and rheumatoid arthritis (Table 1).<sup>43</sup>

Biopsies of skin can diagnose SLE manifestations in the skin and biopsies of the kidney can establish lupus nephritis. Kidney biopsy

### Box. Frequently Asked Questions

#### 1. Is a patient with a positive antinuclear antibody (ANA) result likely to have systemic lupus erythematosus (SLE)?

Although most people with SLE have a positive ANA result (at titer  $\geq 1:80$ ), ANA is not specific for SLE. A positive ANA result occurs in many other rheumatic and nonrheumatic autoimmune conditions, such as Sjögren syndrome, systemic sclerosis, and autoimmune thyroiditis, and may also occur in healthy individuals.

#### 2. Can older patients get SLE?

Although approximately 65% of patients with SLE receive a diagnosis before age 50 years, people in any demographic group can be affected by SLE. When an older adult with medical comorbid conditions presents with symptoms consistent with new-onset SLE, it is important to evaluate for possible drug-induced lupus because it represents a reversible cause of SLE. Procainamide and hydralazine are the drugs most commonly associated with drug-induced SLE.

#### 3. Can patients with SLE discontinue hydroxychloroquine during their lifetime?

Hydroxychloroquine is recommended for continuous use for patients with SLE regardless of disease manifestations and severity, in the absence of contraindications such as allergy or significant retinal disease. Whether patients with long-term disease remission can safely discontinue hydroxychloroquine is not currently known.

#### 4. How should a generalist approach the evaluation of a patient with possible SLE?

A generalist should consider a diagnosis of SLE if the patient has suggestive symptoms or signs, especially those that are more objective, such as joint pain and swelling, photosensitive rash, or unexplained leukopenia, thrombocytopenia, or proteinuria. Checking an ANA level is a logical next step: if the ANA titer is  $\geq 1:80$ , referral to a rheumatologist without further evaluation is appropriate; if the ANA result is negative and routine laboratory test results and serologic markers of inflammation, such as erythrocyte sedimentation rate and C-reactive protein level, are normal, the likelihood of SLE is low and other diagnoses should be pursued.

is indicated for patients with SLE who have an acute increase in serum creatinine level without an alternative explanation, proteinuria level greater than 0.5 g/24 hours or greater than 0.5 g random urine protein to creatinine ratio, hematuria in the presence of proteinuria, or cellular casts.<sup>44</sup>

Diagnosing SLE requires ruling out alternative etiologies that may present with similar signs and symptoms, including infectious diseases such as viral hepatitis, parvovirus, syphilis, and infectious endocarditis, as well as lymphoproliferative disorders such as lymphoma and Castleman disease. Undifferentiated connective tissue disease is defined by the presence of signs and symptoms associated with SLE and other autoimmune rheumatic diseases (most commonly joint involvement, present in 60% of patients), but which are insufficient for a definitive diagnosis of SLE or another autoimmune rheumatic disease.<sup>45</sup> In a review that included 11 studies and 1890 patients that assessed undifferentiated connective tissue disease progression, 2.9% to 13.2% of patients with the disease subsequently received a diagnosis of SLE after 3 to 14 years of follow-up.<sup>45</sup>

Specific medications may cause “drug-induced lupus,” which presents as positive antinuclear antibody result and with symptoms including constitutional symptoms, arthralgia or arthritis, rash, and serositis. These symptoms, which may develop several weeks to months after the medication is initiated, typically improve within a few weeks of drug discontinuation but may persist for several months. For some patients, these medications induce autoantibody production without clinical manifestations of SLE. Medications most frequently associated with drug-induced lupus are procainamide and hydralazine: 15% to 20% of individuals taking procainamide and 7% to 13% of those taking hydralazine develop drug-induced lupus.<sup>46</sup> Other medications that can cause drug-induced lupus include statins,  $\beta$ -blockers, and angiotensin-converting enzyme inhibitors (prevalence among users of these medications was not reported) (Box).<sup>47</sup>

Clinical practice guidelines recommend the Systemic Lupus Erythematosus Disease Activity Index 2000 for monitoring disease activity within the preceding 30 days,<sup>48</sup> and the Systemic Lupus International Collaborating Clinics/ACR Damage Index<sup>49</sup> for monitoring organ pathology.<sup>50</sup> The activity index includes clinical (eg, arthritis, rash, pleuritis, pericarditis) and laboratory measures (eg, anti-double-stranded DNA antibodies, decreased complement levels, leukopenia, thrombocytopenia).<sup>34,48</sup> Attaining remission or a state of low disease activity has been associated with lower risk of lupus flare, decreased organ pathology, and improved quality of life.<sup>51,52</sup> Organ damage—such as chronic kidney disease or end-stage kidney disease, cardiomyopathy, and diseases associated with long-term systemic glucocorticoid exposure, including type 2 diabetes and osteoporosis—is associated with increased mortality.<sup>53</sup>

## Treatment

Treatment for SLE is intended to minimize disease activity, drug toxicity, and organ damage, as well as improve quality of life and survival (Table 2).<sup>50,57</sup> Initial treatment depends on the nature, location, and severity of inflammation, whether inflammation involves 1 or multiple organs, and patient comorbid conditions and potential to become pregnant.<sup>56</sup>

Hydroxychloroquine is standard of care for all patients with SLE regardless of organ involvement and severity of symptoms, except for patients with contraindications such as drug allergy or significant preexisting retinal disease (retinal toxicity is a rare but serious adverse effect of hydroxychloroquine) (Box).<sup>44,50,55,56,58</sup> In a meta-analysis of 21 cohort studies including 26 037 patients, treatment was associated with a 54% reduction in overall mortality (absolute rates not reported; pooled hazard ratio, 0.46; 95% CI, 0.38-0.57).<sup>54</sup> Recommended dosing ( $\leq 5.0$  mg/kg actual body weight) and ophthalmologic screening mitigate risk of drug-induced retinopathy, which occurs in less than 2% of patients who have been taking hydroxychloroquine for 10 years or fewer.<sup>55</sup> Screening is recommended at initiation, 5 years later in the absence of additional risk factors for drug-induced retinopathy (eg, high daily dose, kidney disease, tamoxifen use), and annually thereafter.<sup>55</sup>

Immunosuppressive drugs for treating moderate to severe SLE include azathioprine, mycophenolate mofetil/mycophenolic acid, methotrexate, calcineurin inhibitors (ie, tacrolimus, cyclosporine, and voclosporin), or cyclophosphamide; and biologic agents include belimumab, anifrolumab, and rituximab.<sup>56</sup> Early treatment with immunosuppressive agents reduces cumulative glucocorti-

coid exposure.<sup>56</sup> Most RCTs of treatment have focused on the common and serious manifestation of lupus nephritis. Clinical trial evidence is less available for other manifestations of SLE, such as arthritis, rash, and neuropsychiatric disease.

Lupus nephritis treatment is guided by International Society of Nephrology/Renal Pathology Society histologic classification when kidney biopsy data are available. Classes I and II describe mesangial lesions, classes III and IV describe proliferative lupus nephritis (focal and diffuse, respectively), class V refers to membranous nephropathy, and class VI refers to global sclerosis.<sup>59</sup> Mesangial lesions (classes I and II) generally respond to immunosuppression prescribed for nonkidney manifestations of SLE.<sup>44</sup> Standard of care for proliferative lupus nephritis (classes III and IV) with or without concurrent membranous lesions (class V) is initial treatment with pulse intravenous glucocorticoids and either mycophenolate mofetil/mycophenolic acid or intravenous cyclophosphamide, followed by mycophenolate mofetil/mycophenolic acid or azathioprine, with the goal of tapering oral glucocorticoids to prednisone equivalent less than or equal to 7.5 mg/d by 3 to 6 months.<sup>44,60,61</sup> When “pure class V” disease (ie, membranous disease without concurrent proliferative disease) presents with nephrotic-range proteinuria, the Kidney Disease Improving Global Outcomes 2024 Clinical Practice Guideline recommends combined immunosuppressive treatment including glucocorticoids and 1 other treatment, such as mycophenolate mofetil/mycophenolic acid, cyclophosphamide, or azathioprine.<sup>44</sup> When membranous disease is accompanied by low-level proteinuria, the immunosuppressive regimen will be guided by nonkidney manifestations of SLE.<sup>44</sup> In addition to immunosuppression, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker therapy is recommended for pure class V disease and for chronic combined membranous and proliferative disease.<sup>44</sup>

Anti-B-cell agents (eg, belimumab, rituximab) or calcineurin inhibitors (eg, tacrolimus, cyclosporine, voclosporin) are effective therapies for lupus nephritis when added to standard of care (mycophenolate mofetil/mycophenolic acid alone or cyclophosphamide followed by mycophenolate mofetil/mycophenolic acid or azathioprine). Belimumab, first approved in 2011 for active SLE, is a human monoclonal antibody that impairs B-cell-mediated immunity. Belimumab was approved for use in lupus nephritis in 2020 in accordance with an RCT that demonstrated efficacy and safety when added to standard of care.<sup>62</sup> In this RCT of 448 patients, compared with placebo, belimumab achieved the primary outcome of a complete kidney response (a composite efficacy end point) at week 104 (30% vs 20%; OR, 1.7; 95% CI, 1.1-2.7;  $P = .02$ ). Opportunistic infections, herpes zoster, tuberculosis, and sepsis occurred in 29 participants (13%) receiving belimumab and 34 (15%) receiving placebo.<sup>62</sup> Guidelines support combining calcineurin inhibitors with mycophenolate mofetil/mycophenolic acid to treat lupus nephritis associated with severe nephrotic syndrome and to treat patients with lupus nephritis who have an incomplete response to standard of care.<sup>44,56,61</sup> In 2021, voclosporin was approved in the United States to treat active lupus nephritis in combination with mycophenolate mofetil/mycophenolic acid and glucocorticoids. According to pooled data from 2 RCTs of 534 patients,<sup>63,64</sup> voclosporin, compared with placebo, added to mycophenolate and oral glucocorticoids was associated with a greater incidence of improvement in lupus nephritis at 1 year (43.7% vs 23.3%; OR,



Table 2. Therapies for Systemic Lupus Erythematosus

Treatment	Dose	Mechanism of action	Clinical indication or effect <sup>a</sup>	Select adverse effects <sup>b</sup>	Additional notes
<b>Immunomodulatory</b>					
Hydroxychloroquine	≤5 mg/kg (actual body weight) daily	Several proposed mechanisms: binds nucleic acids, inhibits toll-like receptor signaling, type I interferon production, B-cell class-switching, antigen processing, posttranslational protein modification, and cytokine secretion	Recommended for every patient with SLE unless contraindicated (because of allergy or significant preexisting retinal disease). Reduces SLE disease activity and reduces flare rates; 54% reduction in overall mortality. <sup>54</sup>	Common: gastrointestinal symptoms, headache, rash, skin hyperpigmentation. Rare or severe: retinopathy (<2% with appropriate dosing), <sup>55</sup> cardiotoxicity, neuromuscular toxicity.	Routine monitoring for retinal toxicity is recommended. Fewest adverse effects among antimalarials; chloroquine occasionally substituted for patients with SLE who cannot take hydroxychloroquine; quinacrine no longer commercially available in most places.
<b>Glucocorticoids</b>					
"Pulse" dose (high-dose, brief duration, IV)	250 mg to 1 g IV daily for 3-5 d	Suppresses autoimmune inflammation through effect on lymphatic system, migration of inflammatory cells	Severe disease; typically in conjunction with other immunosuppressive agents	Infection, weight gain, hypertension, hyperglycemia, mood or sleep disturbance, peptic ulcers, osteoporosis, osteonecrosis, myopathy, impaired wound healing, adrenal suppression	Lowest effective dose for the shortest duration needed is recommended to minimize adverse effects; escalation in dose often prompts increase or change in "steroid-sparing" immunosuppressive therapy
Moderate to high dose	>7.5 mg, up to 1 mg/kg/d		Moderate to severe disease, typically in conjunction with other immunosuppressive agents		
Low dose	≤7.5 mg/d		Mild to moderate disease		
<b>Nonbiologic immunosuppressive</b>					
Azathioprine	≤2 mg/kg/d	Blocks purine synthesis, leading to decreased circulating lymphocytes, immunoglobulin synthesis, IL-2 secretion	Moderate disease; can be used as a steroid-sparing agent; LN maintenance therapy (especially during pregnancy)	Gastrointestinal (12%), leukopenia (28%), infection (<1%). Possible increased risk of malignancy.	Risk of severe hematologic toxicity for patients with TPMT and/or NUDIX 15 deficiency; can test for these variants before initiating therapy
Cyclophosphamide	500 mg IV every 2 wk for 6 doses (preferred); 500-1000 mg/m <sup>2</sup> every month for 6 doses (alternative)	Alkylating agent; prevents cells from dividing and replicating by alkylating DNA, which confers an immunosuppressive effect	Severe, organ-threatening disease; LN induction therapy and CNS disease	Cytopenia, infection, hemorrhagic cystitis. Increased risk of premature ovarian insufficiency. Increased risk of malignancy.	Oral cyclophosphamide is not commonly used. Expected platelet and neutrophil nadir with recovery after ≈20 d of dosing
Methotrexate	≤25 mg/wk in combination with folic acid	Folate antimetabolite; inhibits cell division and proliferation, which leads to anti-inflammatory effects	Moderate disease; limited to skin and joint disease manifestations	Gastrointestinal, hepatotoxicity, headache, infection; alopecia, mucositis; interstitial pneumonitis	
Mycophenolate mofetil/ mycophenolic acid	Mycophenolate mofetil: ≤3000 mg/d in 2 divided doses mycophenolic acid: ≤2160 mg/d in 2 divided doses	Inhibits purine synthesis, decreases primarily lymphocyte proliferation and antibody production	Moderate to severe disease; LN therapy, steroid-sparing agent for other organ manifestations	Gastrointestinal (constipation [38%-44%], diarrhea [24%-53%]), cytopenia (anemia [20%-45%], leukopenia [19%-46%], thrombocytopenia [24%-38%]), infection (up to 40%). Possible increased risk of malignancy.	Mycophenolate mofetil is the first-line agent used; EC-MPS can be substituted when mycophenolate mofetil causes prohibitive gastrointestinal adverse effects
Tacrolimus	Typical range: 3-5 mg/d in 2 divided doses	Calcineurin inhibitor; inhibits T-lymphocyte activation	Moderate to severe disease; LN therapy, steroid-sparing agent for other organ manifestations	Nephrotoxicity (40%-56%), hypertension (23%-69%)	May be used as part of multimodal LN therapy; often considered when there are contraindications to other agents (eg, pregnancy). Blood-level monitoring is used to achieve a therapeutic dose and minimize risk of adverse effects.
Cyclosporine	3.5 mg/kg/d in 2 divided doses	Calcineurin inhibitor; inhibits IL-2 and IL-2-mediated T-lymphocyte activation	Moderate to severe disease; LN therapy	Nephrotoxicity (25%-38%), hypertension (13%-53%), hirsutism (21%-45%), gingival hyperplasia (4%-16%), viral infection (16%)	May be used as part of multimodal LN therapy; also an alternative maintenance therapy for hematologic disease. <sup>56</sup> Blood-level monitoring is used to achieve a therapeutic dose and minimize risk of adverse effects.
Voclosporin	23.7 mg twice daily	Calcineurin inhibitor; inhibits T-lymphocyte activation and proliferation, cytokine production	Moderate to severe disease; LN therapy in combination with mycophenolate mofetil/mycophenolic acid and glucocorticoids	Nephrotoxicity (26%), hypertension (19%), infection	May be used as part of multimodal LN therapy. No role for blood-level monitoring.

(continued)

Table 2. Therapies for Systemic Lupus Erythematosus (continued)

Treatment	Dose	Mechanism of action	Clinical indication or effect <sup>a</sup>	Select adverse effects <sup>b</sup>	Additional notes
<b>Biologic agents</b>					
Anifrolumab	300 mg IV every 4 wk	Monoclonal antibody; blocks type I interferon signaling by binding to the interferon alpha/beta receptor	Moderate to severe disease; primarily effective for skin disease	Infusion reaction (9%); infection, specifically herpes zoster (6%), upper respiratory tract infection	Not recommended for use for patients with active LN or CNS disease
Belimumab	10 mg/kg IV every 4 wk or 200 mg subcutaneously weekly	Monoclonal antibody; impedes B-cell-mediated immunity by blocking the interaction between soluble human BLYS and B-lymphocyte receptors	Moderate to severe disease; approved for active disease and specifically for LN in conjunction with standard therapy	Infusion reaction (IV form); infection (71%-82%; serious infection, 6%); depression (5%-6%) and suicidal ideation ( $\leq 1\%$ )	Not recommended for use for patients with active CNS disease
Rituximab	1 g IV given twice 2 wk apart or 375 mg/m <sup>2</sup> IV weekly for 4 doses	Monoclonal antibody; binds to CD20 on B lymphocytes, leading to B-cell cytotoxicity	Moderate to severe disease; can be considered for LN in combination with standard therapy	Infusion reaction (12%-77% with first dose); hypogammaglobulinemia ( $< 1\%$ -58%), neutropenia (8%-14%); infection (19%-63%; serious infection: 2%-11%)	Dosing extrapolated from other disease contexts

Abbreviations: BLYS, B-lymphocyte stimulator protein; CNS, central nervous system; EC-MPS, enteric-coated mycophenolate sodium; GI, gastrointestinal; IL, interleukin; IV, intravenous; LN, lupus nephritis; NUDIX 15, nucleoside diphosphate-linked moiety X motif 15; SLE, systemic lupus erythematosus; TPMT, thiopurine S-methyltransferase.

<sup>a</sup> There are no formal definitions for degree of SLE severity, and treatment decisions are made according to clinical context. Examples of clinical manifestations by severity: mild disease may include constitutional symptoms, limited rash, arthritis, and decreased platelet count ( $> 50 \times 10^9/L$ ); moderate disease may include more extensive rash, severe arthritis, decreased platelet

count ( $20\text{--}50 \times 10^9/L$ ), and serositis; and severe disease includes major organ involvement or life-threatening disease, such as lupus nephritis, severe CNS involvement, pneumonitis, decreased platelet count ( $< 20 \times 10^9/L$ ), and macrophage activation syndrome.

<sup>b</sup> Common or rare and severe adverse effects are presented. Frequencies are included when available, derived from product labeling unless cited and often from studies in which an agent was used in a different disease context (eg, organ transplant, rheumatoid arthritis, malignancy), sometimes with concomitant use of other immunosuppressive medications.

2.76; 95% CI, 1.88-4.05;  $P < .001$ ). The most common treatment-related infections were herpes zoster (10 [3.7%] vs 4 [1.5%] among controls), urinary tract infections (7 [2.6%] vs 2 [0.8%] among controls), and upper respiratory tract infections (7 [2.6%] in both groups).<sup>65</sup>

A meta-analysis evaluating efficacy of rituximab, which included 31 studies and 1112 patients with nonrenal SLE and lupus nephritis that was refractory to other immunosuppressive medications, reported improvements in overall disease activity and reductions in systemic glucocorticoid dose after treatment with rituximab.<sup>66</sup> According to these findings, without RCT evidence to support benefit of rituximab for treatment of SLE or lupus nephritis,<sup>67,68</sup> EULAR recommendations for SLE management suggest reserving rituximab for refractory organ-threatening disease or when there are contraindications to standard therapy.<sup>56</sup>

Anifrolumab, a human monoclonal antibody to the type I interferon receptor subunit 1, was approved in 2021 in the US for SLE. The first phase 3 RCT compared adding either anifrolumab or placebo to standard immunosuppression for 362 patients. Compared with placebo, anifrolumab did not achieve the primary outcome of decreased SLE disease activity, although some secondary outcomes benefited.<sup>69</sup> A subsequent phase 3 trial and post hoc analyses demonstrated efficacy and a potential steroid-sparing effect for patients with active SLE who were receiving standard therapy.<sup>70-72</sup> Patients treated with anifrolumab were more likely to attain the primary outcome, which was improvement in a validated measure of global disease activity, than those who received placebo (47.8% vs 31.5%;  $P = .001$ ).<sup>70</sup> For patients with skin disease, a greater than 50% reduction in a measure of cutaneous lupus activity occurred for 49% of anifrolumab-treated patients compared with 25% for those re-

ceiving placebo.<sup>69,70</sup> Herpes zoster occurred in 13 participants (7.2%) treated with anifrolumab vs 2 controls (1.1%), upper respiratory tract infections in 39 participants (21.7%) vs 18 controls (9.9%), and infusion reactions in 25 participants (13.9%) vs 14 controls (7.7%).<sup>69</sup>

Practice guidelines recommend minimizing systemic glucocorticoids to a low dose (ie, prednisone equivalent  $\leq 5$  or 7.5 mg/d) and discontinuation whenever possible; however, glucocorticoids are often required to control SLE disease activity.<sup>56,58</sup> Pulse-dose intravenous methylprednisolone, consisting of 250 mg to 1 g intravenous methylprednisolone daily for 3 to 5 days, is recommended for patients with organ- or life-threatening SLE manifestations such as severe lupus nephritis or neuropsychiatric disease. The use of pulse-dose intravenous methylprednisolone may facilitate lower subsequent doses and more rapid tapering of oral glucocorticoids than would otherwise be possible.

## Prognosis

In a meta-analysis including 15 articles and 26 101 patients with SLE, people with SLE had significantly higher all-cause mortality compared with the general population (standardized mortality ratio, which is the ratio of deaths observed for patients with SLE to the expected deaths in the general population during a given study period, standardized by age: 2.66; 95% CI, 2.09-3.39).<sup>73</sup> Patients with SLE had higher rates of death due to kidney disease (standardized mortality ratio, 4.69; 95% CI, 2.38-9.33), cardiovascular disease (standardized mortality ratio, 2.25; 95% CI, 1.30-3.89), and infection (standardized mortality ratio, 4.98; 95% CI, 3.88-6.40).<sup>73</sup> Based on 1999 to 2013 data, sex, race, and geographic region were associated with greater SLE mortality risk; the highest adjusted OR (AOR) was for female vs male patients (AOR, 5.33; 95% CI, 5.12-5.55),



non-Hispanic Black vs non-Hispanic White individuals (AOR, 3.91; 95% CI, 3.79-4.05), and age 65 years or older vs younger than 65 years (AOR, 3.20; 95% CI, 3.10-3.31).<sup>74</sup> Residents of the Midwest (AOR, 1.07; 95% CI, 1.01-1.12), South (AOR, 1.30; 95% CI, 1.25-1.36), and West (AOR, 1.36; 95% CI, 1.30-1.43) had significantly higher mortality risk than residents of the Northeast.<sup>74</sup> Absolute mortality rates were not provided.<sup>74</sup>

#### End-Stage Kidney Disease and Kidney Transplant

The incidence of end-stage kidney disease among all patients with SLE in an 1827-participant international inception cohort study at 10-year follow-up was 4.3% (95% CI, 2.8%-5.8%) compared with 10.1% (95% CI, 6.6%-13.6%) among the 700 participants with lupus nephritis.<sup>35</sup> A US nationwide cohort study including 9659 individuals with lupus nephritis and end-stage kidney disease who were on a kidney transplant waiting list reported that all-cause mortality was reduced (mortality rate per 1000 person-years: 22.5 [95% CI, 21.2-24.0] for transplant recipients vs 56.3 [95% CI, 53.7-59.1] for people who did not undergo a transplant; AOR, 0.30 [95% CI, 0.27-0.33]). Participants were enrolled when added to the waiting list (between 1995 and 2014) and followed up until death or study completion in 2015; 971 of 5738 patients (16.9%) with a kidney transplant died compared with 1697 of 3291 patients (51.6%) who had not undergone a kidney transplant. Cause-specific mortality due to cardiovascular disease and infection was reduced for patients with lupus nephritis and end-stage kidney disease who underwent transplant compared with those who did not: 273 of 5738 patients (4.8%) who underwent transplant died because of cardiovascular disease compared with 675 of 3291 patients (20.5%) who did not (adjusted hazard ratio, 0.26 [95% CI, 0.23-0.30]); 124 of 5738 patients (2.2%) who underwent kidney transplant died because of infection compared with 277 of 3291 patients (8.4%) who did not (adjusted hazard ratio, 0.41 [95% CI, 0.32-0.52]).<sup>75</sup>

Recurrent lupus nephritis in a transplanted kidney is infrequent. A case-control study of 6850 individuals with lupus nephritis and end-stage kidney disease who underwent transplants between 1987 and 2006 reported that 167 (2.4%) developed recurrence. Most events occurred during the first 10 years after transplant. Characteristics associated independently with recurrent lupus nephritis included non-Hispanic Black race (AOR, 1.88; 95% CI, 1.37-2.57), female sex (AOR, 1.70; 95% CI, 1.05-2.76), and younger than 33 years (AOR, 1.69; 95% CI, 1.23-2.31). Absolute rates for subgroup analyses were not provided.<sup>76</sup>

#### Cardiovascular Disease

Compared with individuals without SLE, those with SLE have approximately twice the risk of cardiovascular disease, myocardial infarction, cerebrovascular disease, and hypertension.<sup>77-79</sup> A meta-analysis of 16 studies and more than 5 million patients reported risk ratios for stroke for patients with SLE, compared with the general population, of 2.13 (95% CI, 1.73-2.61), and of 2.99 (95% CI, 2.34-3.82) for myocardial infarction, based on 12 included studies and more than 45 million patients (absolute rates not provided).<sup>79</sup> A meta-analysis of studies assessing incidence rates of complications in SLE reported a pooled incidence rate estimate for stroke, based on 10 studies and 719 116 person-years, of 4.72 (95% CI, 3.35-6.32) per 1000 person-years; the incidence rate estimate for myocardial infarction, based on 6 studies and 306 998 person-

years, was 2.81 (95% CI, 1.61-4.32) per 1000 person-years; and the estimate for cardiovascular disease, based on 8 studies and 440 797 person-years, was 11.21 (95% CI, 8.48-14.32) per 1000 person-years (absolute rates and incidence rates in comparators without SLE not reported).<sup>77</sup>

#### Cancer

Rates of cancer are increased among individuals with SLE compared with those without SLE. This association may be due to chronic inflammation, immunosuppressive therapies, viral infections, and genetic and environmental factors. One meta-analysis of 14 studies and 41 763 patients reported a pooled RR for malignancy of 1.28 (95% CI, 1.17-1.41) in people with SLE compared with those without SLE, with a mean follow-up per study (when reported) of 4.8 to 24.0 years.<sup>80</sup> Another meta-analysis of 13 studies reported that 3694 malignancies occurred in 80 833 patients with SLE (4.6%), with a mean follow-up per study (when reported) of 2.1 to 25.7 years.<sup>81</sup> Among specific malignancies, non-Hodgkin lymphoma was most consistently associated with SLE, with a relatively high magnitude of risk. One meta-analysis that included 12 studies and 58 098 patients reported a pooled RR of 5.4 (95% CI, 3.75-7.77), with a 0.40% event rate (235 of 58 098 patients with SLE).<sup>80</sup> Another meta-analysis that included 11 studies and 90 987 patients reported a pooled RR of 4.32 (95% CI, 3.42-5.47), with a 0.47% event rate (424 of 90 987 patients with SLE).<sup>81</sup> Although findings are mixed regarding risk of cervical cancer among patients with SLE,<sup>80,81</sup> these patients have a higher risk of precancerous cervical dysplasia compared with those without SLE.<sup>82,83</sup> One meta-analysis of 7 studies reported a 5.77% rate (24 of 416 patients) of high-grade cervical dysplasia among patients with SLE compared with 0.47% (54 of 11 408) among people without SLE (OR, 8.66; 95% CI, 3.75-20.00).<sup>83</sup>

#### Infection

Markers of active disease and specific disease manifestations (including lymphopenia, thrombocytopenia, anemia, hypocomplementemia, serositis, and kidney disease) and treatment with high-dose glucocorticoids have been associated with increased risk of life-threatening atypical infections for patients with SLE, including invasive fungal or mycobacterial infections.<sup>84-87</sup> In a meta-analysis of 35 studies including 46 327 patients with SLE, the rate of tuberculosis was 1.16 per 100 person-years (95% CI, 0.69-1.93); prevalence of tuberculosis was 3.59% (95% CI, 2.57%-5.02%).<sup>87</sup>

#### Metabolic Bone Disease

People with SLE have an approximately 2-fold increased risk of osteoporosis and fracture compared with healthy controls.<sup>88</sup> Among 10 434 patients with SLE who were older than 40 years (mean [SD] age, 51.3 [9.1] years; 89.7% women) in a national health insurance database, the incidence of osteoporotic fracture was 19.1 per 1000 person-years compared with 6.5 per 1000 person-years in age- and sex-matched people without SLE.<sup>89</sup>

The estimated prevalence of symptomatic avascular necrosis in a meta-analysis including 58 studies and 19 816 people with SLE was 8.96% (95% CI, 7.37%-10.55%; range across studies, 1.45%-33.33%), and the prevalence of incidentally identified asymptomatic avascular necrosis was 28.52% (95% CI, 19.46%-37.60%). The most frequent site of symptomatic avascular necrosis was the femoral head. People with active SLE, defined by the presence of

cutaneous vasculitis, kidney disease, neuropsychiatric involvement, serositis, or cytopenia, as well as those taking high-dose glucocorticoids, had higher risk of avascular necrosis.<sup>90</sup> When avascular necrosis is symptomatic, or if subchondral collapse of the joint occurs, total joint replacement may be needed.

### Limitations

This review has several limitations. First, it was limited to English-language publications. Second, some included studies were published more than 10 years ago. Third, some evidence regarding treatment was based on observational studies. Fourth, the quality of the evidence was not formally assessed. Fifth, because scientific investigation of SLE relies on classification criteria for participant inclu-

sion, findings may not apply to patients with atypical or overlapping clinical presentations. Sixth, some important aspects of SLE were not discussed.

### Conclusions

Systemic lupus erythematosus is associated with immune-mediated damage to multiple organs and increased mortality. Hydroxychloroquine is first-line therapy and reduces disease activity, morbidity, and mortality. When needed, additional immunosuppressive and biologic therapies include azathioprine, mycophenolate mofetil, cyclophosphamide, belimumab, voclosporin, and anifrolumab.

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**Submissions:** We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at [kristin.walter@jamanetwork.org](mailto:kristin.walter@jamanetwork.org).

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