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thyroiditis. Cancers commonly associated with autoimmunity include melanoma, thyroid cancer, and non-small-cell lung cancer. One specific example is the development of encephalitis through generation of Abs to N-methyl-D-aspartate glutamate receptor in women affected by ovarian cancer. In some cases, these events may be associated with favorable disease outcomes that may suggest a beneficial effect from the autoimmune response. The autoimmune manifestations can be severe, and management of these patients is difficult given the coexistent malignancy. ■

■ **IATROGENIC AUTOIMMUNITY** Checkpoint Inhibitors Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment. They act by blocking inhibitory molecules involved in regulating T lymphocytes, promoting the destruction of tumors by the adaptive immune system. Immune-related adverse events (irAEs) have been described as toxic complications related to tissue-specific autoimmunity from the use of ICIs, and they can persist after withholding therapy and using immunomodulatory therapy to control them. Among these complications, DM, arthritis, thyroiditis, and colitis are prevalent. Up to 85% of individuals treated with an ICI may develop irAEs. Most of these are mild, and overall survival and time to malignancy progression are not influenced by the development of these immune complications. **Drug-Induced Autoimmunity** In addition to ICIs, many drugs have been linked to the development of autoimmunity. These include antibiotics, antihypertensives, antiarrhythmics, TNF inhibitors, and antiseizure medications, among many others. Drug-induced lupus is a well-described entity, and patients developing this condition have characteristic detection of antihistone Abs. In many cases, discontinuation of the drug may be sufficient for symptoms to be abrogated or decreased. ■ ■

■ **PREVENTION AND TREATMENT OF AUTOIMMUNITY** The hope is that better understanding of the pathophysiology of overt development of ADs and their associated organ damage will lead to primary or secondary prevention strategies in conditions such as T1DM, RA, and SLE. One promising example is where infants at risk of developing multiple T1DM autoAbs and clinical disease are being studied to determine if certain interventions (oral insulin) can delay or stop progression to overt disease. Studies have also been performed on people considered at risk for RA to assess delayed disease progression, but more studies are needed to better characterize the utility of these preventive strategies. Overall, opportunities to initiate early therapy depend on the availability of serologic tests that can predict disease, to initiate treatments that have a good efficacy-to-safety ratio. Specific treatments for ADs are included in chapters focusing on individual diseases and include a variety of immunomodulatory agents (e.g., antimalarials) and immunosuppressive drugs (spanning those drugs with broad effects on the immune system, such as corticosteroids or

cyclophosphamide, to highly specific biologic agents targeting specific cytokines or immune cells). It is the hope that the development of personalized medicine approaches will lead in the future to the specific targeting of dysregulated immune cell components while sparing other critical cells and functions of the immune system. ■ ■ FURTHER READING Enhancing NIH Research on Autoimmune Diseases. Consensus Study Report. The National Academies of Sciences, Engineering, Medicine, 2022. Gupta S, Kaplan MJ: Bite of the wolf: Innate immune responses propagate autoimmunity in lupus. *J Clin Immunol* 131:e144918, 2021. Johnson D, Jang W: Infectious diseases, autoantibodies and autoimmunity. *J Autoimm* 137:102962, 2023. Singh N et al: Immune-related adverse events after immune check point inhibitors: Understanding the intersection with autoimmunity. *Immunol Rev* 318:81, 2023.

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Systemic Lupus

Erythematosus CHAPTER 368 DEFINITION, PREVALENCE,

AND EPIDEMIOLOGY Systemic lupus erythematosus (SLE) is an autoimmune disease in which overactive innate and adaptive immune systems cause tissue damage through the effects of autoantibodies and immune complexes. Many organ systems can be affected, with cutaneous, musculoskeletal, and renal systems most involved, followed by pulmonary, hematologic, cardiovascular, serosal, and central nervous system involvement. Constitutional symptoms are often present. Autoantibodies can be detected years prior to a clinical diagnosis. Approximately 90% of affected individuals are women, most of childbearing age; however, the disease can also affect neonates and older children, men, and elderly individuals. Certain ethnic and racial groups are at higher risk for more prevalent disease and more severe disease. The Centers for Disease Control and Prevention (CDC) National Lupus Registry estimates the prevalence in the United States to be 204,295 cases, with overall prevalence being nine times higher in women compared to men. The highest prevalence is seen in Black women, followed by Hispanic, White, and Asian/Pacific Islander women. Among men with SLE, Black men have the highest prevalence and White men have the lowest. Prognosis and survival from SLE can vary widely by geographic region, race, ethnicity, and access to both care and medications. Systemic Lupus Erythematosus DIAGNOSIS AND CLASSIFICATION For the diagnosis of SLE, an individualized approach should be taken based on available clinical data and excluding other disease entities. Classification criteria for SLE have been developed for the purposes of enrollment of patients into clinical trials rather than criteria for diagnosis. Currently, the 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for SLE and the 2012 Systemic Lupus International Collaborating Clinics (SLICC) SLE classification criteria are both utilized for enrollment of patients into clinical trials. For the EULAR/ACR criteria, an antinuclear antibody (ANA) titer of at least 1:80 is required. Clinical criteria are then weighed by points within several clinical domains, and a patient requires at least 10 points to meet criteria. No single clinical or laboratory value leads to 10 points except for a renal biopsy revealing class III or IV lupus nephritis. Certain subsets of patients with SLE are currently not included in clinical trials, including patients with incomplete lupus or features of SLE without an established diagnosis and the ~5% of SLE patients who are ANA negative.

Researchers have suggested that if predictive or diagnostic biomarkers for progression are developed, then early treatment for patients with incomplete lupus could prevent progression to SLE. Furthermore, because the EULAR/ACR criteria exclude ANA-negative patients from participating in clinical trials, the opportunity to understand whether new drugs have a role in this disease subset is also underserved. SLE has been classified into two broad categories based on symptoms. Those with predominant classic findings of SLE that have a clear relationship to immune dysregulation, such as nephritis, arthritis, and vasculitis, have been categorized as having type 1 lupus, whereas those with predominant symptoms of fatigue, diffuse body pain, depression, cognitive dysfunction, sleep disturbances, anxiety, and/or brain fog have been categorized as having type 2 lupus. Type 1 symptoms arise from autoimmune inflammation and/or organ damage and often respond to standard immunosuppression, whereas type 2 patients are less responsive to immunosuppressive therapy. This categorization presents an opportunity to explore the genetic and immune association

of each category as well as develop biomarkers and treatments for the distinct types.

PATHOGENESIS ■ ■ OVERVIEW SLE reflects multiple immunoregulatory defects and is characterized by the production of autoantibodies to cellular components, especially nucleic acids and nuclear proteins, that promote inflammation and tissue damage. The interaction of environmental factors with the stochastic dysregulation of genes controlled by common genetic variations underpins the development of SLE (Fig. 368-1).

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders ■ ■ GENETICS SLE has a strong genetic component as evidenced by familial clustering, a greater incidence in monozygotic twins versus dizygotic (24% vs 2%), and the identification of >150 susceptibility loci from genomewide association studies (GWAS). Genetic studies have identified groups of immunoregulatory genes associated with SLE, reflecting common pathways that may contribute to pathogenesis. It is possible that each pathway differentially contributes to the expression of disease, accounting for clinical heterogeneity. The most common genetic association is within the major histocompatibility complex that contains genes for antigen presentation molecules (class I and class II), several complement components, and cytokines. Nearly half of the susceptibility loci are associated with type 1 interferon (IFN) production or its downstream signaling. For example, some susceptibility genes lead to increased IFN through defects in nucleic acid sensing and metabolism (TLR7, ADAR, IFIH1, SAMHD1, RNASEH2B, TREX1) or nucleic acid degradation (DNASE1, DNASE1L3), whereas other IFN-related susceptibility genes amplify the IFN response (IRF5, IRF7, IRF8, STAT4). Many predisposing genes are immune cell type specific, affecting activation and survival of T cells (OX40L) or B cells (BANK1, BACH2). The complement cascade (C1q, C1r, C1s, C2, C4), Neutrophils and dying cells release debris NETosis Predisposing Factors Environmental triggers and potential mechanism UV light - induces apoptosis and autoantigen release. Crystalline silica - induces inflammation. Smoking - causes autoantigen release. Sex hormones - regulate development and function of adaptive immune cells. Microbes (EBV, microbiome) - induce nucleic acid response, increase gut permeability. Toxins (i.e., mercury, diet) - induce cell death, inflammation, epigenetic changes. Cell death

Key immunologic SLE pathways and selected susceptibility genes

Antigen presentation (MHC) - HLA-DR, HLA-DQ IFN induction - IRAK1, SLC15A4, SPP1, TNIP1, UBE2L3 Nucleic acid sensing - TLR7, ADAR, IFIH1, SAMHD1, RNASEH2B, TREX1 Nucleic acid degradation - DNASE1, DNASE1L3 Response to IFN - IRF5, IRF7, IRF8, STAT4, TYK2 Phagocytosis - FCGR2A, C1q, C1r, C1s, C2, C4 T-cell activation ETS1, IL21, IKZF1, IKZF2, PTPN22, STAT4, TCF7, OX40L B-cell activation - ARID5B,

BANK1, BACH2, BLK, CD40, CSK, IKZF3, IRF5 Monocytes infiltrate tissue and are activated by immune complexes binding to FcGR, inducing tissue inflammation FcGR Classic monocyte Non-classical monocyte anti-dsDNA: Anti double-stranded DNA anti-Sm: anti-Smith FcGR: Fc gamma receptor IFN: Type 1 interferon MHC: Major histocompatibility complex Epigenetic changes DNA methylation and histone acetylation can affect the IFN response of T, B, and myeloid subsets. FIGURE 368-1 Pathogenesis of systemic lupus erythematosus (SLE). Autoantigens from neutrophil NETosis and cellular turnover overwhelm clearance mechanisms regulated by the innate immune system in SLE. Consequently, these autoantigens accumulate and induce an immune response. Nucleic acid activates TLR signaling in plasmacytoid dendritic cells (DCs), producing type 1 IFN, sensitizing the innate and adaptive immune responses. DCs present autoantigens to autoreactive T cells, leading to B-cell stimulation and the production of immune complexes against these autoantigens. Immune complexes deposit in tissue and induce local immune responses that lead to inflammation and repair and, eventually, fibrosis after recurrent SLE flares. EBV, Epstein-Barr virus.

which is essential for clearance of apoptotic cellular debris and immune complexes, is often affected in monogenic cases, leading to severe SLE. ■ ■ENVIRONMENT About a quarter of monozygotic twins are clinically concordant for SLE, implicating environmental factors in disease expression. Low socioeconomic status is associated with the development of SLE and may include exposures to environmental toxins, including mercury, pesticides, and diet. Viral infections such as Epstein-Barr virus likely contribute to disease development by inducing the IFN response during an acute infection or by expressing viral proteins that activate SLE susceptibility genes. Ultraviolet light can impact DNA methylation, generate self-stimulatory nucleic acids, activate keratinocyte immune responses, and produce autoreactive T cells. Finally, emerging evidence suggests that the gut microbiome may increase gut permeability, promoting the translocation of certain gut microbes into the blood with the development of lupus-specific autoantibodies contributing to SLE pathogenesis. ■ ■INNATE IMMUNITY Multiple innate immune cell defects contribute to increased cellular breakdown and reduced cell debris clearance, culminating in the production of autoantibodies. Neutrophils are typically short-lived and abundant immune cells, representing a large burden of cellular debris that is usually cleared without inducing an immune response. Patients with SLE, however, have neutrophils with higher turnover, delivering a large load of stimulatory nucleic acids and autoantigens. Cellular debris and immune complexes are typically cleared by macrophages and dendritic cells through complement-mediated phagocytosis and nucleic acid digestion; these mechanisms are dysregulated in SLE. In turn, the burden of cellular debris exceeds that which can be cleared in SLE, triggering nucleic acid sensors and toll-like receptors (TLRs) in plasmacytoid dendritic cells to express type 1 IFN. Consequently, IFN primes neutrophils for further turnover and sensitizes the adaptive Cellular debris induces IFN response that sensitizes the immune response The innate immune system processes debris FcGR TLR Endosome Macrophage phagocytosis Dendritic cell antigen presentation (MHC) to T-cells IFN Plasmacytoid DC Autoreactive B cells produce autoantibody with activation signals from T-helper cells. Autoreactive T cell Autoreactive B cell Autoantibodies Immune complexes deposit in tissue Autoantibodies (i.e., anti-dsDNA, anti-Sm autoantibodies) against cellular debris form immune complexes Legend NETosis: Program for formation of neutrophil extracellular traps (NETs) Plasmacytoid DC: Plasmacytoid dendritic cell TLR: Toll-like receptor

immune system. Other innate immune cells with aberrant function in SLE include classical monocytes that infiltrate and repair injured tissue due to immune complex deposition and

nonclassical monocytes that patrol the vascular lumen for injury. Sustained activation of these subsets from SLE leads to tissue inflammation and scarring. ■ ■ADAPTIVE IMMUNITY B cells play a central role in the SLE pathogenesis based on the production of autoantibodies due to their loss of tolerance. Autoantibodies, especially those complexed with nucleic acid, are pathogenic mediators of tissue inflammation and damage in SLE. These autoantibodies induce type 1 IFN and other inflammatory mediators and activate patrolling monocytes in tissue. A subset of circulating age-associated B cells (ABCs) expands in SLE patients and eventually matures into autoantibody-secreting plasma cells, indicating that SLE patients have an increased population of B cells primed to generate pathogenic autoantibodies. Similar to B cells, T cells lose tolerance and play a central role in the autoimmune response. In particular, both T follicular and T peripheral helper cells promote B-cell differentiation into pathogenic, high-affinity, autoantibody-secreting plasma cells. T regulatory cells meant to maintain tolerance in both T and B cells are defective in SLE. CLINICAL MANIFESTATIONS ■ ■OVERVIEW AND SYSTEMIC MANIFESTATIONS The initial presentation of SLE is variable and may present as nonspecific constitutional symptoms with or without single-organ or multiorgan involvement. Autoantibody presence is helpful in attributing nonspecific symptoms to SLE. Symptoms can be mild to severe at any time over the course of the disease, including at initial presentation. Patients with severe disease often have systemic symptoms such as fever, anorexia, and unintentional weight loss. Approximately 15% of patients have relatively mild disease, which may or may not be accompanied by fatigue, brain fog, and/or mild arthralgia. The majority of SLE patients have active disease despite therapy or have frequent flares of their disease requiring treatment adjustment. Goals for SLE treatment are low-level disease activity or remission on ongoing therapy. (See “Outcomes” section for more details.) ■ ■MUSCULOSKELETAL MANIFESTATIONS Nonspecific arthralgia and myalgia are common in SLE. Lupus arthritis is characterized by a polyarthritis most commonly involving the wrists, the metacarpal-phalangeal and proximal interphalangeal joints of the hands, and the knees. In some cases, damage of the periarticular ligaments may lead to Jaccoud-like changes (Fig. 368-2A). Rheumatoid arthritis and SLE can occur simultaneously, and this overlap is denoted by the term *rhupus*. While radiographs rarely demonstrate erosive changes in lupus arthritis, emerging studies with magnetic resonance imaging (MRI) and ultrasound imaging suggest a possible erosive pattern that is less severe than that seen with rheumatoid arthritis. Pain in a single hip, shoulder, or knee out of proportion to other joints should prompt consideration of avascular necrosis of bone, particularly with history of corticosteroid usage. Inflammatory muscle disease is also seen in lupus, characterized by symmetrical proximal weakness, elevated creatine kinase and aldolase levels, and inflammatory changes on muscle biopsy. Corticosteroids used to treat SLE may cause myopathy, as can antimalarials, although this is rare. ■ ■CUTANEOUS MANIFESTATIONS Three major categories of SLE skin manifestations include acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus (Fig. 368-2B-F). ACLE occurs with SLE disease activity, whereas SCLE and certain forms of chronic cutaneous lupus may be seen in the absence of systemic disease. The most classic form of ACLE is the malar rash, which appears in a “butterfly” distribution across the cheeks of the face with nasolabial sparing. Due to its photosensitive nature, slightly raised lesions, and location on the face, this may be confused with rosacea, which involves the nasolabial folds. ACLE may also present as a generalized maculopapular rash in sun-exposed areas of the body, bullous lupus, toxic

epidermal necrolysis variant, and generalized photosensitivity. SCLE is a photosensitive rash associated with anti-Ro or SSA antibodies that is characterized by flat, red-rimmed annular or

psoriasiform lesions. Discoid lesions are rough, circular lesions that are slightly raised, scaly, and hyperpigmented with depigmented, atrophic centers and erythematous rims, and are the most common chronic dermatitis seen in SLE. Other chronic forms of cutaneous lupus include hypertrophic or verrucous lupus, lupus panniculitis, tumid lupus, chilblains lupus, and discoid lupus/lichen planus overlap. Nonspecific cutaneous manifestations that may be seen in SLE include nonscarring alopecia, oral and nasal painful or nonpainful mucosal ulcers, and the less common leukocytoclastic and urticarial vasculitides. Approximately one-third of SLE patients also experience Raynaud's phenomenon, a condition in which small blood vessels undergo vasospasm with exposure to cold environment or stress, causing a classically triphasic color change of the fingers and/or toes, inducing white (blanching), blue (cyanosis), and red (hyperemia) coloring of the extremities.

CHAPTER 368 Systemic Lupus Erythematosus ■ ■RENAL MANIFESTATIONS Nephritis occurs in ~35% of patients with SLE and is more severe in non-White patients, more frequently leading to end-stage renal disease (ESRD) despite therapy. Nephritis can be seen with or without extrarenal SLE disease and may be present in an asymptomatic patient. Patients should therefore be screened at regular 3-month intervals with a random urine protein-to-creatinine ratio (UPCr) or a 24-h urine protein and creatinine determination. Usually, nephritis is seen in patients with elevated serum anti-double-stranded DNA (dsDNA) antibody titers and decreased serum levels of C3 and/or C4, and trends of these biomarkers over time may serve as warning signs of impending active nephritis. Renal biopsy is generally prompted by a UPCR of >0.5 and/or declining kidney function. Classification is based on renal pathology from a renal biopsy and is defined by the International Society of Nephrology/Renal Pathology Society criteria. Aggressive therapy is generally reserved for patients with class III (focal proliferative glomerulonephritis), class IV (diffuse proliferative glomerulonephritis), or a combination of class III or IV with class V disease (membranous) (Fig. 368-3, Chap. A4). Approximately 20% of lupus nephritis patients with significant proteinuria tend to have class V disease and more often have nephrotic syndrome. Patients with class V lupus nephritis have a better overall prognosis than patients with class III or IV lupus nephritis and are treated in the same manner as class III and IV. Patients who do not respond to treatment may require a repeat biopsy to evaluate for a change in class. In the United States, ~20% of SLE patients with class IV lupus nephritis die or develop ESRD within 10 years. Newer approaches are being developed to both increase renal survival and spare patients from accelerated atherosclerosis, hypertension, hyperglycemia, and hyperlipidemia, all of which can be accelerated by renal disease and corticosteroid usage. ■ ■NERVOUS SYSTEM MANIFESTATIONS

Lupus patients experience neuropsychiatric manifestations of disease that are characterized by diffuse or focal symptoms. The most common diffuse symptom is "brain fog," a cognitive dysfunction or slowing of thought. The etiology is not well understood but may be related to autoantibodies crossing the blood-brain barrier, leading to local inflammation and neuronal damage. Headache is common and often severe, although it may be difficult to distinguish from migraine or tension headache. Seizures of any type may be seen in neuropsychiatric lupus. Acute psychosis and confusional states are uncommon but can occur in SLE without any structural abnormalities. In these cases, glucocorticoid-induced psychosis and infectious encephalitis should be ruled out. Transverse myelitis is a rare SLE complication that manifests as bilateral neurologic deficits such as symmetric motor weakness and decreased sensation due to spinal cord inflammation. ■

■VASCULAR OCCLUSION: MYOCARDIAL INFARCTIONS AND STROKE Coronary heart disease from accelerated atherosclerosis in SLE is a significant cause of morbidity and premature death,

especially in young patients without other risk factors. Vascular injury due to excessive

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders A B C D E F FIGURE 368-2 Characteristic musculoskeletal and cutaneous manifestations seen in systemic lupus erythematosus (SLE). A. Jaccoud arthropathy, characterized by chronic, nonerosive, and reversible deviations caused by joint capsule inflammation with subsequent fibrotic retraction and metacarpophalangeal joint subluxation. B. Patchy, nonscarring alopecia. C. Patchy scarring alopecia. D. Patchy alopecia associated with chronic, scarring discoid lupus changes. E. Classic photosensitive malar rash. F. Subacute cutaneous lupus erythematosus (SCLE) with widespread, nonscarring photosensitive features. (Panels B–E reproduced with permission from Victoria Werth, MD. Panels A and F reproduced with permission from DoQuyen Huynh, MD.) type 1 IFN and cellular death may predispose to atherosclerosis. The risk of coronary artery disease and vascular thrombosis is further increased in SLE patients with antiphospholipid syndrome (APS), an autoimmune syndrome that commonly occurs in SLE and is characterized by arterial, venous, or small vessel thromboembolic events in the presence of antiphospholipid antibodies with prothrombotic properties (Chap. 369). Stroke has been reported in up to 19% of patients with SLE, a result of atherosclerosis and increased risk from APS. In addition to stroke, APS appears to be a significant risk factor for other focal central nervous system manifestations including seizures and transverse myelitis. ■ ■PULMONARY MANIFESTATIONS The most common pulmonary manifestation of SLE is pleuritis, which can occur with or without exudative pleural effusions. Acute pneumonitis may present in active SLE, with pulmonary infiltrates often appearing indistinguishable from infection on imaging. Diffuse alveolar hemorrhage with capillaritis and interstitial lung disease may also be seen. Restrictive lung defect from reduced lung volumes, also known as shrinking lung syndrome, is uncommon but may occur.

Pulmonary arterial hypertension and pulmonary embolism may be present with or without APS. ■ ■CARDIAC MANIFESTATIONS All layers of the heart may be involved in SLE, with pericardial involvement being the most frequent. Pericarditis can typically be managed with anti-inflammatory medications, colchicine, and anti-IL-1-directed therapies, or without glucocorticoids, and rarely leads to tamponade physiology. Myocarditis is rarer and may lead to left-sided heart failure and/or arrhythmia. Libman-Sacks endocarditis, a fibrinous sterile form of endocarditis that may be associated with antiphospholipid antibodies, may increase the risk for embolic events. Right-sided heart failure may be present with pulmonary arterial hypertension or chronic lung disease. ■ ■HEMATOLOGIC MANIFESTATIONS Cytopenias in SLE are often multifactorial and may be associated with disease activity, medication use, or infection. Anemia is the most common hematologic manifestation of SLE and is present in >50% of SLE cases, with anemia of chronic disease representing approximately

Class I Class II Class III/IV Class V Class III/IV + V FIGURE 368-3 Ultrastructural features of lupus glomerulonephritis. Class I: Mesangial immune deposits (black) without mesangial cell (red) hypercellularity or leukocyte infiltration. Class II: Mesangial immune deposits with mesangial cell hypercellularity, no leukocyte infiltration. Class III/IV: Subendothelial immune deposits visible by light microscopy, with infiltration of mesangial and capillary leukocytes (dark green neutrophils and light green monocytes/macrophages). Class III/IV + V: Leukocyte infiltration with subepithelial and subendothelial immune deposits. Class V: Subepithelial immune deposits, no leukocyte infiltration. (Reproduced with permission from IM Bajema et al: Revision of the International Society of

Nephrology/Renal Pathology Society classification for lupus nephritis: Clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int* 93:789, 2018, Figure 2.) one-third of cases; other causes for anemia in SLE include iron deficiency, autoimmune hemolytic anemia, aplastic anemia, micro angiopathic hemolytic anemia, and medication effect. Leukopenia ($<4000/\mu\text{L}$) is common, occurring in about half of SLE patients, and usually consists of lymphopenia ($<1500/\mu\text{L}$), rather than neutropenia. Thrombocytopenia ($<150,000/\mu\text{L}$) is usually mild but can also be severe ($<50,000/\mu\text{L}$) and pose significant bleeding risk. It is most commonly due to immune mechanisms and may be associated with APS or antiphospholipid antibodies against platelet antigens. Splenomegaly, splenic atrophy, and asplenism may all be seen in SLE. Depending on severity of the abnormal blood counts, treatment considerations include glucocorticoids, anti-CD20 biologic agents, platelet growth factors, intravenous immunoglobulin, and/or splenectomy in resistant cases. Rarely, atypical hemolytic-uremic syndrome (formerly designated as thrombotic thrombocytopenic purpura or the syndrome of microvascular thrombotic crisis) may occur. This is a condition that presents with hemolysis, thrombocytopenia, and microvascular thrombosis, as well as brain and other tissue involvement. Laboratory testing shows schistocytes in the peripheral blood smear, low levels of ADAMTS13 activity, and elevated serum lactate dehydrogenase levels. ■ ■ **GASTROINTESTINAL MANIFESTATIONS** Lupus can involve any part of the gastrointestinal tract. Flaring SLE activity has been associated with nonspecific gastrointestinal symptoms including nausea, vomiting, and diarrhea. Abdominal pain may be caused by lupus peritonitis, enteritis, pancreatitis, or vasculitis. Mesenteric vasculitis can lead to intestinal perforation, bleeding, and ischemia and requires high doses of glucocorticoids for treatment. Impaired intestinal motility and protein-losing enteropathy may also occur.

CHAPTER 368 Systemic Lupus Erythematosus Elevated liver enzymes are common and may be associated with flaring disease activity, medications, and/or coexisting autoimmune hepato biliary disease. Mesenteric thrombosis, Budd-Chiari syndrome, and hepatic venoocclusive disease can be observed with concomitant APS. ■ ■ **OCULAR MANIFESTATIONS** Keratoconjunctivitis sicca is common in SLE, even in the absence of secondary Sjögren's syndrome. Retinal vasculitis, optic neuritis, uveitis, scleritis, peripheral ulcerative keratitis, episcleritis, and nonspecific conjunctivitis may all be seen. Retinal vasculitis is rare but, when present, requires aggressive immunosuppression to prevent blindness. Adverse ocular effects from medications include cataracts and glaucoma from glucocorticoid treatment and hydroxychloroquine (HCQ)-induced maculopathy (Table 368-1). **LABORATORY TESTS** ■ ■ **AUTOANTIBODIES** An elevated titer of ANA reflects the underlying immune dysregulation in SLE. Measuring ANA presence and titer is the best screening test for SLE because ANAs are seen in almost all SLE patients. Repeated negative tests by immunofluorescence make a diagnosis unlikely, but rare cases of ANA-negative SLE do occur. Classification of SLE by current EULAR/ACR criteria requires the presence of an ANA titer of 1:80 for enrollment of patients into SLE clinical trials; however, the diagnosis is based on clinical and laboratory features and ultimately, clinical judgement (see "Diagnosis and Classification" section). Numerous ANAs have been identified that target nuclear antigens; in particular, components of the nucleosome (DNA wrapped around a histone

TABLE 368-1 Clinical Manifestations of Systemic Lupus Erythematosus Constitutional Fatigue, malaise, fever, weight loss, anorexia Cutaneous Generalized Photosensitivity, oral and nasal ulcers, alopecia Acute cutaneous Malar rash, maculopapular rash, bullous lupus, toxic epidermal necrolysis variant **PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders** lupus

Subacute cutaneous lupus Chronic forms of Discoid rash, panniculitis, tumid lupus, chilblains, verrucous lupus, cutaneous vasculitis cutaneous lupus Musculoskeletal Arthralgia, myalgia, polyarthritides, Jaccoud hand deformity, inflammatory myopathy, avascular necrosis of bone Hematologic Anemia, leukopenia, lymphopenia, thrombocytopenia, lymphadenopathy, splenomegaly, venous or arterial thrombosis, atypical hemolytic-uremic syndrome Cardiopulmonary Pleurisy, pericarditis, pleural and pericardial effusions, myocarditis, endocarditis, pneumonitis, coronary artery disease, interstitial fibrosis, pulmonary hypertension, diffuse alveolar hemorrhage, shrinking lung syndrome Vascular Pulmonary hypertension, stroke, myocardial infarction, peripheral arterial disease, pulmonary embolism, deep vein thrombosis, Raynaud's phenomenon Neurologic Cognitive dysfunction, mood disorder, depression, headache, seizures, mononeuropathy, polyneuropathy, stroke, transient ischemic attack, psychosis, aseptic meningitis, transverse myelitis Renal Proteinuria ≥ 500 mg/24 h, cellular casts, nephrotic syndrome, end-stage renal disease Gastrointestinal Nausea, abdominal pain, diarrhea, elevated liver enzymes, lupus peritonitis or enteritis, vasculitis, pancreatitis Ocular Sicca syndrome, conjunctivitis, episcleritis, scleritis, uveitis, retinal vasculitis octamer) or RNA-binding proteins (RBPs). In SLE, the most common antinucleosome antibodies are anti-dsDNA antibodies that are present in ~40-60% of patients and highly specific (75-99%). Anti-Smith (anti-Sm) antibodies are the most common anti-RBP, present in ~30% of patients, and are highly specific for SLE (55-100%). Given their high specificity, both anti-dsDNA and anti-Sm antibodies are the only ANA subtypes that are included in the current EULAR/ACR criteria. Anti-Ro (SS-A) antibodies, which recognize a protein complexed primarily to 60-kDa and 52-kDa RNAs, are often seen in ANA-negative SLE patients and are associated with risk for neonatal lupus, sicca symptoms, photosensitivity, and SCLE. Antihistone antibodies may be associated with drug-induced lupus (see "Drug-Induced Lupus" section). Antiphospholipid antibodies, as measured by IgG, IgM, and IgA isotypes of anticardiolipin and anti-beta-2 glycoprotein-1 antibodies (anti- β 2GP-1), and the lupus anticoagulant usually obtained using the dilute Russell venom viper time (dRVVT) are present in ~50% of SLE patients. These antibodies, especially the IgG and IgA isotypes of cardiolipin and β 2GP-1, and the lupus anticoagulant are associated with arterial and venous thrombosis, thrombocytopenia, and recurrent fetal loss (Table 368-2). Many ANA subtypes can be present in SLE and other systemic autoimmune diseases including myositis, rheumatoid arthritis, Sjögren's syndrome, and systemic scleroderma, as well as organ-specific autoimmune diseases such as autoimmune hepatitis, Hashimoto's thyroiditis, and primary biliary cholangitis. ■ ■

STANDARD DIAGNOSTIC TESTS Immunologic, renal, and hematologic domains make up the laboratory testing for the diagnosis of SLE. Among the immunologic domain, elevated titers of ANA confer a high likelihood of SLE. Although ANAs are present at low levels in healthy patients, the threshold for a positive test of 1:80 or higher favors SLE. In the setting of ANA negativity with a clinical presentation highly suggestive of SLE, anti-Ro (SSA) confers a high likelihood of SLE. Further immunologic testing for anti-dsDNA

TABLE 368-2 Autoantibodies in Systemic Lupus Erythematosus PREVALENCE, % CLINICAL ASSOCIATIONS ANTIBODY ANA

Titers of 1:80 or higher are considered positive and are sensitive for SLE but not specific. Anti-dsDNA

Higher titers are more specific for SLE. Levels correlate with disease activity and nephritis. Anti-Sm

Most specific autoantibody for SLE and more common in black and Asian patients. May correlate with CNS manifestations and incidence of nephritis. Anti-RNP

Not SLE-specific. Associated with overlap syndromes and increased risk for pulmonary hypertension. Correlates with high interferon gene signature. Anti-Ro (SS-A)

Not SLE-specific. Associated with sicca syndrome, neonatal lupus and congenital heart block, and subacute cutaneous lupus. Anti-La (SS-B)

Associated with anti-Ro. Antiribosomal P

May be associated with CNS involvement. Specific for SLE but not sensitive. Antihistone

Associated with drug-induced lupus. Anti-U1-RNP

Associated with musculoskeletal and lung impairment. Antiphospholipid Anticardiolipin Anti-β₂-glycoprotein Lupus anticoagulant

Arterial or venous thrombosis, pregnancy morbidity and fetal loss, thrombocytopenia. Associated with CNS manifestations, Libman-Sacks endocarditis, hypertension, pulmonary hypertension. Abbreviations: ANA, antinuclear antibody; CNS, central nervous system; dsDNA, double-stranded DNA; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus; Sm, Smith. and anti-Sm autoantibodies confers specificity. Anti-dsDNA antibodies and reduced levels of complement components C3 and C4 suggest a propensity for lupus nephritis, as these tests indirectly reflect the pathogenic production of autoantibodies and the high load of cellular debris. Laboratory testing is required at initial presentation to screen for hematologic abnormalities including leukopenia, lymphopenia, thrombocytopenia and anemia of chronic inflammation, hemolytic anemia, and atypical hemolytic-uremic syndrome. Initial testing for renal abnormalities is necessary to determine an estimated glomerular filtration rate (eGFR), serum creatinine, and either a random or 24-h UPCr. When commercially available, consideration should be given to measuring urinary biomarkers recently noted to be associated with renal inflammatory and fibrotic disease, including urinary interleukin 16, CD163, type 1 IFN, and transforming growth factor-beta (TGF-β). ■ ■TESTS FOR FOLLOWING DISEASE COURSE Clinical manifestations of SLE vary over time, likely in response to the aberrant immunologic mechanisms that are driving disease. In particular, anti-dsDNA antibody titers are important to track disease activity. These autoantibodies are produced by a short-lived population of B-cell plasmablasts that turn over rapidly, reflecting the presence or absence of immunologic activity. Levels of the complement factors C3 and C4 can drop during episodes of high disease activity, as these are affected by the formation of autoimmune immune complexes and apoptotic cells. In lupus nephritis, the extent of proteinuria and the eGFR are also frequently monitored. Quarterly testing is suggested in asymptomatic patients because hematologic and renal manifestations can be present in the absence of symptoms. Testing should be performed to consider the presence of leukopenia, lymphopenia,

thrombocytopenia, anemia (both anemia of chronic inflammation and hemolytic anemia), and rarely, atypical hemolytic-uremic syndrome. Testing for eGFR, serum creatinine, and a random or 24-h UPCr level is essential for routine follow-up care with consideration of a renal biopsy when urinary protein exceeds a new level of UPCr of 0.5 to rule out active lupus nephritis. Consideration

should be given to measuring urinary biomarkers on a quarterly basis when available.

MANAGEMENT EULAR recently updated recommendations for the management of SLE and lupus nephritis. Goals for SLE treatment include improved disease activity with minimal symptoms, prevention of damage, and improved quality of life (Figs. 368-4 and 368-5). Adherence to treatment plans is essential. Achieving these goals with safe treatments and minimal corticosteroids is an integral aspect of achieving low levels of disease activity and remission. If corticosteroids are utilized for active or flaring disease, the goal should be to utilize the lowest possible dose to suppress disease activity. Aggressive therapy should be reserved for life-threatening manifestations or those that could lead to damage. Consideration should be given to minimize both the effects of active disease and complications from treatment. Renal treatment goals based on EULAR recommendations include (1) a goal that all patients should at least achieve a state of low disease activity, defined by a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of 0–4; or (2) remission, defined as a SLEDAI score of 0, both with stable use of HCQ, immunosuppressives or biologics, and a daily dose of 5 mg of prednisone (or glucocorticoid equivalent) or less (see “Outcomes” section). Treatment of Non-Renal Systemic Lupus Erythematosus

	Mild*	Moderate*	Severe*	1st line	2nd line	1st line	2nd line	1st line	2nd line	General measures
HCQ	(all patients unless contraindicated)									Balanced diet
Vaccinations	Normal body weight									
Blood pressure, lipid, glucose control										
GC	PO/IV (if needed, short-term use to control active disease; taper to ≤ 5 mg/day as quickly as possible and discontinue, if possible)									
MTX										
AZA										
MMF										
Acetylsalicylic acid, VKA										
Immunosuppressive or biological agents	at stable, tolerated dose									
Assess adherence to treatment										
Grade	A	B	C	D						

FIGURE 368-4 Treatment of nonrenal systemic lupus erythematosus (SLE). Notes: Top-to-bottom sequence does not imply order of preference (e.g., MTX, AZA, and MMF are equal options for second-line therapy in mild disease or first-line therapy in moderate disease). *Mild disease: constitutional symptoms; mild arthritis; rash $\leq 9\%$ body surface area; platelet count (PLTs) $50\text{--}100 \times 10^9/\text{L}$; SLEDAI ≤ 6 ; BILAG C or ≤ 1 BILAG B manifestation. *Moderate disease: moderate-to-severe arthritis (“rheumatoid arthritis-like”; rash 9–18% body surface area [BSA]; PLTs $20\text{--}50 \times 10^9/\text{L}$; serositis; SLEDAI 7–12; ≥ 2 BILAG B manifestations). *Severe disease: major organ-threatening disease (e.g., cerebritis, myelitis, pneumonitis, mesenteric vasculitis); thrombocytopenia with platelets $<20 \times 10^9/\text{L}$; thrombotic thrombocytopenic purpura-like disease or acute hemophagocytic syndrome; rash $>18\%$ BSA; SLEDAI >12 ; ≥ 1 BILAG A manifestation. †Recommendation of belimumab and anifrolumab as first-line therapy in severe disease refers to cases of extrarenal SLE with nonmajor organ involvement but extensive disease from skin, joints, and so on. The use of anifrolumab as add-on therapy in severe disease refers mainly to severe skin disease. For patients with severe neuropsychiatric disease, anifrolumab and belimumab are not recommended. ANI, anifrolumab; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; AZA, azathioprine; BEL, belimumab; BILAG, British Isles Lupus Assessment Group; CNI, calcineurin inhibitor; CYC, cyclophosphamide; GC, glucocorticoids; HCQ, hydroxychloroquine; IV, intravenous; MMF, mycophenolate mofetil; MTX, methotrexate; PO, per os; RTX, rituximab; SLEDAI, SLE Disease Activity Index; VKA, vitamin K antagonists. (Reproduced with permission from A Fanouriakis et al: Ann Rheum Dis 83:15, 2024.)

■ ■ ESSENTIAL LUPUS THERAPEUTIC APPROACHES AND ANTIMALARIALS All SLE patients should use daily sunscreen on sun-exposed areas, maintain a healthy diet and weight, avoid smoking, exercise regularly, maintain compliance with vaccination recommendations, and regularly monitor and achieve control of their blood pressure, lipid, and glucose levels. Antimalarials should be used

in all patients unless contraindicated, as they have been shown to prevent flares, increase overall survival, and decrease the risk of developing renal disease and accelerated atherosclerosis, among other benefits. HCQ, one of the first drugs approved by the U.S. Food and Drug Administration (FDA) for use in SLE, is the most common antimalarial used and is first-line therapy for patients with skin manifestations and arthritis. It is the most useful drug to improve fatigue in SLE. Use during pregnancy and during breastfeeding has been demonstrated to be safe. Appropriate dosing of HCQ is under investigation, as higher doses may be associated with better disease control. Current recommendations are for dosing up to 5 mg/kg per day (actual body weight) with performance of retinal evaluations at baseline and at yearly intervals to monitor for macular effects, which are associated with prolonged usage. Risk factors for retinal toxicity from HCQ include higher dose and longer duration of use; however, higher doses may also confer better disease control, and overall risk for maculopathy remains low. The most appropriate dose of HCQ for SLE treatment thus remains unclear. Other side effects of HCQ may include rash, nausea, vomiting and diarrhea, and skin dyspigmentation. Tobacco use may interfere with the efficacy of antimalarials. Alternative antimalarials include chloroquine, which has a higher risk of retinal toxicity, and quinacrine, which has a higher

CHAPTER 368 Systemic Lupus Erythematosus Target Remission Clinical SLEDAI = 0 HCQ GC $\leq$ 5 mg/day or Low disease activity SLEDAI $\leq$ 4 HCQ GC $\leq$ 5 mg/day BEL† ANI† CNI CNI CYC RTX RTX

Treatment of Lupus Nephritis Initial Subsequent HCQ (all patients unless contraindicated) Adjunct treatment for kidney protection# PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders GC PO/IV (consider pulse IV MP, then 0.3–0.5 mg/kg/day depending on severity; taper to $\leq$ 5 mg/day as quickly as possible) ACEi/ARBs Consider SGLT2i (if decreased eGFR) Low-dose CYC VKA, heparin (if concomitant APS nephropathy) MMF/AZA + BEL§ MMF/low-dose CYC + BEL§ MMF + CNI (esp. VOC, TAC)^ High-dose CYC *,¶ Any of the above- mentioned unless contraindicated^ RTX† Assess adherence to treatment Grade A Grade B Grade C Grade D FIGURE 368-5 Treatment of lupus nephritis. Notes: Top-to-bottom sequence does not imply order of preference. #In addition to general protective measures, as outlined in Figure 368-3. §BEL should always be given in combination with MMF or low-dose CYC as initial therapy and with MMF or AZA as maintenance therapy. ^CNIs should be given in combination with MMF. *Particularly recommended in the presence of poor prognostic factors: reduced eGFR, histologic presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation. ¶Extension of high-dose CYC to subsequent phase refers to severe lupus nephritis cases, in which bimonthly or quarterly CYC pulses may be given following 6 monthly pulses. †In relapsing/refractory disease, especially after failure of CYC-based regimens. ACEi, angiotensin-converting enzyme inhibitors; APS, antiphospholipid syndrome; ARB, angiotensin receptor blockers; AZA, azathioprine; BEL, belimumab; CNI, calcineurin inhibitor; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; GC, glucocorticoids; HCQ, hydroxychloroquine; IV, intravenous; MMF, mycophenolate mofetil; MP, methylprednisolone; PO, per os; RTX, rituximab; SGLT2i, sodium-glucose cotransporter 2 inhibitors; TAC, tacrolimus; Upr, urine protein; VKA, vitamin K antagonists; VOC, voclosporin. (Reproduced with permission from A Fanouriakis et al: Ann Rheum Dis 83:15, 2024.) risk of skin dyspigmentation. Quinacrine can be used as alternative therapy in cases of toxic retinopathy or as add-on therapy to HCQ for patients with inadequate response. For arthritis and arthralgia, non steroidal anti-inflammatory drugs (NSAIDs) can be useful but should be used with caution in SLE patients due to increased risk for aseptic meningitis, hypertension, renal dysfunction, elevated serum transaminases, and increased

myocardial infarction risk with cyclooxygenase-2 inhibition. ■ ■GLUCOCORTICOIDS Glucocorticoid dosing is based on the organ-specific needs and severity of disease. While effective at reducing inflammation quickly, their use is associated with dose-dependent side effects including cushingoid metabolic effects, hyperglycemia, hypertension, osteoporosis, and avascular necrosis. If needed, corticosteroids should be tapered as quickly as possible to maintenance doses of 5 mg or less of daily prednisone or its equivalent, and withdrawn as soon as feasible. Use of intravenous methylprednisolone (usually 125–1000 mg daily for 1–3 days) is limited to emergent needs such as active nephritis, severe central nervous system or vascular involvement, and hematologic manifestations such as life-threatening hemolytic anemia or thrombocytopenia. A major goal of novel SLE therapies is the ability to develop treatment algorithms that are less dependent on chronic glucocorticoid use. ■ ■SKIN AND MUSCULOSKELETAL MANIFESTATIONS:

IMMUNOMODULATING AND IMMUNOSUPPRESSANT DRUGS All SLE patients and especially those with skin manifestations of disease should be treated with topical sunscreens and antimalarials. If unresponsive to these approaches, topical glucocorticoids and/or calcineurin inhibitors can be utilized. Persistent mucocutaneous disease and/or arthritis may prompt consideration of additional oral immunomodulating drugs such as azathioprine (6-thioguanine purine analogue), leflunomide (lymphocyte-specific pyrimidine synthesis inhibitor), mycophenolate mofetil (MMF), or mycophenolic acid (purine synthesis inhibitors). Biological drugs such as belimumab

Targets 3 months $\geq 25\%$ reduction in UPr MMF 6 months $\geq 50\%$ reduction in UPr to < 3 gr/day AZA/MMF 12 to 24 months UPr < 0.5 – 0.7 gr/day (all with eGFR within 10% from baseline) (anti-BAFF, administered intravenously or subcutaneously) and anifrolumab (anti-type 1 IFN receptor, administered intravenously) are FDA-approved approaches shown to improve outcomes in these clinical domains, with better ability to taper glucocorticoids. Thalidomide and lenalidomide may be used for some cutaneous subtypes but with caution due to risk for polyneuropathy and teratogenicity. Methotrexate (a folinic acid antagonist) is another option for arthritis associated with SLE. ■ ■RENAL DISEASE: SUCCESSES WITH COMBINATION THERAPIES Treatment approaches have been recommended by EULAR for class III and IV lupus nephritis, as well as combination of class V lupus nephritis with either class III or IV (Fig. 368-5). The recommended targets are a 3-month target of 25% or more reduction in UPCr level, a 6-month target of 50% or more reduction in UPCr to < 3 g/d, and a 12- to 24-month target in UPCr to < 0.5 – 0.7 g/d, with each of these targets associated with an eGFR within 10% from baseline. All patients with class III, IV, or V nephritis should receive an angiotensin-converting enzyme (ACE) inhibiting agent or an angiotensin receptor blocking (ARB) agent to decrease proteinuria and reduce systemic and glomerular hypertension. With a baseline decreased eGFR, use of a sodium-glucose cotransporter 2 (SGLT2) inhibitor should be considered to reduce glomerular hyperfiltration, lower blood pressure, and decrease proteinuria. Patients with active lupus nephritis with concomitant antiphospholipid nephropathy as noted by biopsy should receive a vitamin K antagonist or heparin. Current initial regimens include either cyclophosphamide (an alkylating agent administered intravenously) or MMF (administered orally) plus glucocorticoids to reduce progression to ESRD and death. Rates of infection and death are similar in both treatment approaches. Induction in Black or Hispanic patients with MMF 2–3 g daily is appropriate given better response to MMF in these ethnic groups, while use of either MMF or cyclophosphamide may be an option for White and Asian patients. Low doses of cyclophosphamide (500 mg every 2 weeks for six doses) followed by either azathioprine or MMF maintenance are

as effective as standard high doses of cyclophosphamide with improved tolerability. High-dose cyclophosphamide monthly for 6 months followed by azathioprine or MMF may be more appropriate for patients with crescentic proliferative glomerulonephritis or rapidly progressive glomerulonephritis. Ovarian failure is a potential consequence of high-dose cyclophosphamide, and therefore, a gonadotropin-releasing hormone agonist may be given prior to each cyclophosphamide dose. Dosing of glucocorticoids as part of the initial therapeutic approach is controversial, with more recent data suggesting the use of intermediate doses for shorter periods of time with more rapid dose reduction. For subsequent therapy, MMF is superior to azathioprine in maintaining renal function and survival, but both may be used, and azathioprine is the preferred agent for lupus nephritis in pregnancy. Patients using azathioprine should be screened for homozygous deficiency of the thiopurine S-methyltransferase (TMPT) gene, which increases the risk for severe bone marrow suppression, as this gene is responsible for the TPMT enzyme necessary for metabolizing thiopurine drugs. Calcineurin inhibitors such as tacrolimus and cyclosporine may be beneficial for decreasing proteinuria, and tacrolimus can be used in pregnancy. Two immunomodulating therapies have recently been approved by the FDA for use in lupus nephritis for patients on standard therapy for active nephritis: belimumab, approved in 2020, and the cyclosporine analogue voclosporin, approved in 2021. The randomized controlled trials for these medications demonstrate favorable outcomes without the use of high-dose steroids. Voclosporin-based triple immunotherapy (with MMF and glucocorticoids) or belimumab-based triple therapy (with either low-dose cyclophosphamide or MMF and glucocorticoids) can be considered as an initial approach in active lupus nephritis. Patients with active lupus nephritis and inadequate response to conventional therapies may also consider alternative biologics targeting B cells such as rituximab. While rituximab studies in lupus nephritis did not demonstrate efficacy compared to standard therapies, issues with the trial designs may have hampered the demonstration of an effect. Treatment approaches for patients with pure class V membranous glomerulonephritis have not been well studied, and commonly patients with this presentation are treated only in the setting of significant proteinuria. All patients with class III, IV, or V nephritis, including combinations of class III or IV with class V, should be considered for treatment with ARB or ACE inhibition to reduce proteinuria.

■ ■ THERAPIES FOR OTHER ORGAN-BASED SYSTEMS Few studies have focused on central and peripheral nervous system, cardiac, pulmonary, serosal, gastrointestinal, or hematologic manifestations of SLE. Anti-CD20 agents such as rituximab are used for lupus-related hemolytic anemia and severe thrombocytopenia. Colchicine can be used to treat pleural, pericardial, or peritoneal inflammatory symptoms. MMF, cyclophosphamide, and rituximab plus corticosteroids are the mainstay of treatment for serious central and peripheral inflammatory nervous system presentations including psychosis, vasculitis, and transverse myelitis. Plasmapheresis and high levels of glucocorticoids can be lifesaving in atypical hemolytic-uremic syndrome. In refractory patients, rituximab and a C5 inhibitor, eculizumab, are used. Concomitant APS should be treated with warfarin for long-term anticoagulation rather than direct oral anticoagulants (Chap. 369).

■ ■ EMERGING THERAPIES AND TREATMENT APPROACHES SGLT2 inhibitors are being studied in lupus nephritis for their effects on preserving function through tubular protection with effects on inflammation and fibrosis. Obinutuzumab, a CD20-targeted monoclonal antibody that is commercially available for oncologic indications, has recently demonstrated efficacy in a phase 3 study for lupus nephritis, and is also being investigated for use in SLE without nephritis. Anecdotal experience with obinutuzumab by rheumatologists in treating SLE patients off-label suggests that this drug may be more clinically effective than rituximab due to improved CD20 tissue depletion. Deucravacitinib, an oral Tyk2 inhibitor, is in phase 3 study for SLE.

Telitacicept, a TACI-Fc fusion protein that targets BLyS and APRIL growth factors for B cells, has been approved in China for use in

patients with SLE, and global phase 3 studies are underway. Litifilimab, a drug in late-stage development with initial promising results, is a monoclonal antibody targeting BDCA2, a protein expressed on plasmacytoid dendritic cells, that suppresses activation of type I interferons and other proinflammatory cytokines. Initial results show achievement of remission, according to the Definition of Remission in Systemic Lupus Erythematosus (DORIS), from nonrandomized CD19-directed chimeric antigen receptor T-cell treatment, which has prompted interest in further study of this approach. Other cell-based therapeutic programs under investigation include both allogenic and autologous natural killer cell-based programs and mesenchymal embryonic stem cell transplantation for severe SLE.

CHAPTER 368 Systemic Lupus Erythematosus ■ ■ GUIDELINES Besides the recent EULAR (2013) and Pan-American League of Associations for Rheumatology (2018) guidelines for SLE and lupus nephritis, the ACR (2012) and the Kidney Disease Improving Global Outcomes (KDIGO) organization (2021) have published guidelines specifically for lupus nephritis. These guidelines address medication-based, lifestyle, and nonpharmacologic approaches, as well as infection screening and vaccination recommendations. The KDIGO guidelines include recommendations prior to the approval of belimumab and voclosporin. An important concept that the KDIGO group emphasizes is the unsettled question of duration of immunosuppression. The group notes that the risk of lupus relapse should be balanced with risk of adverse events secondary to immunosuppressive drugs. They suggest that for patients who have achieved a complete renal response and have no ongoing extrarenal SLE manifestations, the total duration of immunosuppression (initial plus maintenance) should not be <36 months. The EULAR guidelines provide consensus guidance for SLE management that combines evidence and expert opinion concerning the use of HCQ, glucocorticoids, immunosuppressive drugs, calcineurin inhibitors, and biologics, with suggestions for treatment strategies, response assessment, combination approaches, and therapy tapering (see Figures 368-4 and 368-5). Most of the concepts and strategies presented in these guidelines are described in the sections above.

DRUG-INDUCED LUPUS Drug-induced lupus (DIL) is an autoimmune phenomenon in which a positive ANA and clinical features of SLE arise from a drug exposure. DIL accounts for ~6–12% of all lupus cases. Symptoms may include fever, rash, arthralgia, myalgia, and serositis. Antihistone antibodies are commonly associated with DIL, with dsDNA antibodies occurring less frequently. DIL tends to be less severe than SLE, rarely involving kidneys or brain, and symptoms typically resolve within several weeks after discontinuation of the offending agent. The first agent identified to cause lupus symptoms was hydralazine in 1954. Over the years, >100 drugs have been identified as potential triggers for DIL. The highest incidence of DIL occurs with the antiarrhythmic procainamide, with risk reported to be as high as 30%. Other substances associated with DIL include the antihypertensives hydralazine and methyldopa; other antiarrhythmics; antibiotics including minocycline, isoniazid, rifampin, and nitrofurantoin; the antirheumatic drug sulfasalazine; anticonvulsants such as phenytoin and carbamazepine; antipsychotics including chlorpromazine and lithium; several ACE inhibitors and beta blockers; the diuretic hydrochlorothiazide; the antithyroid propylthiouracil; proton pump inhibitors; NSAIDs; and oral contraceptives. Biologic agents include antitumor necrosis factor α medications, particularly infliximab and etanercept, and IFN- α . Diagnosis can be difficult, as DIL symptoms may start weeks to several months after drug initiation. Furthermore, skin biopsy may be indistinguishable from

SLE, and laboratory characteristics including histone antibody may be seen in the majority of SLE cases. In DIL, the ANA pattern is most commonly homogeneous, and histone is positive in 75% of DIL cases. Cytopenias may be present but are typically mild. The presence of other autoantibodies may help to distinguish SLE from DIL, as these are rarely seen in DIL. The ANA test typically appears before symptoms, although many of the same medications will

induce a positive ANA in patients who never develop symptoms. If DIL is suspected, these laboratory tests should help to inform the clinical picture to decide if medication discontinuation is appropriate. If symptoms resolve after medication discontinuation, this helps to confirm a diagnosis of DIL.

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders PREGNANCY AND REPRODUCTIVE HEALTH ■ ■ FERTILITY Lupus activity can affect the menstrual and ovulation cycle. Lower measures of ovarian reserve are seen in SLE patients compared to healthy controls. Women with SLE have a higher risk for infertility if they have active disease, comorbidities such as APS or nephritis, and prior exposure to treatments such as cyclophosphamide. Cyclophosphamide use may lead to amenorrhea, ovarian insufficiency, and early menopause. ■

■ CONTRACEPTION/HORMONE REPLACEMENT Contraception and family planning should be discussed with all women of reproductive age with SLE. SLE patients with antiphospholipid antibodies and those with moderate-to-severe or active lupus should avoid estrogen compounds due to increased risk for thromboembolism. Progestin-only contraceptive options such as the levonorgestrel intra uterine device or etonogestrel implant, as well as emergency contraception, may be used safely in women with SLE. Estrogen compounds as a part of postmenopausal hormone replacement therapy should similarly be avoided in the presence of antiphospholipid antibodies. ■

■ PREGNANCY SLE pregnancies are high risk. Disease activity in pregnancy is unpredictable, and the disease can flare during any trimester. Active disease at time of conception is associated with more flares during pregnancy. HCQ reduces the risk of flares during pregnancy and postpartum. Women with SLE are at a higher risk for adverse pregnancy outcomes including pregnancy loss, preterm birth, preeclampsia and pregnancy-induced hypertension, intrauterine growth restriction, cesarean section, and maternal death. Flaring or active disease increases the risk for these adverse outcomes. The presence of maternal hypertension, use of glucocorticoids during pregnancy, maternal renal disease, discontinuation of HCQ, non-White ethnicity, and lupus anticoagulant positivity are all associated with worse pregnancy outcomes. SLE patients at the highest risk for maternal death are those with pulmonary arterial hypertension, prior arterial thrombosis, and severe end-organ damage, and these patients should strongly consider avoiding pregnancy. Outcomes are generally favorable for women with SLE with mild-to-moderate disease activity on pregnancy-compatible medications. Low-dose aspirin is used during pregnancy for preeclampsia prevention. HCQ is safe and the standard of care for all SLE pregnancies.

Azathioprine and tacrolimus may be used safely in pregnancy for more severe disease and/or renal disease. MMF and methotrexate are teratogenic and should be avoided. Belimumab, anifrolumab, and voclosporin should currently be avoided due to lack of safety data. Patients who get pregnant on these medications may be switched to azathioprine or tacrolimus. Rituximab should be discontinued at conception but may be used during pregnancy in organ-threatening disease.

Prednisone may be used for disease flares and can suppress disease activity, but the dose should be tapered to the lowest effective dose by adding pregnancy-compatible immunosuppressant medications. Warfarin is teratogenic; low-molecular-weight heparin is used in SLE pregnancies with

APS or prior pregnancy morbidity. ■ ■ NEONATAL LUPUS SS-A (Ro) antibodies may cross the placenta into the fetal circulation and put the infant at risk for neonatal lupus. Neonatal lupus can consist of a transient cutaneous rash or lab abnormalities that present after birth or, less commonly, congenital heart block that presents in utero. The presence of Ro antibodies, particularly in high titer, should prompt referral to high-risk obstetricians who can perform fetal echocardiography to screen for congenital heart block. The use of fluorinated

steroids may be considered if first- or second-degree heart block is detected. The use of HCQ in pregnancy significantly reduces the risk of congenital heart block in women who have had a prior fetus with congenital heart block. OUTCOMES Measuring SLE outcomes both in clinical trials and in clinical practice is complex given the multisystem nature of the disease. Various aspects of disease require unique treatment approaches and often at differing rates, which makes measuring response challenging. Modern SLE treatment outcomes include improvement in inflammatory type 1 and chronic type 2 symptoms, quality of life, and the prevention of frailty and damage. New drugs and interventions are constantly being explored as potential treatments for SLE in clinical trials. Goals of clinical trials for novel therapies include improved disease activity and acceptable safety. Long-term extension studies focus on long-term safety and maintenance of improved disease activity. The Systemic Lupus Erythematosus Responder Index (SRI) and the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) are validated instruments for use in clinical trials. The Cutaneous Lupus Disease Area and Severity Index (CLASI) is also utilized specifically for trials involving cutaneous lupus. Several instruments are utilized in clinical trials to assess quality of life and fatigue, although few are specific to SLE. ■ ■ TREAT-TO-TARGET APPROACHES Treat-to-target goals for clinical trials and clinical practice have been developed and validated, including the definition of a lupus low disease activity state (LLDAS) and remission (DORIS). Both LLDAS and DORIS remission scoring utilize the SLEDAI-2K instrument, a validated instrument that measures SLE disease activity. Achievement of remission by these measures is defined by low disease activity (LLDAS) or no disease activity (DORIS), with minimal use of steroids and stable use of antimalarials, immunosuppressants, and/or biologics and by low levels (LLDAS) or no evidence of disease activity (DORIS) as assessed by the evaluating physician. LLDAS has been shown to be attainable in up to 80% of patients, and the achievement of sustained LLDAS for 2 more years is associated with significantly less overall damage. ■ ■ DAMAGE Organ or structural damage occurs in SLE due to the use of medications to treat the disease or because of persistent disease activity. Use of glucocorticoids is associated with the development of irreversible organ damage that is independent of disease activity. Cataracts, osteoporosis-associated fractures, avascular necrosis, and diabetes mellitus are the complications from glucocorticoid treatment that are most commonly observed. Development of damage accrues in a dose-dependent manner, but even low doses of 5 mg of prednisone or equivalent appear to be associated with damage accrual. Accelerated atherosclerosis is a major cause of death after 5 years of SLE disease duration. Increased myocardial infarction and cerebrovascular event rates are due to both traditional cardiovascular risk factors and non traditional factors including presence of antiphospholipid antibodies, increased disease activity, low C3 levels, high glucocorticoid dose, and high homocysteine and leptin levels. Statin use has been demonstrated to reduce all-cause mortality in SLE patients with renal transplantation. Studies of malignancy rates in SLE have been inconsistent; however, recent meta-analyses suggest an increased risk of overall cancer and cancer-related death in SLE patients. Seventeen site-specific cancers noted include digestive cancers (esophagus, colon, anus, hepatobiliary, liver, and pancreas), hematologic cancers (lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, and multiple myeloma),

and cancer involving lung, larynx, cervix, vagina/vulva, kidney, bladder, skin, and thyroid. ■
■FURTHER READING Aringer M et al: 2019 European League Against Rheumatism/American College of Rheumatology classification for systemic lupus erythematosus. *Ann Rheum Dis* 78:1151, 2019. Aringer M et al: A glimpse into the future of systemic lupus erythematosus. *Ther Adv Musculoskelet Dis* 14:1759720X221086719, 2022.

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