TABLE 378-1 AUTOANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Antibody	Prevalence, %	Antigen Recognized	Clinical Utility
Antinuclear antibodies	98	Multiple nuclear	Best screening test; repeated negative tests make SLE unlikely
Anti-dsDNA	70	DNA (double-stranded)	High titers are SLE-specific and in some patients correlate with disease activity, nephritis, vasculitis
Anti-Sm	25	Protein complexed to 6 species of nuclear U1 RNA	Specific for SLE; no definite clinical correlations; most patients also have anti-RNP; more common in blacks and Asians than whites
Anti-RNP	40	Protein complexed to U1 RNA	Not specific for SLE; high titers associated with syndromes that have overlap features of several rheumatic syndromes including SLE; more common in blacks than whites
Anti-Ro (SS-A)	30	Protein complexed to hY RNA, primarily 60 kDa and 52 kDa	Not specific for SLE; associated with sicca syndrome, predisposes to subacute cutaneous lupus, and to neonatal lupus with congenital heart block; associated with decreased risk for nephritis
Anti-La (SS-B)	10	47-kDa protein complexed to hY RNA	Usually associated with anti-Ro; associated with decreased risk for nephritis
Antihistone	70	Histones associated with DNA (in nucleosome, chromatin)	More frequent in drug-induced lupus than in SLE
Antiphospholipid	50	Phospholipids, β_2 glycoprotein 1 (β_2G1) cofactor, prothrombin	Three tests available—ELISAs for cardiolipin and β_2G1, sensitive prothrombin time (DRVVT); predisposes to clotting, fetal loss, thrombocytopenia
Antierythrocyte	60	Erythrocyte membrane	Measured as direct Coombs test; a small proportion develops overt hemolysis
Antiplatelet	30	Surface and altered cytoplasmic antigens on platelets	Associated with thrombocytopenia, but sensitivity and specificity are not good; this is not a useful clinical test
Antineuronal (includes antiglutamate receptor)	60	Neuronal and lymphocyte surface antigens	In some series, a positive test in CSF correlates with active CNS lupus
Antiribosomal P	20	Protein in ribosomes	In some series, a positive test in serum correlates with depression or psychosis due to CNS lupus

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; DRVVT, dilute Russell viper venom time; ELISA, enzyme-linked immunosorbent assay.

estrogen-containing oral contraceptives or hormone replacement have an increased risk of developing SLE (1.2- to 2-fold). Estradiol binds to receptors on T and B lymphocytes, increasing activation and survival of those cells, thus favoring prolonged immune responses. Genes on the X chromosome that influence SLE, such as *TREX-1*, may play a role in gender predisposition, possibly because some genes on the second X in females are not silent. People with XXY karyotype (Klinefelter's syndrome) have a significantly increased risk for SLE.

Several environmental stimuli may influence SLE (Fig. 378-1). Exposure to ultraviolet light causes flares of SLE in approximately 70% of patients, possibly by increasing apoptosis in skin cells or by altering DNA and intracellular proteins to make them antigenic. Some infections induce normal immune responses that involve certain T and B cells that recognize self-antigens; such cells are not appropriately regulated, and autoantibody production occurs. Most SLE patients have autoantibodies for 3 years or more before the first symptoms of disease, suggesting that regulation controls the degree of autoimmunity for years before quantities and qualities of autoantibodies and pathogenic B and T cells cause clinical disease. Epstein-Barr virus (EBV) may be one infectious agent that can trigger SLE in susceptible individuals. Children and adults with SLE are more likely to be infected by EBV than age-, sex-, and ethnicity-matched controls. EBV contains amino acid sequences that mimic sequences on human spliceosomes (RNA/protein antigens) often recognized by autoantibodies in people with SLE. Current tobacco smoking increases risk for SLE (odds ratio [OR] 1.5). Prolonged occupational exposure to silica (e.g., inhalation of soap powder dust or soil in farming activities) increases risk (OR 4.3) in African-American women. Thus, interplay between genetic susceptibility, environment, gender, and abnormal immune responses results in autoimmunity (Chap. 377e).

PATHOLOGY

In SLE, biopsies of affected skin show deposition of Ig at the dermal-epidermal junction (DEJ), injury to basal keratinocytes, and inflammation dominated by T lymphocytes in the DEJ and around blood vessels and dermal appendages. Clinically unaffected skin may also show Ig deposition at the DEJ.

In renal biopsies, the pattern and severity of injury are important in diagnosis and in selecting the best therapy. Most recent clinical studies of lupus nephritis have used the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) classification (Table 378-2). In the ISN/RPS classification, the addition of "a" for active and "c" for chronic changes gives physicians information regarding the potential reversibility of disease. The system focuses on glomerular disease, although the presence of tubular interstitial and vascular disease is important to clinical outcomes. In general, class III and IV disease, as well as class V accompanied by III or IV disease, should be treated with aggressive immunosuppression if possible, because there is a high risk for end-stage renal disease (ESRD) if patients are untreated or undertreated. In contrast, treatment for lupus nephritis is not recommended in patients with class I or II disease or with extensive irreversible changes. In the recent Systemic Lupus International Collaborating Clinic (SLICC) criteria for classification of SLE, a diagnosis can be established on the basis of renal histology without meeting additional criteria (Table 378-3).

Histologic abnormalities in blood vessels may also determine therapy. Patterns of vasculitis are not specific for SLE but may indicate active disease: leukocytoclastic vasculitis is most common (Chap. 385).

Lymph node biopsies are usually performed to rule out infection or malignancies. In SLE, they show nonspecific diffuse chronic inflammation.

DIAGNOSIS

The diagnosis of SLE is based on characteristic clinical features and autoantibodies. Current criteria for classification are listed in Table 378-3, and an algorithm for diagnosis and initial therapy is shown in Fig. 378-2. The criteria are intended for confirming the diagnosis of SLE in patients included in studies; the author uses them in individual patients for estimating the probability that a disease is SLE. Any combination of four or more criteria, with at least one in the clinical and one in the immunologic category, well documented at any time during an individual's history, makes it likely that the patient has SLE. (Specificity and sensitivity are ~93% and ~92%, respectively.) In many patients, criteria accrue over time. Antinuclear antibodies (ANA) are positive in >98% of patients during the course of disease; repeated negative tests by immunofluorescent methods suggest that the diagnosis is not SLE, unless other autoantibodies are present (Fig. 378-2). High-titer IgG antibodies to double-stranded DNA and antibodies to the Sm antigen are both specific for SLE and, therefore, favor the diagnosis in the presence of compatible clinical manifestations. The