Although systemic lupus erythematosus (SLE) is often called “lupus,” there are actually 4 different kinds of lupus, of which SLE is the most common form. In addition to SLE, there is discoid lupus erythematosus, drug-induced lupus erythematosus, and neonatal lupus. Discoid, or cutaneous, lupus is limited to the skin, where it manifests as a variety of different rashes.\(^1\) Drug-induced lupus, which appears similar to SLE, usually dissipates within several weeks of discontinuation of the drugs that caused it.\(^2,3\) Neonatal lupus is quite rare, and is caused by a mother’s antibodies being passed on to the fetus. SLE is usually what is referred to when the word “lupus” is used.\(^4\)

SLE is a rare autoimmune disease. In 2008, it has been estimated that between 161,000 and 322,000 American adults had SLE.\(^5\) Most of these adults are women in their childbearing years. The Euro Lupus Project analyzed 1000 patients with SLE; 91% were women, and the mean age at the onset of symptoms was 29 years (Figure 1).\(^6\) The impact of SLE on pregnancies can be severe. A meta-analysis calculated that 16% of pregnancies in women with SLE resulted in spontaneous abortion and 6.1% resulted in stillbirth or neonatal death. Overall, nearly a quarter of all pregnancies were unsuccessful in women with SLE and 39% of births were premature.\(^7\)

**Figure 1. The Euro Lupus Project: Analysis of 1000 Patients With SLE\(^6\)**

<table>
<thead>
<tr>
<th>Patients With SLE (%)</th>
<th>Age at onset of symptoms</th>
<th>Age at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10</td>
<td>11-20</td>
</tr>
</tbody>
</table>

SLE indicates systemic lupus erythematosus.

In addition, persons of certain ethnicities are more frequently affected by SLE.\(^5\) For example, African American women more frequently develop SLE compared with Caucasian women (Table 1).\(^8\) A similar trend is observed in men.\(^8\)

**Table 1. Incidence of SLE\(^8\)**

<table>
<thead>
<tr>
<th>Population</th>
<th>Incidence per 100,000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American women</td>
<td>9.2</td>
</tr>
<tr>
<td>Caucasian women</td>
<td>3.5</td>
</tr>
<tr>
<td>African American men</td>
<td>0.7</td>
</tr>
<tr>
<td>Caucasian men</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Systemic Lupus Erythematosus Disease Overview

SLE can affect many organ systems, including hematologic, musculoskeletal, dermatologic, renal, cardiac, pulmonary, gastrointestinal, reticulo-endothelial, and central nervous systems (Figure 2).7,9,10 Permanent organ damage is observed in more than half of patients with SLE, which may have implications for comorbidities and additional healthcare costs.11,12 The wide variation in symptom presentation and organ systems that can be affected can make it difficult for medical professionals to diagnose and manage SLE.13-15

Pathogenesis of SLE

The cause, or causes, of SLE are not fully understood. Environmental, genetic, neuroendocrine, and hormonal factors have all been shown to be part of the pathogenesis of SLE. As shown in Figure 3, various factors can influence a person’s autoimmune response, eventually leading to tissue injury and damage.16

Much like the symptoms of SLE, the list of possible environmental factors involved in the pathogenesis of SLE is fairly extensive and includes sunlight18 and medications.17,18 Examples of drugs that may be associated with the development of SLE are procainamide, hydralazine, chlorpromazine, isoniazid, phenytoin, and penicillamine.16

Hormones and environmental estrogens may also be involved in the pathogenesis of SLE. For example, low estrogen levels in women are associated with a lower risk of developing SLE, whereas higher estrogen-to-androgen ratios in men can increase their risk of developing SLE.16,19 Unfortunately, how these hormonal changes lead to SLE is still poorly understood. Studies have shown that estrogen can influence various aspects of the immune system but how this may lead to the development of SLE is not certain. Furthermore, hormonal changes in women tend to be associated with SLE flares and symptoms.16 However, a study in which 183 premenopausal women with inactive or stable active SLE were randomized to receive either an oral contraceptive or placebo found that the 12-month rates of severe flare were similar in both groups.20

Finally, genetics plays an important role in SLE. The concordance rates for identical twins is 24%, compared with 2% for nonidentical twins.21 Many genes are associated with increased susceptibility to SLE, but the current consensus is that SLE may be the result of an accumulative effect of numerous genes.22-25

ESRD indicates end-stage renal disease; SLE, systemic lupus erythematosus.
Pathophysiology of SLE

SLE involves a disruption of the immune response that impacts B cells and T cells (Figure 3). SLE is also associated with elevated levels of various cytokines, including soluble B-lymphocyte stimulator (BLyS or BAFF), interleukin-6, interleukin-10, tumor necrosis factor-alpha, and interferon-alpha.26-31 The multitude of cellular changes that can occur in SLE are believed to account for the 3 main immune abnormalities observed in these patients.

- First, there is defective clearance and subsequent necrosis of apoptotic cells, causing the release of nuclear material that can become antigenic.32,33
- Second, there is an overexpression of several cytokines, which can lead to the prolonged survival and increased activity of autoreactive B cells.34-38
- Third, there is defective clearance of immune complexes that cause injury to body tissues.39-43

Because of the heterogeneous nature of the clinical manifestations of SLE, it is difficult to describe the “typical” symptoms of SLE or the “typical” patient with SLE.

SLE Symptoms and Diagnosis

One of the most challenging issues for people with SLE is receiving a timely and accurate diagnosis. Misdiagnosis is common, and there can be a 2-year delay between the onset of symptoms and a diagnosis of SLE.6,44-46 The consequences of this delay can be very serious, including the development of end-stage renal disease.45-47 In many patients, the most severe periods of disease activity occur early in the course of SLE. As a result, any delay in early detection and diagnosis can increase morbidity.6

The American College of Rheumatology (ACR) has developed a set of classification criteria for SLE.10 These criteria were most recently revised in 1999.10 According to the ACR, the classification of a patient as having SLE usually requires the presence of 4 or more of the following 11 criteria at some point in the patient’s history:

1) Malar rash
2) Discoid rash
3) Photosensitivity
4) Oral ulcers
5) Nonerosive arthritis
6) Pleuritis or pericarditis
7) Renal disorder
8) Neurologic disorder
9) Hematologic disorder
10) Immunologic disorder
11) Antinuclear antibody positive

SLE diagnosis normally takes into account other factors along with the ACR criteria, employing additional laboratory tests and clinical observations, while the ACR criteria constitute a useful starting point for diagnosis.9 When a
The patient is observed to have exhibited 4 of these criteria during his or her medical history, a diagnosis can be conferred with approximately 96% specificity and 96% sensitivity. The diagnosis of SLE involves differentiating SLE from other chronic conditions such as Sjögren’s syndrome and fibromyalgia (although the patient may simultaneously have these other conditions).

There is currently no single test that can predict disease flare activity. There are, however, several indices available that can monitor SLE disease activity (Table 2) and have been validated in numerous international studies. At present, these indices are primarily used in clinical trials, although they can be used in the clinical setting.

The assessment of patients with SLE is dependent upon the experience of the physician and is subject to variability between physicians.

### Disease Burden

SLE is associated with an increased risk of mortality. Bernatsky et al conducted an international multicenter cohort study of 9547 patients with SLE and found that patients with SLE had a 2.4-fold increased risk of death compared with the general population. The broad spectrum of symptoms that may be associated with SLE is reflected in the numerous causes of death observed in this study. Patients with SLE are at increased risk of death due to infections (SMR [standardized mortality ratio, the ratio of deaths observed to deaths expected], 5.0), renal disease (SMR, 7.9), heart disease (SMR, 1.7), non-Hodgkin lymphoma (SMR, 2.8), and lung cancer (SMR, 2.3). These numbers seem grim; however, it should be noted that with improvements in the understanding of SLE, mortality rates in patients with SLE dramatically improved between 1970 and 2000.

SLE is also associated with substantial morbidity. Urowitz et al conducted an international multicenter cohort study of 298 patients with SLE who were followed for a minimum of 5 years. Over the 5 years, disease activity decreased (as assessed by the Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K]), while cumulative damage increased (as assessed by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index [SLICC/ACR SDI]), a validated measure of damage in SLE. Lopez et al conducted a prospective cohort study of 350 patients with SLE who were observed over a 12-month period. During the follow-up period, 39.6% of patients experienced new organ damage (defined as a change of 1 or more units in SDI score), and 10.4% of patients experienced severe organ damage (defined as a total SDI score of 3 or greater). Greater disease activity (assessed by total BILAG score) was associated with a higher risk of organ damage (defined as a change of 1 or more units in SDI score).

### Quality of Life

Patients with SLE experience diminished quality of life; fatigue is one of the most frequently reported SLE symptoms and greatly impacts quality of life. One study found that up to 86% of patients with SLE reported fatigue; increased fatigue was strongly associated with decreasing physical and mental functions, as well as disease severity. A study by Jump et al noted that fatigue is also positively associated with pain, depression, and perceived social support, and that pain is among the most common reasons that individuals seek medical care. In addition to fatigue, factors contributing to decreased quality of life in patients with SLE include depression, pain, poor sleep quality, poor physical fitness, perceived

### Table 2. SLE Disease Activity Indices

<table>
<thead>
<tr>
<th></th>
<th>BILAG</th>
<th>SLEDAI</th>
<th>SLAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of descriptors</td>
<td>86</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>Number of organ systems</td>
<td>8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Review period</td>
<td>28 d</td>
<td>10 d</td>
<td>28 d</td>
</tr>
<tr>
<td>Objective/subjective</td>
<td>Both</td>
<td>Objective</td>
<td>Subjective</td>
</tr>
<tr>
<td>Weighted variables</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Severity assessment</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Immunologic variables</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Updates</td>
<td>BILAG 2004</td>
<td>SELENA-SLEDAI, SLEDAI-2K</td>
<td>SLAM-R</td>
</tr>
<tr>
<td>Definition of flares</td>
<td>Yes</td>
<td>Yes (SELENA)</td>
<td>No</td>
</tr>
<tr>
<td>Relevance to clinical trials</td>
<td>Individual severity scores will vary if organ system is improving or worsening</td>
<td>Global severity score does not record if an organ system is improving or worsening</td>
<td>Difficult to distinguish multiple mild manifestations vs 1 severe feature</td>
</tr>
</tbody>
</table>

Figure 4. Health-Related Quality of Life in Patients With SLE Is Similar to Congestive Heart Failure and Depression". A study by Jolly showed that quality of life scores for patients with SLE are comparable to those for patients with depression or congestive heart failure (Figure 4). The reduction in quality of life in patients with SLE has also been found to be similar to the reduction in quality of life in patients with other chronic rheumatic conditions, such as Sjögren’s syndrome and rheumatoid arthritis. Although these other autoimmune diseases can be enormously destructive to a patient’s quality of life, they are rarely lethal. In contrast, in its more severe forms, SLE can cause damage to major organs, and may be fatal.

One study found that SLE disease activity (as assessed by SLAM-2) was associated with decreased health-rela-

Figure 5. Average Annual Direct and Indirect Cost of Illness per Patient by Condition (in 2005 Dollars)".

COPD indicates chronic obstructive pulmonary disease; SLE, systemic lupus erythematosus.
ted quality of life, specifically with lower scores on the general health subscale of the Medical Outcome Survey Short Form 36 (SF-36), which was used to assess quality of life. Damage (as assessed by SLICC/ACR SDI) was also associated with decreased health-related quality of life, specifically with lower scores on the physical and social function subscales of the SF-36.69

Cost of SLE

The medical costs of SLE are significantly higher than medical costs associated with other chronic conditions, such as diabetes, asthma, and rheumatoid arthritis.70 As shown in Figure 5, the average annual cost of SLE per patient was $25,215 (in 2005 dollars).70

Slawsky et al conducted a structured literature review to evaluate the direct costs of SLE in a US population. They found that mean annual direct costs of SLE ranged from $13,735 to $20,926 (in 2009 dollars).71

Lau and Mak calculated the indirect costs of SLE in US dollars72 based on the results of the Tri-Nation study.69,73 The mean annual indirect cost per patient in the United States was $14,513 (in 2009 dollars).72-74

It should be noted, however, that medical costs will vary greatly per patient and costs will be dependent on the severity of the symptoms and the organ impacted. Carls et al noted that mean annual medical costs for patients with SLE but without nephritis were $8628 greater than those in matched control patients, whereas mean medical expenditures for patients with SLE and nephritis were $46,862 greater than those in controls.70

SLE impacts patients’ ability to work. A study by Yelin et al examined the effects of SLE on employment. Ten years after diagnosis, 36% of people with SLE had stopped working; at 15 years after, 51% had stopped; and at 20 years after, 63% were no longer working.75

Concluding Remarks

The humanitarian, societal, and economic burdens of SLE are substantial and are manifested as reduced life span, high symptom burden, significant functional impairment and disability, poor quality of life, and high healthcare resource utilization, direct costs, and indirect costs.

Please visit ajmc.com/sle for the interactive presentation on SLE that provides healthcare professionals with a better understanding of this condition and how SLE impacts a patient’s health, quality of life, and healthcare costs.

References


