

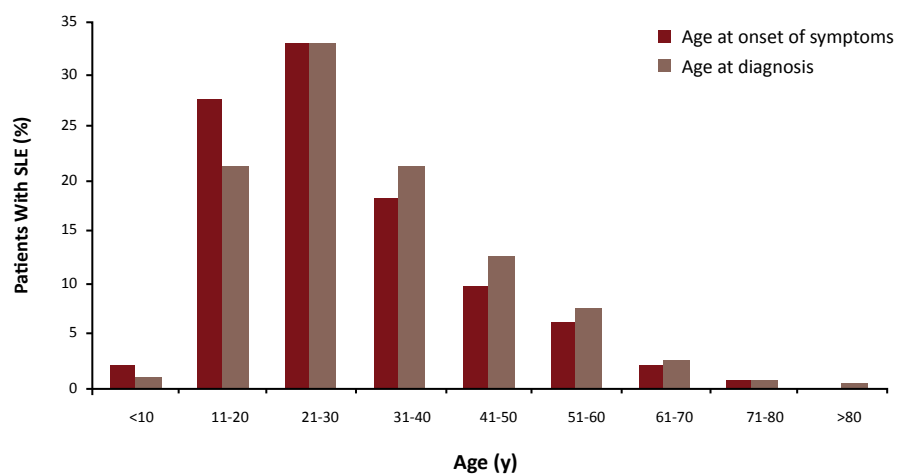
SYSTEMIC LUPUS ERYTHEMATOSUS: A PRIMER FOR MANAGED CARE

APRIL 2012

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 SLE⁶



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

This newsletter was funded and developed by Human Genome Sciences, Inc and The GlaxoSmithKline Group of Companies.

**HUMAN
GENOME
SCIENCES**

gsk
GlaxoSmithKline

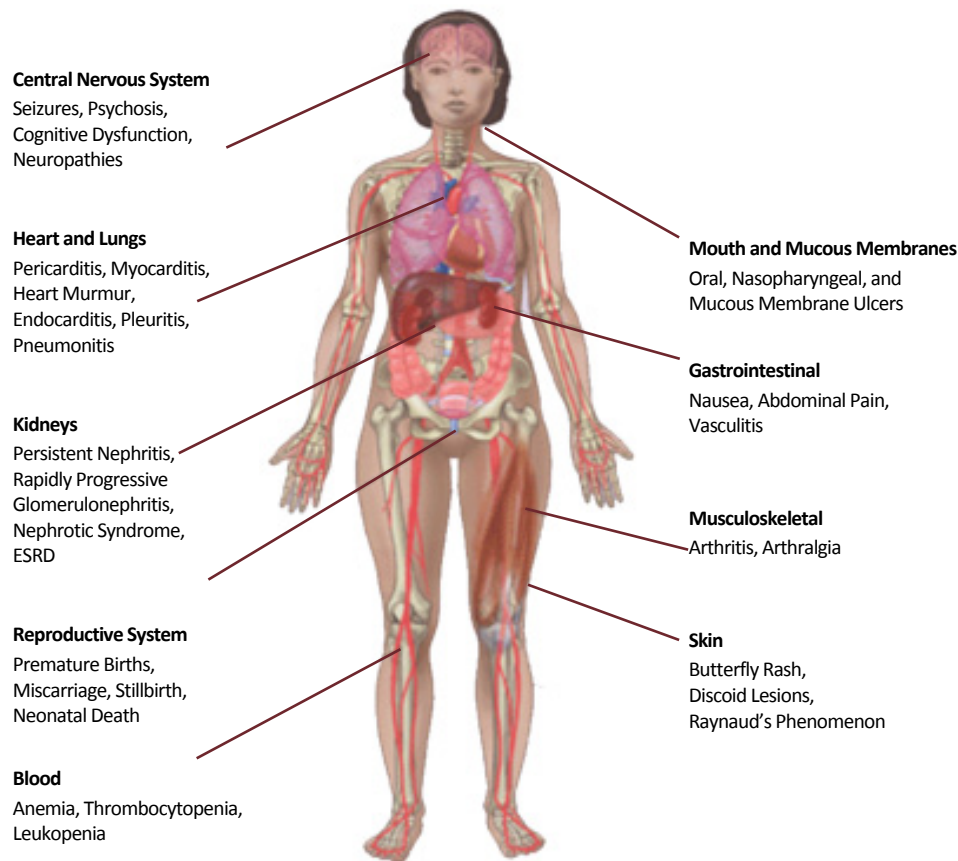
Table 1. Incidence of SLE⁸

Population	Incidence per 100,000 person-years
African American women	9.2
Caucasian women	3.5
African American men	0.7
Caucasian men	0.4

Please visit ajmc.com/sle for the interactive presentation on SLE.



Figure 2. SLE Is a Multisystem Disease^{7,9,10}



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

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 sunlight¹⁶ and medications.^{17,18} Examples of drugs that may be associated with the development of SLE are procainamide, hydrala-

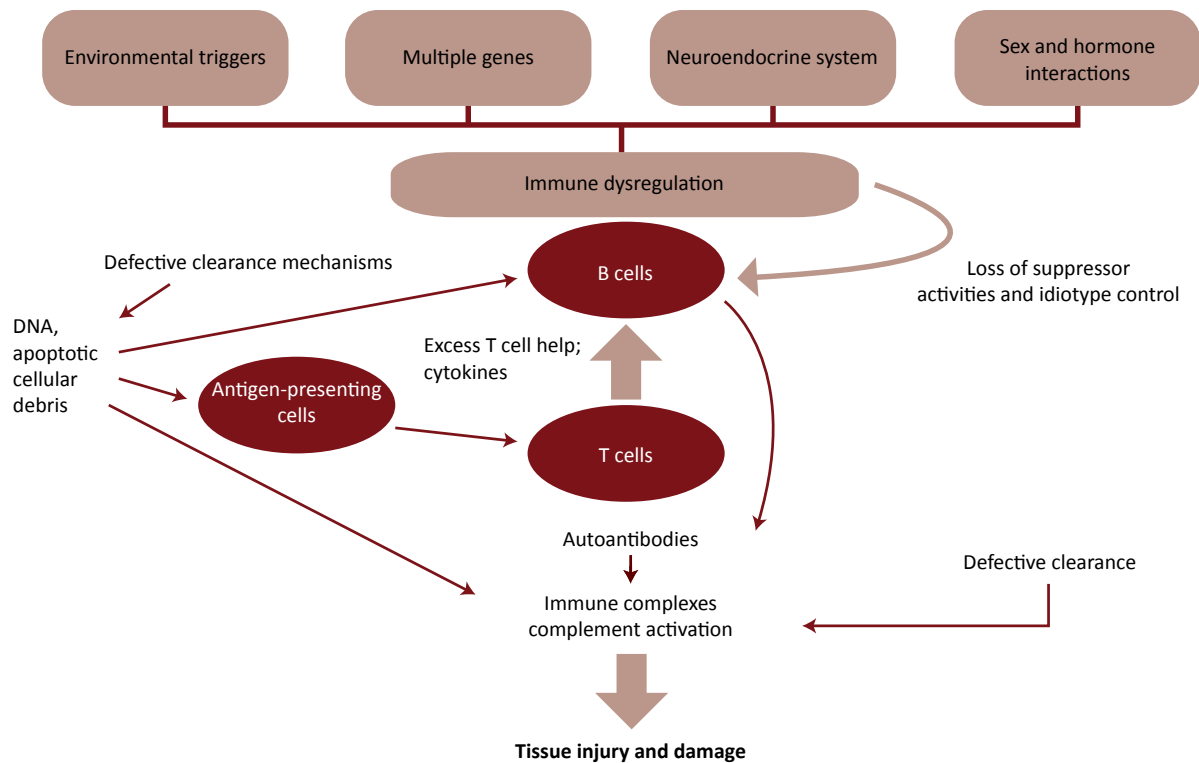
zine, chlorpromazine, isoniazid, phenytoin, and penicillamine.¹⁶

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



Figure 3. Pathogenesis of SLE¹⁶



DNA indicates deoxyribonucleic acid; 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- α , and interferon- α .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

**Table 2. SLE Disease Activity Indices**⁵⁰⁻⁵⁴

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

BILAG indicates British Isles Lupus Assessment Group; SELENA, Safety of Estrogens in Lupus Erythematosus-National Assessment; SLAM, Systemic Lupus Activity Measure; SLAM-R, SLAM-Revised; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLEDAI-2K, SLEDAI 2000.

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.⁴⁸

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).⁶

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)⁴⁹⁻⁵³ and have been validated in numerous international studies.^{50,53,54} At present, these indices are primarily used in clinical trials, although they can be used in the clinical setting.⁵⁶

The assessment of patients with SLE is dependent upon the experience of the physician and is subject to variability between physicians.⁵⁷

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.⁵⁸ 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).⁵⁸ 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 2000.⁵⁸

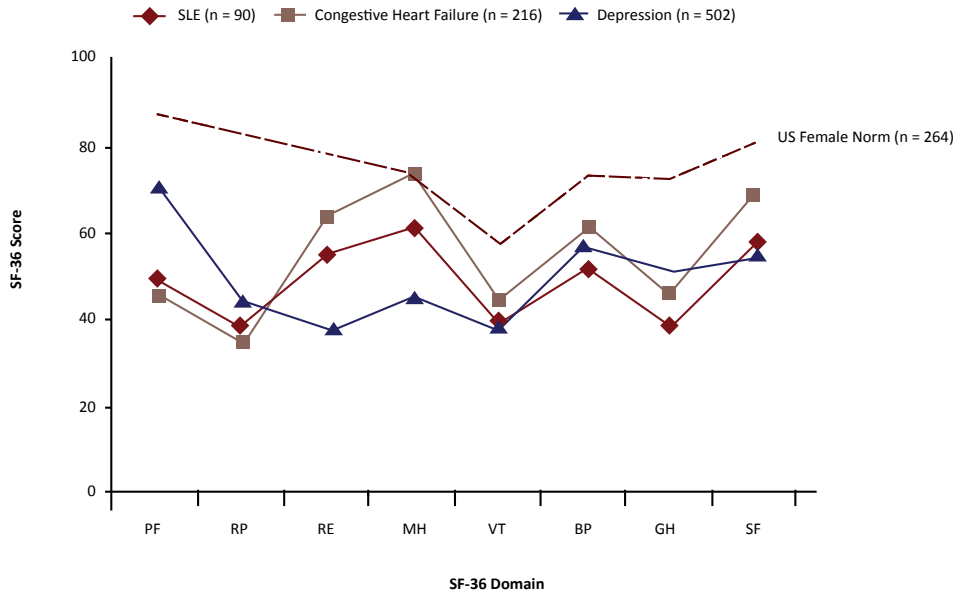
SLE is also associated with substantial morbidity. Urowitz et al conducted an international multicenter cohort study of 298 patients with SLE who were followed for a minimum of 5 years.⁵⁹ Over the 5 years, disease activity decreased (as assessed by the Systemic Lupus Erythematosus Disease Activity Index 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],⁶⁰ 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).⁶¹

Quality of Life

Patients with SLE experience diminished quality of life⁶²; 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.⁶³ 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.⁶⁴ 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



Figure 4. Health-Related Quality of Life in Patients With SLE Is Similar to Congestive Heart Failure and Depression⁶⁵



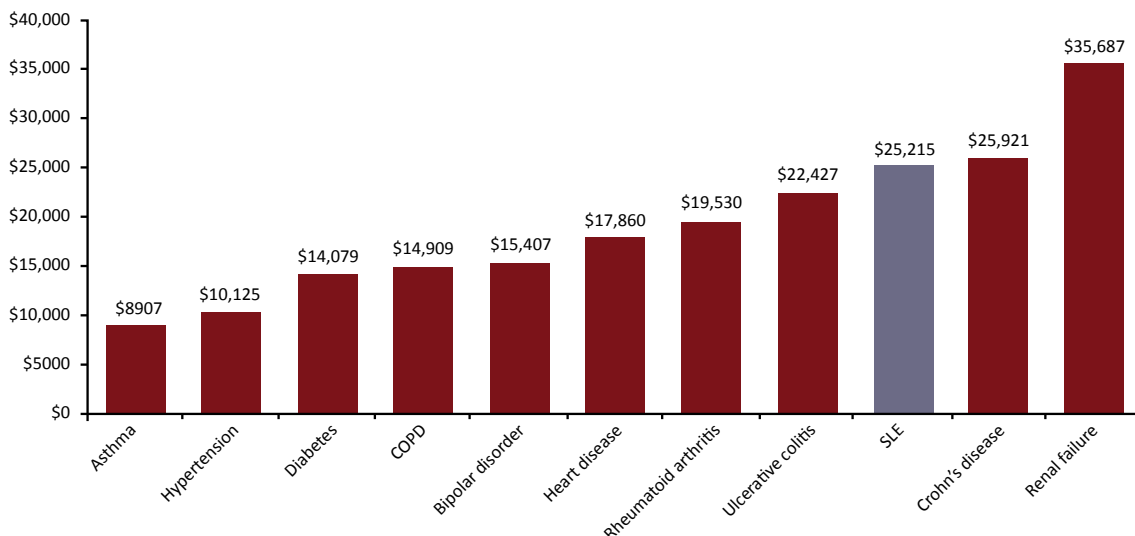
BP indicates bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role-emotional; RP, role-physical; SF, social functioning; SF-36, Short Form-36; VT, vitality.

social support, and disease activity.^{63,64} 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).⁶⁵ 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.^{12,66-68} 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.⁵⁸

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)⁷⁰



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 humanistic, 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

1. Yancey KB, Lawley TJ. Immunologically mediated skin diseases. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. <http://www.accessmedicine.com/content.aspx?aID=9098448>. Accessed January 10, 2012.

2. Costner MI, Sontheimer RD. Lupus erythematosus. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, eds. *Fitzpatrick's Dermatology in General Medicine*. 7th ed. New York: McGraw-Hill; 2008. <http://www.accessmedicine.com/content.aspx?aID=2991998>. Accessed January 10, 2012.

3. Hahn BH. Systemic lupus erythematosus. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw-Hill; 2012. <http://www.accessmedicine.com/content.aspx?aID=9136499>. Accessed January 10, 2012.

4. Mayeaux E Jr. Lupus erythematosus (systemic and cutaneous). In: Usatine RP, Smith MA, Chumley H, Mayeaux E Jr, Tysinger J, eds. *The Color Atlas of Family Medicine*. New York: McGraw-Hill; 2009. <http://www.accessmedicine.com/content.aspx?aID=8208514>. Accessed January 10, 2012.

5. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: part I. *Arthritis Rheum*. 2008;58(1):15-25.

6. Cervera R, Khamashta MA, Font J, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. *Medicine*. 1993;72(2):113-124.

7. Smyth A, Oliveira GH, Lahr BD, Bailey KR, Norby SM, Garovic VD. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol*. 2010;5(11):2060-2068.

8. McCarty DJ, Manzi S, Medsger TA Jr, Ramsey-Goldman R, LaPorte RE, Kwok CK. Incidence of systemic lupus erythematosus: race and gender differences. *Arthritis Rheum*. 1995;38(9):1260-1270.

9. Delafuente JC, Cappuzzo KA. Systemic lupus erythematosus and other collagen-vascular diseases. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. New York, NY: McGraw-Hill; 2008:1431-1445.

10. ACR Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Guidelines for referral and management of systemic lupus erythematosus in adults. *Arthritis Rheum*. 1999;42(9):1785-1796.

11. Chambers SA, Allen E, Rahman A, Isenberg D. Damage and mortality in a group of British patients with systemic lupus erythematosus followed up for over 10 years. *Rheumatology (Oxford)*. 2009;48(6):673-675.

12. Sutcliffe N, Stoll T, Pyke S, Isenberg D. Functional disability and end organ damage in patients with SLE, SLE and Sjogren's syndrome and primary SS. *J Rheumatol*. 1998;25:63-68.

13. Grigor R, Edmonds J, Lewkonja R, Bresnihan B, Hughes GR. Systemic lupus erythematosus: a prospective analysis. *Ann Rheum Dis*. 1978;37(2):121-128.

14. Wallace DJ, Pistiner M, Nessim S, Metzger AL, Klinenberg Jr. Cutaneous lupus erythematosus without systemic lupus erythematosus: clinical and laboratory features. *Semin Arthritis Rheum*. 1992;21(4):221-226.

15. Norris DG, Colón AR, Stickler GB. Systemic lupus erythematosus in children: the complex problems of diagnosis and treatment encountered in 101 such patients at the Mayo Clinic. *Clin Pediatr (Phila)*. 1977;16(9):774-778.

16. Mok CC, Lau CS. Pathogenesis of systemic lupus erythematosus. *J Clin Pathol*. 2003;56(7):481-490.

17. Cameron HA, Ramsay LE. The lupus syndrome induced by hydralazine: a common complication with low dose treatment. *Br Med J (Clin Res Ed)*. 1984;289(6442):410-412.



18. Fritzler MJ, Tan EM. Antibodies to histones in drug-induced and idiopathic lupus erythematosus. *J Clin Invest.* 1978;62(3):560-567.
19. Sequeira JF, Keser G, Greenstein B, et al. Systemic lupus erythematosus: sex hormones in male patients. *Lupus.* 1993;2:315-317.
20. Petri M, Kim MY, Kalunian KC, et al; OC-SELENA Trial. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med.* 2005;353(24):2550-2558.
21. Deapen D, Escalante A, Weinrib L, et al. A revised estimate of twin concordance in systemic lupus erythematosus. *Arthritis Rheum.* 1992;35(3):311-318.
22. Crispin JC, Liossis SNC, Kis-Toth K, et al. Pathogenesis of human systemic lupus erythematosus: recent advances. *Trends Microbiol.* 2010;16(2):47-57.
23. Rahman A, Isenberg DA. Systemic lupus erythematosus (mechanism of disease). *New Engl J Med.* 2008;358(7):929-939.
24. Kono DH, Burlingame RW, Owens DG, et al. Lupus susceptibility loci in New Zealand mice. *Proc Natl Acad Sci U S A.* 1994;91(21):10168-10172.
25. Winchester RJ. Genetic aspects. In: Schur PH, ed. *Clinical Management of Systemic Lupus Erythematosus.* New York, NY: Grune & Stratton; 1983:17-27.
26. Gross J, Dillon S, Mudri S, et al. TACI-Ig neutralizes molecules critical for B cell development and autoimmune disease: impaired B cell maturation in mice lacking BLyS. *Immunity.* 2001;15(2):289-302.
27. Linker-Israeli M, Deans RJ, Wallace DJ, et al. Elevated levels of endogenous IL-6 in systemic lupus erythematosus: a putative role in pathogenesis. *J Immunol.* 1991;147:117-123.
28. Edwards C, Zhou T, Zhang J, et al. Inhibition of superantigen-induced proinflammatory cytokine production and inflammatory arthritis in MRL-lpr/lpr mice by a transcriptional inhibitor of TNF- α . *J Immunol.* 1996;157(4):1758-1772.
29. Brennan D, Yui M, Wuthrich R, Kelley V. Tumor necrosis factor and IL-1 in New Zealand Black/White mice: enhanced gene expression and acceleration of renal injury. *J Immunol.* 1989;143(11):3470-3475.
30. Jacob C, McDevitt H. Tumour necrosis factor- α in murine autoimmune 'lupus' nephritis. *Nature.* 1988;331(6154):356-358.
31. Bengtsson A, Sturfelt G, Truedsson L, et al. Activation of type I interferon system in systemic lupus erythematosus correlates with disease activity but not with antiretroviral antibodies. *Lupus.* 2000;9(9):664-671.
32. Herrmann M, Voll RE, Zoller OM, Hagenhofer M, Ponner BB, Kalden JR. Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. *Arthritis Rheum.* 1998;41(7):1241-1250.
33. Baumann I, Kolowos W, Voll RE, et al. Impaired uptake of apoptotic cells into tingible body macrophages in germinal centers of patients with systemic lupus erythematosus. *Arthritis Rheum.* 2002;46(1):191-201.
34. Davidson A, Diamond B. Autoimmune diseases. *N Engl J Med.* 2001;345(5):340-350.
35. Craxton A, Draves KE, Gruppi A, Clark EA. BAFF regulates B cell survival by downregulating the BH3-only family member Bim via the ERK pathway. *J Exp Med.* 2005;202(10):1363-1374.
36. Lesley R, Xu Y, Kalled SL, et al. Reduced competitiveness of autoantigen-engaged B cells due to increased dependence on BAFF. *Immunity.* 2004;20(4):441-453.
37. Do RK, Hatada E, Lee H, Tourigny MR, Hilbert D, Chen-Kiang S. Attenuation of apoptosis underlies B lymphocyte stimulator enhancement of humoral immune response. *J Exp Med.* 2000;192(7):953-964.
38. Fields ML, Seo SJ, Nish SA, Tsai JH, Caton AJ, Erikson J. The regulation and activation potential of autoreactive B cells. *Immunol Res.* 2003;27(2-3):219-234.
39. Salmon JE, Millard S, Schachter LA, et al. Fc gamma RIIA alleles are heritable risk factors for lupus nephritis in African Americans. *J Clin Invest.* 1996;97:1348-1354.
40. Frank MM, Hamburger MI, Lawley TJ, Kimberly RP, Plotz PH. Defective reticuloendothelial system Fc-receptor function in systemic lupus erythematosus. *N Engl J Med.* 1979;300(10):518-523.
41. Parris TM, Kimberly RP, Inman RD, McDougal JS, Gibofsky A, Christian CL. Defective Fc receptor-mediated function of the mononuclear phagocyte system in lupus nephritis. *Ann Intern Med.* 1982;97(4):526-532.
42. Kimberly RP, Gibofsky A, Salmon JE, Fotino M. Impaired fc-mediated mononuclear phagocyte system clearance in HLA-DR2 and MT1-positive healthy young adults. *J Exp Med.* 1983;157(5):1698-1703.
43. Kimberly RP, Parris TM, Inman RD, McDougal JS. Dynamics of mononuclear phagocyte system Fc receptor function in systemic lupus erythematosus: relation to disease activity and circulating immune complexes. *Clin Exp Immunol.* 1983;51(2):261-268.
44. Font J, Cervera R, Ramos-Casals M, et al. Clusters of clinical and immunologic features in systemic lupus erythematosus: analysis of 600 patients from a single center. *Semin Arthritis Rheum.* 2004;33(4):217-230.
45. Narain S, Richards HB, Satoh M, et al. Diagnostic accuracy for lupus and other systemic autoimmune diseases in the community setting. *Arch Intern Med.* 2004;164(22):2435-2441.
46. Ozbek S, Sert M, Paydas S, Soy M. Delay in the diagnosis of SLE: the importance of arthritis/arthralgia as the initial symptom. *Acta Med Okayama.* 2003;57(4):187-190.
47. Fauschou M, Starklint H, Halberg P, Jacobsen S. Prognostic factors in lupus nephritis: diagnostic and therapeutic delay increases the risk of terminal renal failure. *J Rheumatol.* 2006;33(8):1563-1569.
48. Tan E, Cohen A, Fries J, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982;25:1271-1277.
49. Griffiths B, Mosca M, Gordon C. Assessment of patients with systemic lupus erythematosus and the use of lupus disease activity indices. *Best Pract Res Clin Rheumatol.* 2005;19(5):685-708.
50. Isenberg DA, Rahman A, Allen E, et al. BILAG 2004: development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology.* 2005;44(7):902-906.
51. Buyon JP, Petri M, Kim M, et al. Estrogen/cyclic progesterone replacement is associated with an increased rate of mild/moderate but not severe flares in SLE patients in the SELENA Trial. *Arthritis Rheum.* 2003;48(9)(suppl 1):3659-3660.
52. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol.* 2002;29(2):288-291.



53. Bae SC, Koh HK, Chang DK, Kim MH, Park JK, Kim SY. Reliability and validity of systemic lupus activity measure-revised (SLAM-R) for measuring clinical disease activity in systemic lupus erythematosus. *Lupus*. 2001;10(6):405-409.
54. Gladman DD, Goldsmith CH, Urowitz MB, et al. Crosscultural validation and reliability of 3 disease activity indices in systemic lupus erythematosus. *J Rheumatol*. 1992;19(4):608-611.
55. Bombardier C, Gladman DD, Urowitz MB, et al. Derivation of the SLEDAI: a disease activity index for lupus patients: the Committee on Prognosis Studies in SLE. *Arthritis Rheum*. 1992;35(6):630-640.
56. Bertsias G, Ioannidis JP, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis*. 2008;67(2):195-205.
57. Mosca M, Tani C, Aringer M, et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. *Ann Rheum Dis*. 2010;69(7):1269-1274.
58. Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum*. 2006;54(8):2550-2557.
59. Urowitz MB, Gladman DD, Ibañez D, et al. Evolution of disease burden over five years in a multicenter inception systemic lupus erythematosus cohort. *Arthritis Care Res (Hoboken)*. 2012;64(1):132-137.
60. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum*. 1996;39(3):363-369.
61. Lopez R, Davidson JE, Beeby MD, Egger PJ, Isenberg DA. Lupus disease activity and the risk of subsequent organ damage and mortality in a large lupus cohort [published online ahead of print November 21, 2011]. *Rheumatology (Oxford)*.
62. Abu-Shakra M, Mader R, Langevitz, et al. Quality of life in systemic lupus erythematosus: a controlled study. *J Rheumatol*. 1999;26(2):306-309.
63. Zonana-Nacach A, Roseman JM, McGwin G Jr, et al. Systemic lupus erythematosus in three ethnic groups: VI: factors associated with fatigue within 5 years of criteria diagnosis. *Lupus*. 2000;9(2):101-109.
64. Jump RL, Robinson ME, Armstrong AE, et al. Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support. *J Rheumatol*. 2005;32(9):1699-1705.
65. Jolly M. How does quality of life of patients with systemic lupus erythematosus compare with that of other common chronic illness? *J Rheumatol*. 2005;32(9):1706-1708.
66. Gilboe IM, Kvien TK, Husby G. Health status in systemic lupus erythematosus compared to rheumatoid arthritis and healthy controls. *J Rheumatol*. 1999;26:1694-1700.
67. Burckhardt CS, Archenholtz B, Bjelle A. Quality of life of women with systemic lupus erythematosus: a comparison with women with rheumatoid arthritis. *J Rheumatol*. 1993;20:977-981.
69. McElhone K, Abbott J, Teh LS. A review of health related quality of life in systemic lupus erythematosus. *Lupus*. 2006;15(10):633-643.
69. Wang C, Mayo NE, Fortin PR. The relationship between health related quality of life and disease activity and damage in systemic lupus erythematosus. *J Rheumatol*. 2001;28(3):525-532.
70. Carls G, Li T, Panopalis P, et al. Direct and indirect costs to employers of patients with systemic lupus erythematosus with and without nephritis. *J Occup Environ Med*. 2009;51(4):66-79.
71. Slawsky KA, Fernandes AW, Fufeld L, Manzi S, Goss TF. A structured literature review of the direct costs of adult systemic lupus erythematosus in the US. *Arthritis Care Res (Hoboken)*. 2011;63(9):1224-1232.
72. Lau C, Mak A. The socioeconomic burden of SLE. *Nat Rev Rheumatol*. 2009;5(7):400-404.
73. Clarke AE, Petri M, Manzi S, et al. The systemic lupus erythematosus Tri-nation Study: absence of a link between health resource use and health outcome. *Rheumatology (Oxford)*. 2004;43(8):1016-1024.
74. Panopalis P, Petri M, Manzi S, et al. The systemic lupus erythematosus Tri-Nation study: cumulative indirect costs. *Arthritis Rheum*. 2007;57(1):64-70.
75. Yelin E, Trupin L, Katz P, et al. Work dynamics among persons with systemic lupus erythematosus. *Arthritis Rheum*. 2007;57(1):56-63.