Mortality and causes of death in systemic lupus erythematosus

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Cohort studies of survival in systemic lupus erythematosus (SLE) often have been limited by methodologic problems. In studies of inception cohorts of patients followed since 1980, survival at 5 years has exceeded 90%. These estimates are generally higher than survival estimates from earlier studies, suggesting that short-term survival in SLE has improved. There is less evidence to support major improvements over time in survival after 10 years or more of SLE. Infections, atherosclerotic disease, and active systemic lupus erythematosus or organ damage caused by SLE are the main causes of death in patients with SLE, but the proportion of early deaths caused by active SLE has decreased over time.

Curr Opin Rheumatol 2001, 13:345–351

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Current Opinion in Rheumatology 2001, 13:345–351

Abbreviations

SLE systemic lupus erythematosus

ISSN 1040–8711

Despite improvements in short-term survival, systemic lupus erythematosus (SLE) remains a potentially fatal disease. The most common causes of death include infections, atherosclerotic disease, and active SLE or organ failure resulting from active SLE. Here we review recent studies of mortality and causes of death in SLE, and examine trends in mortality over time and evidence for changes in the principal causes of death.

Cohort studies of survival

Four recent studies have reported survival in cohorts of patients with SLE. Stahl-Hallengren *et al.* [1••] reported survival in a population-based inception cohort of 81 patients with SLE diagnosed between 1981 and 1991 in a region in southern Sweden. Survival at 5 years was 93%, and at 10 years was 83%. Survival did not differ between those diagnosed in 1981 to 1986 and those diagnosed in 1987 to 1991. The median age at diagnosis was 47 years; the relatively old age of this cohort may have contributed to the finding that 76% of deaths were caused by cardiovascular diseases. Peschken and Esdaile [2••] reported survival in a population-based inception cohort of 179 patients with SLE diagnosed between 1980 and 1996 in Manitoba, Canada. Survival at 5 years, 10 years, and 15 years in a group of white and American Indian patients was approximately 97%, 92%, and 87%, respectively. Mok *et al.* [3•] reported 5-year survival of 93% in an inception cohort of 182 patients followed from 1992 to 1999 at a tertiary referral center in Hong Kong, China. In a multicenter study from Argentina that did not examine an inception cohort, survival at 5 years and 10 years was 91% and 85%, respectively [4].

These studies add to a growing list of survival studies in SLE dating from 1955 [5–40] (Table 1). When examining these studies for trends in survival over time, it is important to consider the periods over which patients were recruited and person-years of follow-up were accrued, rather than the date of publication. For example, in many instances, publications in the mid-1980s report the survival experience of cohorts followed since the mid-1950s or 1960s, and reflect treatment practices common in those decades. Several additional factors complicate comparisons among reported survival rates. First, most studies report on cohorts followed at particular clinics or referral centers, and differences in patient selection and referral patterns among centers may confound comparisons of estimates of survival among studies. The few

Table 1. Cohort studies of survival and causes of death in systemic lupus erythematosus

Study	Location	Year started	Year follow-up ended	Community-based or clinic-based	Patients, *n*	Patient deaths, *n*	Survival, %			Cause of death, %		
							5 yr	10 yr	15 yr	SLE	Infection	CVD
Not Inception Cohorts												
Merrell and Shulman [5], 1955	USA	ND	1953	Clinic	99	31	51	ND	ND	ND	ND	ND
Kellum and Haserick [6], 1964	USA	1949	1960	Clinic	299	86	69	54	ND	90	ND	ND
Siegel *et al.* [7], 1969	USA	1955	1968	Community	292	ND	63	ND	ND	ND	ND	ND
Urman and Rothfield [8], 1977	USA	1957	1968	Clinic	209	49	70	63	ND	65	22	ND
Estes and Christian [9], 1971	USA	ND	1969	Clinic	150	53	77	59	ND	73	14	4
Dubois *et al.* [10], 1974	USA	1950	1973	Clinic	491	249	ND	ND	ND	57	14	9
Urowitz *et al.* [11], 1976	Canada	1970	1974	Clinic	81	11	75	63	53	18	36	45
Fries and Holman [12], 1975	USA	1969	1974	Clinic	146	8	95	92	ND	ND	ND	ND
Feinglass *et al.* [13], 1976	USA	ND	1975	Clinic	140	19	94	82	ND	37	21	ND
Urman and Rothfield [8], 1977	USA	1968	1975	Clinic	156	19	93	84	ND	63	16	ND
Lee *et al.* [14], 1977	Canada	1970	1975	Clinic	110	13	91	ND	ND	ND	ND	ND
Ginzler *et al.* [15], Rosner *et al.* [16], 1982	USA	1965	1978	Clinic	1103	222	77	71	ND	33	33	6
Wallace *et al.* [17], 1981	USA	1950	1979	Clinic	609	128	88	79	74	34	21	20
Ballou *et al.* [18], 1982	USA	1960	1979	Clinic	138	ND	77	ND	ND	ND	ND	ND
Halberg *et al.* [19], 1987	Denmark	1965	1983	Clinic	148	39	90	80	ND	33	18	ND
Hashimoto *et al.* [20], 1987	Japan	1955	1985	Clinic	570	77	86	ND	ND	78	22	ND
Swaak *et al.* [21], 1989	Netherlands	1970	1986	Clinic	110	14	94	87	ND	79	7	7
Seleznick and Fries [22], 1991	USA	1970	1982	Clinic	310	51	88	64	ND	ND	ND	ND
Massardo *et al.* [23], 1994	Chile	1970	1991	Clinic	218	48	87	79	ND	79	8	4
Reveille *et al.* [24], 1990	USA	1975	1985	Clinic	389	89	89	83	79	16	47	11
Breban *et al.* [25], 1991	France	1976	1988	Clinic	51	13	86	78	74	7	62	7
Worrall *et al.* [26], 1990	United Kingdom	1978	1989	Clinic	100	13	88	ND	ND	31	15	7
Abu-Shakra *et al.* [27], 1995	Canada	1970	1993	Clinic	665	124	93	85	79	19	32	25
Jacobsen *et al.* [28], 1999	Denmark	1975	1995	Clinic	513	122	91	76	64	29	20	20
Gripenberg and Helve [29], 1991	Finland	1980	1987	Clinic	66	12	98	91	81	67	0	8
Drenkard *et al.* [30], 1994	Mexico	ND	1989	Clinic	658	49	96	92	ND	ND	ND	ND
Cervera *et al.* [31], 1999	Europe	1990	1995	Clinic	1000	45	95	ND	ND	29	29	27
Bellomio *et al.* [4], 2000	Argentina	1990	1998	Clinic	366	44	91	85	ND	32	54	ND
Inception cohorts												
Fessel [32], 1974	USA	1965	1973	Clinic	74	5	ND	90	ND	ND	ND	ND
Michet *et al.* [33], 1985	USA	1950	1979	Community	25	8	76	63	ND	75	13	ND
Ward *et al.* [34,35], 1995	USA	1969	1991	Clinic	408	144	82	71	63	34	22	22
Pistiner *et al.* [36], 1991	USA	1970	1989	Clinic	256	26	97	93	83	34	19	31
Gudmundsson and Steinsson [37], 1990	Iceland	1975	1988	Community	76	17	84	78	ND	12	6	29
Williams *et al.* [38], 1998	USA	1982	ND	Clinic	57	4	92	ND	ND	ND	ND	ND
Jonsson *et al.* [39], 1989*	Sweden	1981	1986	Community	38	ND	97	ND	ND	ND	ND	ND
Uramoto *et al.* [40], 1999	USA	1980	1997	Community	48	ND	93	74	ND	ND	ND	ND
Stahl-Hallengren *et al.* [1], 2000*	Sweden	1981	1991	Community	81	17	93	83	ND	24	6	76
Peschken and Esdaile [2••], 2000	Canada	1980	1996	Community	179	ND	97	92	87	ND	ND	ND
Mok *et al.* [3•], 2000	China	1992	1999	Clinic	182	9	93	ND	ND	33	67	ND

*Same cohort. CVD, cardiovascular disease; ND, no data measured; SLE, systemic lupus erythematosus.

population-based studies are much less susceptible to this problem, but differences among population-based cohorts in ethnic or socioeconomic composition, access to care, and local treatment practices may also complicate comparisons of survival estimates. Second, differences among studies in the inclusion or exclusion criteria used to assemble cohorts, or differences in the demographic composition of the cohorts, may affect survival rates. For example, the lower 10-year survival rate in the Swedish population-based inception cohort than in the Canadian population-based inception cohort may be associated with the age of these cohorts, which was on average 10 years higher in the Swedish group [1••,*2*••]. Third, different studies use different starting points to begin patient follow-up: some use the date of the first SLE-related symptom, some use the date of diagnosis, and some use the date on which American College of Rheumatology classification criteria were first met. If there is a long period between the onset of symptoms and diagnosis, studies that use the date of the first SLE-related symptom as the starting date may report substantially higher survival than studies using the time of diagnosis as the starting date, though there may not have been any difference in patient survival had a similar starting date been used. Fourth, lead time bias may account for an apparent increase in survival over time if patients in more recent studies were diagnosed earlier in the course of their illness as a result of wider availability of more specific serological tests for SLE. Though this factor likely contributed somewhat to increases in survival estimates from the 1950s to the 1980s, it is less likely to have had an impact on survival estimates of cohorts assembled in the 1980s or later. Fifth, studies often fail to report the proportion of patients lost to follow-up at the close of the study. Survival estimates will be spuriously high if a large proportion of unaccounted patients are dead.

Perhaps the most important problem in assessing survival in SLE is that relatively few studies have examined inception cohorts. Studies that do not examine the survival experience of a cohort of patients who each have been followed from the time of diagnosis may underestimate mortality by missing patients who die soon after the onset of SLE, or may overestimate mortality by missing patients with mild disease who are lost to observation soon after diagnosis. Among the 11 studies of ten inception cohorts, survival at 5 years was greater than 90% in all studies of cohorts assembled after 1980 [1••,*2*••, 3•,32–40] (Table 1). These estimates generally were higher than those of inception cohorts followed in earlier years. Fewer studies reported data on survival at 10 years, and evidence of an increase in 10-year survival between cohorts assembled before and after 1980 is less striking.

Three groups have directly examined changes in survival over time in cohorts of patients with SLE. Uramoto *et al.* [40] reported a significant improvement in survival in an inception cohort of patients in Olmsted County, Minnesota, followed from 1980 to 1997, compared with an earlier inception cohort followed from 1950 to 1979. Stahl-Hallengren *et al.* [1••] reported no difference in survival between population-based inception cohorts assembled from 1981 to 1986 and from 1987 to 1991. In a single-center study, Urowitz *et al.* [41] reported marked improvements in survival among patients first evaluated in 1986 to 1994 compared with those first evaluated in 1977 to 1986 or 1970 to 1977, but the absence of inception cohorts and possible changes in patient referral or selection over time complicate the interpretation of these results.

Survival in selected patient subgroups

In the Canadian study by Peschken and Esdaile [*2*••], the likelihood of mortality was 4.6 times higher among American Indians than among whites, demonstrating that ethnic minorities and members of socially disadvantaged groups have poorer survival than members of socially advantaged groups, even in countries with universal access to health care. In a retrospective inception cohort study of 263 patients with SLE, the presence of any permanent organ damage within the first year of SLE as assessed by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index was associated with poorer survival at 10 years (75% *vs* 92% in those with no permanent organ damage) [42].

Among 86 patients with lupus nephritis who participated in a randomized trial of plasmapheresis, survival at 5 years was 95% for those who achieved remission of their nephritis and only 69% for those who did not [43]. In a national study of outcomes of renal transplantation in patients with end-stage renal disease caused by lupus nephritis, Ward [44] reported 1-year and 5-year survival of 94% and 83%, respectively, after cadaveric transplantation, and 99% and 94% after living-related transplantation. Patient survival and graft survival after transplantation did not differ between patients with lupus nephritis and those with other causes of end-stage renal disease.

Causes of death

In almost all studies, the three most commonly reported causes of death are active SLE or associated organ failure, infection, and cardiovascular diseases (Table 1). Examination of trends among these causes of death in patients with SLE is complicated not only by the problems noted, but also by the small number of deaths reported in many studies. In addition, studies that do not examine inception cohorts may provide biased information on causes of death if the likelihood of death from a particular cause varies with the duration of SLE. For example, such studies may underestimate the proportion of deaths

caused by active SLE if such deaths predominantly occur early in SLE. Also, attribution of the cause of death can be difficult without extensive clinical information, and multiple causes may contribute. Nonetheless, it appears that a reduction in early deaths caused by active SLE has occurred, and this reduction accompanies the improved short-term survival in these patients. Among more recent studies of inception cohorts, there is a plurality among SLE, infection, and cardiovascular diseases as the main cause of death.

Active systemic lupus erythematosus or organ failure

Active SLE most commonly causes death because of nephritis, multisystem organ failure, or central nervous system disease. Several characteristics of patients with lupus nephritis are predictive of poor outcome. Among patients in the Hopkins Lupus Cohort, patients who were either hypertensive or poorly compliant with treatment were more likely to develop renal failure [45•]. A study at Duke University revealed that smoking and hypertension were associated with an increased risk of renal failure [46]. Black and Hispanic patients with SLE in the LUMINA (Lupus in Minority Populations, Nature versus Nurture) cohort were at higher risk for renal failure than were white patients [47•]. Laboratory predictors of renal failure include elevated serum creatinine, proteinuria, thrombocytopenia, decreased C3 level, and elevated anti-DNA antibody levels [48–50].

The 5-year survival rate of patients with lupus nephritis has improved considerably since the early 1950s, particularly in patients with World Health Organization class IV lupus nephritis. As reviewed by Cameron [51], 5-year survival in these patients has increased from 55% in the 1970s to 90% currently. The improved survival is most likely the result of better immunosuppressive therapy, improvements in dialysis, and renal transplantation.

Infections

Infections remain an important cause of mortality in patients with SLE (Table 1). Infectious causes of death may be underreported; autopsy studies have shown that most fatal opportunistic infections are not diagnosed before death [52,53]. Risk factors for serious bacterial infections include immunosuppressive treatment with cytotoxic medications or corticosteroids, proteinuria, renal insufficiency, and active SLE [54,55]. Up to 37% of patients treated with cyclophosphamide have been reported to develop a serious infection [54].

Fatal bacterial infections in patients with SLE are most commonly caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, Group D *Streptococcus*, *Klebsiella pneumoniae*, and *Escherichia coli* [35]. *E. coli* is the most common bacterial infection in patients with SLE who are treated with cyclophosphamide [52]. Infections caused by *Salmonella* are also common, and have led to the diagnosis of SLE in some patients [56]. Several studies have reported an increased incidence of mycobacterial infections in SLE [57,58]. The diagnosis of tuberculosis may be delayed in patients with SLE because of a frequently atypical radiographic appearance, including miliary disease and patchy consolidations, rather than cavitation and granulomatous changes. The delayed diagnosis may be associated with higher mortality. The most common sites of fatal infections in patients with SLE are the lung, bladder, and joints. Adult respiratory distress syndrome is a common *pre mortem* event and has a high mortality rate. In a recent study in Korea, the most common cause of adult respiratory distress syndrome in patients with SLE was sepsis caused by gram-negative bacilli [59]. In this study, 68.4% of patients with adult respiratory distress syndrome died, and 32% of all deaths were related to adult respiratory distress syndrome.

Risk factors for opportunistic infections in patients with SLE include high dose corticosteroid treatment, immunosuppressive therapy, and leukopenia [54]. The most common fatal opportunistic pathogens are *Pneumocystis carinii* and *Candida*. In a 12-year study of 233 patients with connective tissue disease hospitalized with *P. carinii* pneumonia (42% of whom had SLE), in-hospital mortality was 45.7% [60]. In another study of 100 patients with SLE treated with cyclophosphamide, three patients were diagnosed with *P. carinii*, and one patient died [54]. Fatal opportunistic infections caused by *Cryptococcus neoformans*, *Nocardia asteroides*, *Coccidioides immitis*, *Toxoplasma gondii*, herpes zoster, and cytomegalovirus also have been reported. Several opportunistic infections can mimic central nervous systemic involvement caused by SLE, including toxoplasmosis, nocardiosis, and cryptococcal meningitis [61,62]. Diagnosis of these infections is often delayed, and mortality is high.

Cardiovascular diseases

Cardiovascular disease resulting from accelerated atherosclerosis is increasingly recognized as an important cause of mortality in patients with SLE, and has been the subject of several reviews [63–66]. A recent study has shown that 13% of patients have atherosclerosis manifesting as angina, myocardial infarction, or peripheral vascular disease [64•]. Autopsy studies reveal that one half of patients had moderate to severe atherosclerosis at the time of death as either an incidental finding or the primary cause of death [27].

Several studies have searched for risk factors for accelerated atherosclerosis in patients with SLE. Of 200 patients studied at State University of New York-Brooklyn, 15% were found to have coronary artery disease, and significant risk factors included hypertension, postmenopausal status, and older age [65]. Risk factors for coronary

artery disease among patients with SLE followed at the University of Pittsburgh included older age, longer disease duration, longer corticosteroid use, hypercholesterolemia, and postmenopausal status [67]. A recent study at the University of Toronto evaluated the influence of hypercholesterolemia on the development of coronary artery disease in patients with SLE [68]. Coronary artery-related events occurred in 3% of patients with normal serum cholesterol levels, 6.4% of those with variable hypercholesterolemia, and 27.8% of those with sustained hypercholesterolemia. Older age, higher cumulative doses of steroids, and lack of prior antimalarial therapy were significant predictors of sustained hypercholesterolemia.

Traditional risk factors alone do not appear to account for the increased risk of cardiovascular disease in patients with SLE. For example, a Canadian study has shown an 8.3-fold increased risk of myocardial infarction in patients with SLE compared with control subjects matched for sex, age, and the presence of hypertension, smoking, diabetes, and hypercholesterolemia [69]. The search for proatherogenic risk factors specifically associated with SLE is continuing. Elevated levels of plasma homocysteine and antiphospholipid antibodies are associated with an elevated risk of atherosclerosis and may have a role [70•]. Elevated plasma homocysteine levels were found in 15% of patients in the Hopkins Lupus Cohort [45•]. Homocysteine has multiple adverse effects on vascular endothelium, including a direct toxic effect. Several studies have shown that the presence of antiphospholipid antibodies in patients with SLE is associated with an increased risk not only of thrombosis but also of atherosclerosis [71,72]. In a national study of patients with end-stage renal disease, patients whose disease was caused by lupus nephritis did not have higher risks of myocardial infarction or stroke than patients with other causes of renal failure, despite being predisposed to atherosclerotic disease by both SLE and renal failure [73]. This finding suggests that the atherosclerotic risk associated with renal failure eclipsed that associated with SLE so that patients with renal failure from any cause had a similar risk of atherosclerotic complications.

Modification of known risk factors for atherosclerotic disease is recommended as a first step to decrease cardiovascular mortality in patients with SLE. Patients with hypercholesterolemia may benefit from minimization of corticosteroid use, modification of diet, and use of antimalarial agents. Limited data exist on the safety and efficacy of lipid lowering agents in patients with SLE. Rheumatologists' management of risk factors for coronary artery disease may be less than optimal. In a recent quality improvement study, rheumatologists limited steroid use, controlled disease activity, and managed hypertension aggressively, but did not consistently treat obesity, smoking, or hyperlipidemia [74].

Conclusions

Further improvement in the survival of patients with SLE will depend on reducing ethnic and socioeconomic disparities in health, improving the balance of the benefits and toxicities of immunosuppressive medications, aggressively treating atherosclerotic risk factors, and understanding better the causes of late mortality.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

1 •• Stahl-Hallengren C, Jonsen A, Nived O, et al.: Incidence studies of systemic lupus erythematosus in southern Sweden: increasing age, decreasing frequency of renal manifestations and good prognosis. J Rheumatol 2000, 27:685–691.
In a population-based inception cohort, 93% of patients survived 5 years, and 83% survived 10 years.

2 •• Peschken CA, Esdaile JM: Systemic lupus erythematosus in North American Indians: a population based study. J Rheumatol 2000, 27:1884–1891.
In a population-based inception cohort in Canada, 97% of patients survived 5 years, 92% survived 10 years, and 87% survived 15 years.

3 • Mok CC, Lee KW, Ho CTK, et al.: A prospective study of survival and prognostic indicators of systemic lupus erythematosus in a southern Chinese population. Rheumatology 2000, 39:399–406.
In this inception cohort study at a referral center, survival at 5 years was 93%.

4 Bellomio V, Spindler A, Lucero E, et al.: Systemic lupus erythematosus: mortality and survival in Argentina: a multicenter study. Lupus 2000, 9:377–381.

5 Merrell M, Shulman LE: Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosus. J Chronic Dis 1955, 1:12–32.

6 Kellum RE, Haserick JR: Systemic lupus erythematosus: a statistical evaluation of mortality based on a consecutive series of 299 patients. Arch Intern Med 1964, 113:200–207.

7 Siegel M, Gwon N, Lee SL, et al.: Survivorship in systemic lupus erythematosus: relation to race and pregnancy. Arthritis Rheum 1969, 12:117–125.

8 Urman JD, Rothfield NF: Corticosteroid treatment in systemic lupus erythematosus: survival studies. JAMA 1977, 238:2272–2276.

9 Estes D, Christian CL: The natural history of systemic lupus erythematosus by prospective analysis. Medicine 1971, 50:85–95.

10 Dubois EL, Wierzchowiecki M, Cox MB, et al.: Duration and death in systemic lupus erythematosus: an analysis of 249 cases. JAMA 1974, 227:1399–1402.

11 Urowitz MB, Bookman AAM, Koehler BE, et al.: The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 1976, 60:221–225.

12 Fries JF, Holman HR: Systemic Lupus Erythematosus: A Clinical Analysis. Philadelphia: WB Saunders; 1975.

13 Feinglass EJ, Arnett FC, Dorsch CA, et al.: Neuropsychiatric manifestations of systemic lupus erythematosus: diagnosis, clinical spectrum, and relation to other features of the disease. Medicine 1976, 55:323–339.

14 Lee P, Urowitz MB, Bookman AAM, et al.: Systemic lupus erythematosus: a review of 110 cases with reference to nephritis, the nervous system, infections, aseptic necrosis and prognosis. Q J Med 1977, 46:1–32.

15 Ginzler EM, Diamond HS, Weiner M, et al.: A multicenter study of outcome in systemic lupus erythematosus. I. Entry variables as predictors of prognosis. Arthritis Rheum 1982, 25:601–611.

16 Rosner S, Ginzler EM, Diamond HS, et al.: A multicenter study of outcome in systemic lupus erythematosus. II. Causes of death. Arthritis Rheum 1982, 25:612–617.

17 Wallace DJ, Podell T, Weiner J, et al.: Systemic lupus erythematosus–survival patterns: experience with 609 patients. JAMA 1981, 245:934–938.

18 Ballou SP, Khan MA, Kushner I: Clinical features of systemic lupus erythematosus: differences related to race and age of onset. Arthritis Rheum 1982, 25:55–60.

19 Halberg P, Alsbjorn B, Trolle-Balslov J, et al.: Systemic lupus erythematosus: follow-up study of 148 patients. I. Classification, clinical and laboratory findings, course and outcome. Clin Rheumatol 1987, 6:13–21.

20 Hashimoto H, Tsuda H, Hirano T, et al.: Differences in clinical and immunologic findings of systemic lupus erythematosus related to age. J Rheumatol 1987, 14:497–501.

21 Swaak AJG, Nossent JC, Bronsveld W, et al.: Systemic lupus erythematosus. I. Outcome and survival: Dutch experience with 110 patients studied prospectively. Ann Rheum Dis 1989, 48:447–454.

22 Seleznick MJ, Fries JF: Variables associated with decreased survival in systemic lupus erythematosus. Semin Arthritis Rheum 1991, 21:73–80.

23 Massardo L, Martinez ME, Jacobelli S, et al.: Survival of Chilean patients with systemic lupus erythematosus. Semin Arthritis Rheum 1994, 24:1–11.

24 Reveille JD, Bartolucci A, Alarcon GS: Prognosis in systemic lupus erythematosus: negative impact of increasing age at onset, black race, and thrombocytopenia, as well as causes of death. Arthritis Rheum 1990, 33:37–48.

25 Breban M, Meyer O, Bourgeois P, et al.: The actual survival rate in systemic lupus erythematosus: study of a 1976 cohort. Clin Rheumatol 1991, 10:283–288.

26 Worrall JG, Snaith ML, Batchelor JR, et al.: SLE: a rheumatological view: analysis of the clinical features, serology and immunogenetics of 100 SLE patients during long-term follow-up. Q J Med 1990, 74:319–330.

27 Abu-Shakra M, Urowitz MB, Gladman DD, et al.: Mortality studies in systemic lupus erythematosus: results from a single center. I. Causes of death. J Rheumatol 1995, 22:1259–1264.

28 Jacobsen S, Petersen J, Ullman S, et al.: Mortality and causes of death of 513 Danish patients with systemic lupus erythematosus. Scand J Rheumatol 1999, 28:75–80.

29 Gripenberg M, Helve T: Outcome of systemic lupus erythematosus: a study of 66 patients over 7 years with special reference to the predictive value of anti-DNA antibody determinations. Scand J Rheumatol 1991, 20:104–109.

30 Drenkard C, Villa AR, Alarcon-Segovia D, et al.: Influence of the antiphospholipid syndrome in the survival of patients with systemic lupus erythematosus. J Rheumatol 1994, 21:1067–1072.

31 Cervera R, Khamashta MA, Font J, et al.: Morbidity and mortality in systemic lupus erythematosus during a 5-year period: a multicenter prospective study of 1000 patients. Medicine 1999, 78:167–175.

32 Fessel WJ: Systemic lupus erythematosus in the community. Arch Intern Med 1974, 134:1027–1035.

33 Michet CJ, McKenna CH, Elveback LR, et al.: Epidemiology of systemic lupus erythematosus and other connective tissue diseases in Rochester, Minnesota, 1950 through 1979. Mayo Clin Proc 1985, 60:105–113.

34 Ward MM, Pyun E, Studenski S: Long-term survival in systemic lupus erythematosus: patient characteristics associated with poorer outcomes. Arthritis Rheum 1995, 38:274–283.

35 Ward MM, Pyun E, Studenski S: Causes of death in systemic lupus erythematosus: long-term follow-up of an inception cohort. Arthritis Rheum 1995, 38:1492–1499.

36 Pistiner M, Wallace DJ, Nessim S, et al.: Lupus erythematosus in the 1980s: a survey of 570 patients. Semin Arthritis Rheum 1991, 21:55–64.

37 Gudmundsson S, Steinsson K: Systemic lupus erythematosus in Iceland 1975 through 1984: A nationwide epidemiological study in an unselected population. J Rheumatol 1990, 17:1162–1167.

38 Williams HJ, Alarcon GS, Neuner R, et al.: Early undifferentiated connective tissue disease. V. An inception cohort 5 years later: disease remissions and changes in diagnoses in well established and undifferentiated connective tissue diseases. J Rheumatol 1998, 25:261–268.

39 Jonsson H, Nived O, Sturfelt G: Outcome in systemic lupus erythematosus: a prospective study of patients from a defined population. Medicine 1989, 68:141–150.

40 Uramoto KM, Michet CJ Jr, Thumboo J, et al.: Trends in the incidence and mortality of systemic lupus erythematosus, 1950–1992. Arthritis Rheum 1999, 42:46–50.

41 Urowitz MB, Gladman DD, Abu-Shakra M, et al.: Mortality studies in systemic lupus erythematosus: results from a single center. III. Improved survival over 24 years. J Rheumatol 1997, 24:1061–1065.

42 Rahman P, Gladman DD, Urowitz MB, et al.: Early damage as measured by the SLICC/ACR damage index is a predictor of mortality in systemic lupus erythematosus. Lupus 2001, 10:93–96.

43 Korbet SM, Lewis EJ, Schwartz MM, et al.: Factors predictive of outcome in severe lupus nephritis. Am J Kidney Dis 2000, 35:904–914.

44 Ward MM: Outcomes of renal transplantation among patients with end-stage renal disease caused by lupus nephritis. Kidney Int 2000, 57:2136–2143.

45 • Petri M: Hopkins Lupus Cohort 1999 update. Rheum Dis Clin North Am 2000, 26:199–213.
A comprehensive clinical review of a large, well-characterized cohort of patients.

46 Ward MM, Studenski S: Clinical prognostic factors in lupus nephritis: the importance of hypertension and smoking. Arch Intern Med 1992, 152:2082–2088.

47 • Alarcon GS, Friedman AW, Straaton KV, et al.: Systemic lupus erythematosus in three ethnic groups. III. A comparison of characteristics early in the natural history of the LUMINA cohort. Lupus 1999, 8:197–209.
Hispanic patients and black patients with SLE have more active disease at an earlier age of onset than white patients, and a less favorable socioeconomic condition predisposes them to a less favorable disease course.

48 Baqi N, Moazami S, Singh A, et al.: Lupus nephritis in children: a longitudinal study of prognostic factors and therapy. J Am Soc Nephrol 1996, 7:924–929.

49 Goulet JR, Mackenzie Y, Levington C, et al.: The long term prognosis of lupus nephritis: the impact of disease activity. J Rheumatol 1993, 20:59–65.

50 Donadio JV, Hart GM, Bergstralh EJ, et al.: Prognostic determinants in lupus nephritis: a long-term clinicopathologic study. Lupus 1995, 4:109–115.

51 Cameron JS: Lupus nephritis. J Am Soc Nephrol 1999,10:413–424.

52 Petri M: Infection in systemic lupus erythematosus. Rheum Dis Clin North Am 1998, 24:423–456.

53 Rubin LA, Urowitz MB, Gladman DD: Mortality in systemic lupus erythematosus: the bimodal pattern revisited. Q J Med 1985, 55:87–98.

54 Pryor BD, Bologna SG, Kahl LE: Risk factors for serious infection during treatment with cyclophosphamide and high-dose corticosteroids for systemic lupus erythematosus. Arthritis Rheum 1996, 39:1475–1482.

55 Yuhara T, Takemura H, Akama T, et al.: Predicting infection in hospitalized patients with systemic lupus erythematosus. Intern Med 1996, 35:629–636.

56 Li EK, Cohen MG, Ho AK, et al.: Salmonella bacteraemia occurring concurrently with the first presentation of systemic lupus erythematosus. Br J Rheumatol 1993, 32:66–67.

57 Victorio-Navarra ST, Dy EE, Arroyo CG, et al.: Tuberculosis among Filipino patients with systemic lupus erythematosus. Semin Arthritis Rheum 1996, 26:628–634.

58 Kim HY, Im JG, Goo JM, et al.: Pulmonary tuberculosis in patients with systemic lupus erythematosus. AJR Am J Roentgenol 1999, 173:1639–1642.

59 Kim WU, Kim SI, Yoo WH, et al.: Adult respiratory distress syndrome in systemic lupus erythematosus: causes and prognostic factors: a single center, retrospective study. Lupus 1999, 8:552–557.

60 Ward MM, Donald F: Pneumocystis carinii pneumonia in patients with connective tissue diseases: the role of hospital experience in diagnosis and mortality. Arthritis Rheum 1999, 42:780–789.

61 Zamir D, Amar M, Groisman G, et al.: Toxoplasma infection in systemic lupus erythematosus mimicking lupus cerebritis. Mayo Clin Proc 1999, 74:575–578.

62 Zimmermann B, Spiegal M, Lally EV: Cryptococcal meningitis in systemic lupus erythematosus. Semin Arthrtis Rheum 1992, 22:18–24.

63 Bruce IN, Galdman DD, Urowtiz MB: Premature atherosclerosis in systemic lupus erythematosus. Rheum Dis Clin North Am 2000, 26:257–278.

64 • Urowitz MB, Gladman DD: How to improve morbidity and mortality in systemic lupus erythematosus. Rheumatology 2000, 39:238–244.
Late morbidity and mortality in SLE are discussed, including atherosclerosis, dementia, bone disease, and fibromyalgia.

65 Aranow C, Ginzler EM: Epidemiology of cardiovascular disease in systemic lupus erythematosus. Lupus 2000, 9:166–169.

66 Manzi S: Systemic lupus erythematosus: a model for atherogenesis? Rheumatology 2000, 39:353–359.

67 Manzi S, Meilahn EN, Rairie JE, et al.: Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham cohort. Am J Epidemiol 1997, 145:408–415.

68 Bruce IN, Urowtiz MB, Gladman DD, et al.: Natural history of hypercholesterolemia in systemic lupus erythematosus. J Rheumatol 1999, 26:2137–2143.

69 Esdaile JM, Abrahamwica M, Grodzicky T, et al.: Myocardial infarction and stroke in SLE: marked increased incidence after controlling for risk factors [abstract]. Arthritis Rheum 1998, 41:S139.

70 Petri M: Detection of coronary artery disease and the role of traditional risk • factors in the Hopkins Lupus cohort. Lupus 2000, 9:170–175.
This study extends the risk factors for coronary artery disease in patients with SLE to elevated homocysteine levels, antiphospholipid antibodies, and renal insufficiency.

71 Hamsten A, Norberg R, Bjorkholm M, et al.: Antibodies to cardiolipin in young survivors of myocardial infarction: an association with recurrent cardiovascular events. Lancet 1986, 1:113–116.

72 Hasunuma Y, Matsuura E, Makita Z, et al.: Involvement of beta2-glycoprotein 1 and anticardiolipin antibodies in oxidatively modified low-density lipoprotein uptake by macrophages. Clin Exp Immunol 1997, 107:569–573.

73 Ward MM: Cardiovascular and cerebrovascular morbidity and mortality among women with end-stage renal disease attributable to lupus nephritis. Am J Kidney Dis 2000, 36:516–525.

74 Bruce IN, Gladman DD, Urowitz MB: Detection and modification of risk factors for coronary artery disease in patients with systemic lupus erythematosus: a quality improvement study. Clin Exp Rheumatol 1998, 16:435–440.