The Systemic Lupus Activity Measure-Revised, the Mexican Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and a Modified SLEDAI-2K Are Adequate Instruments to Measure Disease Activity in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To assess the validity, reliability, and feasibility of the Systemic Lupus Activity Measure-Revised (SLAM-R), the Mexican version of the Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI), and a Modified SLEDAI-2000 (SLEDAI-2K) compared with the SLEDAI-2K in a multiethnic population of patients with SLE.

Methods. We studied 92 SLE patients from 3 US geographic areas (Alabama, Texas, and Puerto Rico). Assessment occurred during regular outpatient, inpatient, or study encounters. A trained physician scored the 4 instruments and also assessed disease activity globally [physician global assessment (PGA)]. Convergent (with SLEDAI-2K) and construct validity (with PGA) were determined by Spearman rank (r_s) correlation test. Level of agreement between the instruments was assessed using Bland-Altman plots. Discriminant validity (distinguishing clearly active vs mildly/nonactive disease) was assessed considering the SLEDAI-2K (and the PGA) as the gold standard. Feasibility was explored by cost analyses.

Results. The SLAM-R, the MEX-SLEDAI, and the Modified SLEDAI-2K were highly correlated with the SLEDAI-2K (r_s = 0.566, 0.755, 0.924, respectively) and with the PGA (r_s = 0.650, 0.540, 0.634, respectively). The 3 instruments showed good agreement with the SLEDAI-2K (Bland-Altman plots). The Modified SLEDAI-2K had better discriminant validity than the SLAM-R and the MEX-SLEDAI. The Modified SLEDAI-2K was the least expensive instrument.

Conclusion. The SLAM-R, the MEX-SLEDAI, and the Modified SLEDAI-2K are adequate options for assessment of SLE disease activity; they are also less costly than the SLEDAI-2K. (J Rheumatol 2004;31:1934–40)

Key Indexing Terms:
DISEASE ACTIVITY SYSTEMIC LUPUS ACTIVITY MEASURE-REVISED
MEXICAN SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX
SLEDAI-2K SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a complex autoimmune disease that affects multiple organ systems with variable severity. It has an unpredictable course, with remissions and relapses occurring over time. Given the broad spectrum of disease manifestations (symptoms, physical findings, and laboratory abnormalities), SLE is difficult to monitor[1,2]. Although experienced clinicians have a good intuitive sense of what disease activity means in SLE and how to assess it[3], a standardized method to quantify it is desirable in clinical and research settings[4-6]. To date, there is no universal agreement about the optimal instrument that should be used to assess disease activity in SLE. Numerous

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attempts have been made to develop indices of disease activity for clinical studies, but few have been extensively tested for their reliability, validity, and responsiveness (i.e., sensitivity to change)[5,7]; for example the British Isles Lupus Assessment Group Index (BILAG) developed in the United Kingdom[8], the European Consensus Lupus Activity Measurement Index (ECLAM) in Continental Europe[9], or the US National Institutes of Health SLE Index System (SIS)[10,11], the Lupus Activity Index (LAI)[12], the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and the Systemic Lupus Activity Measure (SLAM) in North America[13-15] have been shown to share good metric properties and high reliability, validity, and internal consistency[15-18]. The SLAM is considered by some, however, to be less than optimal compared to the SLEDAI because subjective measures (e.g., fatigue, arthralgias) are included; however, these manifestations should only be scored if the evaluator considers they are attributable to SLE disease activity.

The SLAM was first introduced in Boston in 1989[15] and was modified more than 10 years ago, the last version known as SLAM-R (SLAM-Revised)[19,20]. The SLEDAI was succinctly described in 1986[13]; it was modified by the Safety of Estrogen in Lupus Erythematosus National Assessment group (SELENA)[21,22] and has recently been updated by Gladman, *et al*[23]. This latter validated version, referred to as the SLEDAI-2K (for SLEDAI-2000), has proven to be useful in the clinical setting, including its ability to predict mortality[23]. The MEX-SLEDAI is another modification of the SLEDAI[24]; it was developed by Mexican researchers in an effort to diminish the cost of the laboratory tests included in the SLEDAI. Another option is to simply omit from the SLEDAI-2K the immunologic measures (Modified SLEDAI-2K, used here).

These instruments have not previously been formally compared. Further, the MEX-SLEDAI has never been used in non-Hispanic populations. We compared them in terms of their overall metric properties and cost in a multiethnic US patient population with SLE.

MATERIALS AND METHODS

Patients. Ninety-two patients with SLE were studied between August 2002 and June 2003. Patients were recruited from the rheumatology clinics of institutions located in 3 geographic areas in the US: The University of Alabama at Birmingham (UAB), The University of Texas-Houston Health Science Center (UTH), and The University of Puerto Rico Medical Sciences Campus (UPR), according to patient's place of residence. Evaluations took place while patients were hospitalized due to a lupus flare, during a regularly scheduled followup clinic visit, or during a study visit while participating in the LUMINA study (LUpus in MInority populations: NAture versus nurture)[25]. All patients satisfied ≥ 4 of the American College of Rheumatology (ACR) criteria for SLE[26,27]. Obtaining the clinical and laboratory information needed to score these instruments was felt to be part of standard clinical practice and thus a written informed consent was not obtained. No experimental or therapeutic maneuver or intervention was otherwise performed as part of this study.

Measurements. All patients had a face-to-face interview and a physical examination by one of the study physicians during their clinic or research encounters. Laboratory tests were performed the same day in all patients, except for those that were hospitalized, in whom they were obtained within a few days of the interview and physical examination. Laboratory tests included complete blood cell count with differential, Westergren erythrocyte sedimentation rate (ESR), urinalysis, and serum creatinine and immunologic tests (anti-dsDNA by *Crithidia luciliae*[28] and serum complement concentrations).

Instruments. After completion of the interview, physical examination, and laboratory tests, the SLAM-R, the MEX-SLEDAI, the Modified SLEDAI-2K, and the SLEDAI-2K were completed and scored.

The SLAM-R[19] is a standardized, weighted index for the clinical assessment of SLE activity manifestations (categorized as absent or present) and their severity (from 0 to 3 points), covering events occurring within the preceding 4 weeks. The revised version includes 23 clinical manifestations and the same 7 laboratory measures of the original instrument (complete blood count with differential, ESR, creatinine, urinalysis); it has a possible range of 0–81 points. This index does not include immunological tests.

The SLEDAI-2K[23] is the 2002 version of the original SLEDAI, which was developed by the Committee on Prognostic Studies in SLE, and published in detail by Bombardier, *et al* in 1992[13]. This index records disease manifestations occurring within the 10 days preceding the assessment; it contains 24 self-explanatory items for different manifestations using fixed weights (ranging from 1 to 8) with a maximum score of 105. In the original index the variables rash, alopecia, mucous membrane lesions, and proteinuria were counted as active only if they represented their first occurrence or a recurrence (to distinguish them from chronic lesions); in contrast, the 2K version scores the presence of any rash, alopecia, or mucosal ulcers, and a new, recurrent, or persistent proteinuria > 0.5 g/24 h. The Modified SLEDAI-2K was calculated by omitting the immunologic variables from the SLEDAI-2K.

The MEX-SLEDAI was proposed by Guzmán, *et al* in 1992 in an attempt to simplify the SLEDAI and reduce the cost of its application, while preserving the quality of the information obtained[24]. Different weights, as compared to the SLEDAI, were given to various SLE manifestations; some clinical manifestations were added (fatigue, lymphopenia) and others (lupus headache and visual abnormalities) were excluded altogether. This modified score includes 24 specifically defined main variables grouped by target organ, with a maximum score of 32 points. The modifications of the SLEDAI-2K were built into the MEX-SLEDAI [Discussed with Dr. J. Sánchez-Guerrero, Instituto Nacional Ciencias Médicas y Nutrición, Mexico City, August 2002.]

Analyses. Convergent validity was assessed by comparing the total score of the 3 instruments using the Spearman rank correlation test. The physician's global assessment (PGA) of disease activity, assessed on a 10 cm anchored visual analog scale (VAS), was used as a measure of construct validity. Bland-Altman plots[29] were used to assess the level of agreement between these indices; a plot was not obtained for the PGA because of its different scale properties. To assess the sensitivity, specificity, and predictive values (discriminant validity) of the other instruments, the SLEDAI-2K was considered the gold standard; based on the available literature we considered the following cutoff values to distinguish between clearly active versus mildly active/nonactive disease: 7 points for the SLAM-R, 5 for the MEX-SLEDAI, and 6 for the SLEDAI-2K and the Modified SLEDAI-2K[30]. In a second set of calculations, the PGA was used as the gold standard. The differences in costs for the various instruments were assessed as a function of the laboratory expenses as they all required an interview and examination. Thus, the costs for a standard outpatient visit and laboratory studies at one of the 3 centers (UAB) were used for these analyses.

All data were processed with the Statistical Package for the Social Sciences, v. 10.0 for Windows (SPSS, Chicago, IL, USA), except for the Bland-Altman plots that were processed with SAS, v. 8.1 (SAS Institute, Cary, NC, USA). Significance was set at $p \leq 0.05$ in all cases.

RESULTS

Patient characteristics. In total, 92 SLE patients were evaluated, 32 UAB, 26 UTH, and 34 UPR patients. Seven evaluations were completed in hospitalized patients, 43 during regularly scheduled office visits, and 42 were done during LUMINA study visits. Eighty-eight percent of patients were women; 45% were Hispanics, 30% African Americans, 21% Caucasians, and 4% Asians. As shown in Table 1, patients were middle aged and had established disease. The distribution of clinical manifestations at the time the study was performed is shown in Table 1; the definition of these manifestations is noted in the Appendix.

Overall, patients included in these analyses had relatively mild disease activity (Table 2). The SLAM-R scores ranged from 0 to 28, with a median of 6.0; the MEX-SLEDAI scores ranged between 0 and 18 (median 3.0); the Modified SLEDAI-2K scores ranged between 0 and 26 (median 2.0); the SLEDAI-2K scores ranged between 0 and 29 (median 4.0).

Comparison between instruments

Convergent validity. Spearman correlation coefficients between the SLAM-R, the MEX-SLEDAI, the SLEDAI-2K, and the modified SLEDAI-2K were 0.566, 0.595, and 0.555, respectively, whereas between the MEX-SLEDAI and the Modified SLEDAI-2K and the SLEDAI-2K, they were 0.804 and 0.755, respectively ($p \leq 0.0001$ for all comparisons). The correlation between the Modified SLEDAI-2K and the SLEDAI-2K was very high (0.924), but it was only moderate with the PGA (0.634). These data are shown in Table 3.

Construct validity. Correlation coefficients between the SLAM-R, the MEX-SLEDAI, the Modified SLEDAI-2K, and the SLEDAI-2K, with the PGA were: 0.650, 0.540, 0.634, and 0.677, respectively ($p \leq 0.0001$ for all comparisons) (Table 3).

Table 1. Sociodemographic and clinical features of SLE patients.

Feature	Value (n = 92)
Women, %	88
Age, mean (SD) yrs	39.2 (11.8)
Ethnicity, %	
Hispanic*	45
African American	30
Caucasian	21
Asian	4
Disease duration†, mo, mean (SD)	69.4 (68.4)
Clinical manifestations††, %	
Constitutional	79
Mucocutaneous	52
Musculoskeletal	16
Serosal	8
Neuropsychiatric	16
Renal	16
Cardiovascular	25
Gastrointestinal	9
Hematologic	40
Immunologic	30

* From Texas (mainly from Mexican American ancestry) and Puerto Rico. † From date patients met 4 ACR criteria. †† See Appendix for definitions.

Table 2. SLAM-R, MEX-SLEDAI, Modified SLEDAI-2K, SLEDAI-2K, and PGA scores.

Instrument	Value
SLAM-R	
Median	6.0
Range	0–28
MEX-SLEDAI	
Median	3.0
Range	0–18
Modified SLEDAI-2K	
Median	2.0
Range	0–26
SLEDAI-2K	
Median	4.0
Range	0–29
PGA, 0–10cm VAS	
Median	0.9
Range	0–8.4

PGA: physical global assessment; VAS: visual analog scale.

Agreement between the instruments. There was better agreement between the Modified SLEDAI-2K and the SLEDAI-2K, followed by the MEX-SLEDAI and the SLAM-R. The agreement diminished as the scores increased, particularly for the MEX-SLEDAI and the SLAM-R. This can be appreciated in the corresponding Bland-Altman plots shown in Figures 1 to 3.

Discriminant validity. The sensitivity, specificity, and accuracy of the SLAM-R, MEX-SLEDAI, and Modified SLEDAI-2K are shown in Table 4. Not surprisingly, the Modified SLEDAI-2K had the best metric properties, with an overall accuracy of 91% and a moderate sensitivity (76%). Overall, the MEX-SLEDAI had better metric characteristics than the SLAM-R (overall accuracy 84% vs 66%), with the exception of a somewhat higher sensitivity for the SLAM-R than for the MEX-SLEDAI (73% and 58%, respectively).

Costs. Cost analyses are shown in Table 5. Overall, the least expensive instrument was the Modified SLEDAI-2K, followed by the MEX-SLEDAI and the SLAM-R (about 24%, 20%, and 18% less costly than the SLEDAI-2K, respectively). However, when only the laboratory costs are considered, the Modified SLEDAI-2K was about 73% less costly than the SLEDAI-2K, whereas the MEX-SLEDAI and the SLAM-R were about 62% and 53% less expensive than the SLEDAI-2K.

DISCUSSION

Both the SLAM-R and the SLEDAI have proven to be adequate for the assessment of disease activity in patients

Table 3. Comparison between the SLAM-R, MEX-SLEDAI, Modified SLEDAI-2K, SLEDAI-2K, and PGA. Results are expressed as Spearman correlation coefficients.

Instrument	SLAM-R	MEX-SLEDAI	Modified SLEDAI-2K	SLEDAI-2K	PGA
SLAM-R					
r_s	1.000	0.566	0.555	0.595	0.650
p	1.000	< 0.001	< 0.001	< 0.001	< 0.001
MEX-SLEDAI					
r_s	0.566	1.000	0.804	0.755	0.540
p	< 0.001	1.000	< 0.001	< 0.001	< 0.001
Modified SLEDAI-2K					
r_s	0.555	0.804	1.000	0.924	0.634
p	< 0.001	< 0.001	1.000	< 0.001	< 0.001
SLEDAI-2K					
r_s	0.595	0.755	0.924	1.000	0.677
p	< 0.001	< 0.001	< 0.001	1.000	< 0.001
PGA					
r_s	0.650	0.540	0.634	0.677	1.000
p	< 0.001	< 0.001	< 0.001	< 0.001	1.000

PGA: physical global assessment.

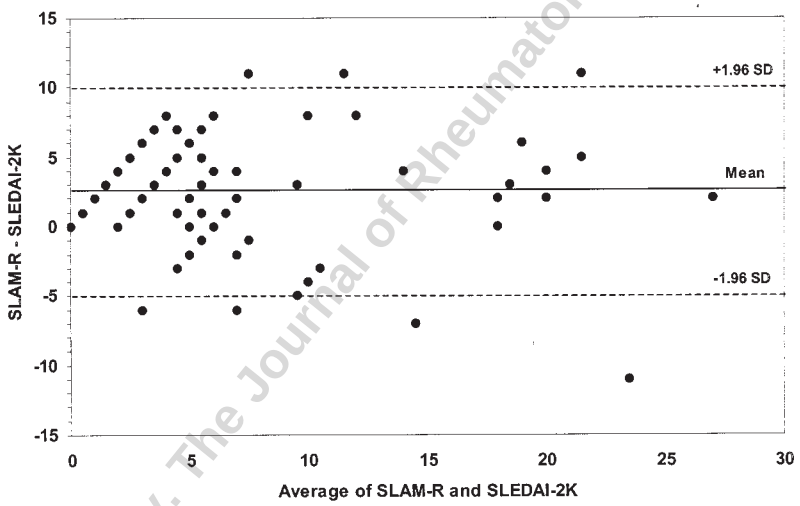

Figure 1. Bland-Altman plots comparing the SLAM-R and the SLEDAI-2K.

with SLE from different countries and ethnic groups[5,15,16,20]. The MEX-SLEDAI has also proven to be adequate for the assessment of disease activity in lupus[31-33], but in contrast with the SLAM-R and SLEDAI-2K, it has been used only in Spanish-speaking countries[34,35]. This is the first time the MEX-SLEDAI has been applied to non-Hispanic patients, and the first time it has been applied using the modifications corresponding to those introduced in the SLEDAI-2K. This is also the first time in which the SLEDAI-2K has been used omitting the immunological measures.

In this study the SLAM-R, the MEX-SLEDAI, and the Modified SLEDAI-2K proved to have adequate convergent validity, as shown by their moderate to high degree of correlation with the SLEDAI-2K; their acceptable construct validity was confirmed by their high correlation with the PGA. The 3 instruments were found to reach a high level of agreement, confirmed by the Bland-Altman plots, although the agreement tended to decrease at higher levels of disease activity (particularly for the MEX-SLEDAI and the SLAM-R).

Our results concur with data from reports describing high degree of correlation between the original SLAM and SLEDAI, and the MEX-SLEDAI and the original SLEDAI[4,15,16,18]. The correlation found between the MEX-SLEDAI and the SLAM-R has not been previously reported. The high degree of correlation between the Modified SLEDAI-2K and the SLEDAI-2K is not surprising, given that the first was computed from the second.

When an objective instrument comprising tangible clin-

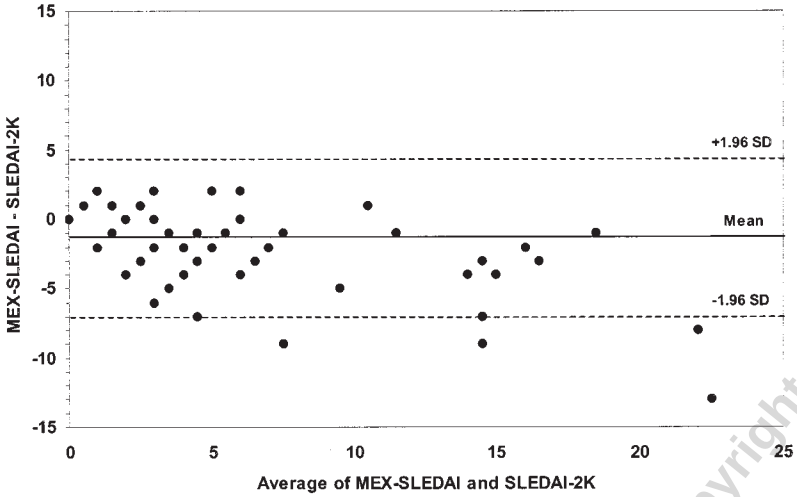

Figure 2. Bland-Altman plots comparing the MEX-SLEDAI and SLEDAI-2K.

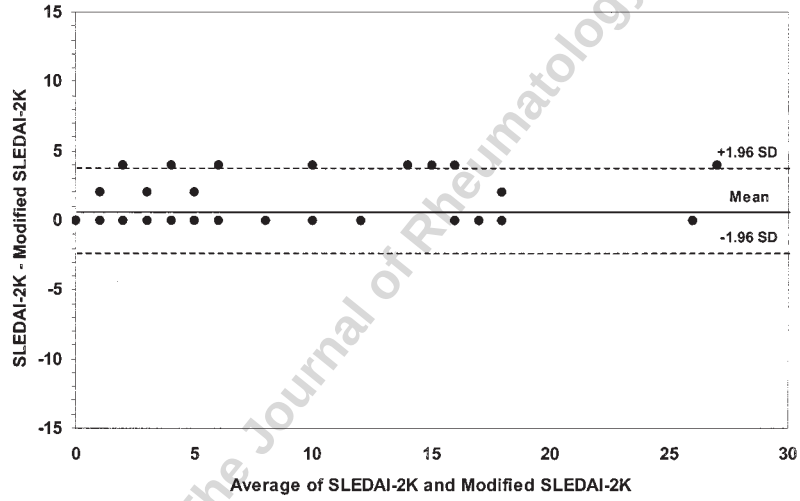

Figure 3. Bland-Altman plots comparing the Modified SLEDAI-2K and SLEDAI-2K.

Table 4. Discriminant validity* of the SLAM-R, the MEX-SLEDAI, and the Modified SLEDAI-2K. The SLEDAI-2K is the gold standard.

Measure, %	SLAM-R	MEX-SLEDAI	Modified SLEDAI-2K
Sensitivity	73	58	76
Specificity	63	93	100
Positive predictive value	52	84	100
Negative predictive value	80	79	88
Overall accuracy	66	84	91

* Between clearly active vs non active/mildly active disease.

ical and laboratory items, such as the SLEDAI-2K, is considered the gold standard, the Modified SLEDAI-2K has overall the best metric properties, with a moderate sensitivity of 76%. The overall metric properties of the MEX-SLEDAI were also quite satisfactory, with the exception of a moderately low sensitivity (58%). In contrast, the SLAM-R did not perform as well in distinguishing patients with active and nonactive disease. When the PGA (considered a more subjective measure of disease activity, possibly subject to bias) was used as the gold standard to calculate the metric properties of all the instruments (a cutoff value of 3.0 points as described by Guzmán, *et al*[24] was used), comparable results were obtained: the MEX-SLEDAI had an overall accuracy of 89%, followed by the Modified SLEDAI-2K (84%), the SLEDAI-2K (77%), and the SLAM-R (63%) (data not shown). This cutoff value corresponds roughly to 1 point in a 0–3 point VAS described by Petri, *et al*[36].

The SLAM-R, the MEX-SLEDAI, and the Modified

Table 5. Cost analyses of the SLAM-R, MEX-SLEDAI, Modified SLEDAI-2K, SLEDAI-2K.

Variable	SLAM-R	MEX-SLEDAI	Modified SLEDAI-2K	SLEDAI-2K
Assessment (in US dollars)				
Physician	146	146	146	146
Laboratory tests	32	26	18	68
Total cost	178	172	164	216
Percentage cost (% savings)*				
Including physician assessment	82 (18)	80 (20)	76 (24)	100
Excluding physician assessment	47 (53)	38 (62)	27 (73)	100

* SLEDAI-2K used as reference.

SLEDAI-2K do not include immunologic laboratory tests (anti-dsDNA antibodies and complement levels). We do not believe this characteristic limits their validity since the association of these variables with activity levels is controversial, being probably more useful in the context of serious organ involvement, e.g., lupus nephritis or hematological activity, than in patients with mildly active or nonactive disease[37-40]. Furthermore, complement levels need to be assayed in freshly obtained serum samples, and this may not be feasible in places that are technologically limited. Even if they are readily available, these tests tend to be expensive. Indeed, if only the laboratory costs are taken into consideration, the 3 instruments were considerably less expensive than the SLEDAI-2K, largely due to the cost of immunologic laboratory tests. It is relevant to consider this issue when choosing an instrument to assess disease activity in both the clinic and research settings, particularly when dealing with disadvantaged populations.

Certain limitations of our study must be noted. Each instrument was applied once and by one physician only; thus, we were not able to determine the inter- and intraobserver reliability (although all the investigators had received training in the use of the 4 instruments) or discriminant validity over time (sensitivity to change). Both the SLAM-R and the original version of the SLEDAI have been shown to have adequate sensitivity to change[17,18,41,42], but data regarding this property for the MEX-SLEDAI are scarce[24]. Of course, no such data exist for the Modified SLEDAI-2K.

The SLAM-R, the MEX-SLEDAI, and the Modified SLEDAI-2K are reasonable alternatives to the SLEDAI-2K for assessment of disease activity in patients with lupus around the world in either clinical or research settings; notably, the Modified SLEDAI-2K showed better metric properties at the lowest cost, and thus it may be the best option of all.

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APPENDIX Clinical manifestations and definitions.

1. Constitutional: Fatigue, fever, significant weight loss (≥ 10% body weight).
2. Mucocutaneous: Malar rash, photosensitivity, oral ulcers, alopecia, discoid lupus.
3. Musculoskeletal: Arthralgias, arthritis, myositis.
4. Serosal: Pleuritis, pericarditis.
5. Neuropsychiatric: Stroke, organic brain syndrome, peripheral or cranial neuropathy, seizures, psychosis, visual abnormalities, lupus headache.
6. Renal: Cellular casts, significant pyuria and/or hematuria, proteinuria, acute elevations of serum creatinine levels.
7. Cardiovascular: Raynaud's phenomenon, hypertension, myocarditis.
8. Gastrointestinal: Peritonitis, pancreatitis, ischemic bowel.
9. Hematological: Hemolytic anemia, leukopenia (< 3000 white blood cells per mm^3), lymphopenia (< 1200 lymphocytes/mm^3), thrombocytopenia (< 150,000 platelets/mm^3).
10. Immunological: High titers of anti-dsDNA antibodies and/or low complement.

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