

# Invasive Fungal Infections in Patients with Systemic Lupus Erythematosus

MARCO ULISES MARTÍNEZ-MARTÍNEZ, DAVID HERRERA-VAN OOSTDAM, SUSANA ROMÁN-ACOSTA, MARTÍN MAGAÑA-AQUINO, LOURDES BARANDA-CÁNDIDO, and CARLOS ABUD-MENDOZA

**ABSTRACT.** *Objective.* Invasive fungal infections (IFI) are catastrophic diseases associated with a high mortality. Relatively few cases of IFI have been described in systemic lupus erythematosus (SLE) and their related factors have not been completely explored. We evaluated factors associated with IFI in patients with SLE.

*Methods.* All patients with both IFI and SLE admitted to our hospital in the last 7 years were evaluated and each was compared with 5 hospitalized patients with SLE (controls). Demographic factors, duration of SLE, and treatment in the previous month were compared.

*Results.* Sixty patients with SLE were evaluated (10 with IFI and 50 controls). Median age was 29 years. High C-reactive protein levels were associated with IFI, along with other factors such as high disease activity, mechanical ventilation, treatment with antibiotics, hemodialysis, high doses of glucocorticoids (GC), and treatment with mycophenolate mofetil. Mortality was 4 times more frequent in patients with IFI than in SLE patients without the deep fungal infection.

*Conclusion.* IFI is a rare infection observed in patients with rheumatic diseases. We describe factors associated with IFI in patients with SLE. IFI is associated with elevated morbidity and mortality. Early diagnosis and treatment are desirable. (First Release June 15 2012; J Rheumatol 2012;39:1814–18; doi:10.3899/jrheum.111498)

*Key Indexing Terms:*

SYSTEMIC LUPUS ERYTHEMATOSUS INFECTIONS INVASIVE FUNGAL INFECTIONS

Infection is a frequent cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE)<sup>1</sup>. Predisposing risk factors for infections in patients with SLE are diverse; they include genetic or acquired immune deficiencies such as defects in phagocytic cell function, lymphopenia, and decreases in the production of some cytokines, immunoglobulins, and in complement levels<sup>2</sup>. Moreover, SLE therapy may increase the risk of infectious processes<sup>1</sup>.

Invasive fungal infection (IFI) is a life-threatening condition occurring most often in patients with hematological malignancy, hematopoietic stem cell transplant recipients, and solid organ transplant recipients<sup>3</sup>. Although predisposing risk factors have been described in these diseases, the character of SLE and its complications related to IFI are not completely understood. We retrospectively analyzed associated factors for the development of deep fungal infections in patients with SLE in our institution over a 7-year period.

---

*From the Regional Unit of Rheumatology and Osteoporosis, Central Hospital "Dr. Ignacio Morones Prieto" and Faculty of Medicine, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México.*

*M.U. Martínez-Martínez, MD; D. Herrera-van Oostdam, MD; S. Román-Acosta, MD; M. Magaña-Aquino, MD; L. Baranda-Cándido, MD; C. Abud-Mendoza, MD, Regional Unit of Rheumatology and Osteoporosis, Central Hospital "Dr. Ignacio Morones Prieto" and Faculty of Medicine, Universidad Autónoma de San Luis Potosí.*

*Address correspondence to Dr. C. Abud-Mendoza, Regional Unit of Rheumatology and Osteoporosis, Central Hospital "Dr. Ignacio Morones Prieto," Av. V. Carranza 2395, San Luis Potosí, S.L.P., México, 78240. E-mail: c\_abud@hotmail.com*

*Accepted for publication April 26, 2012.*

## MATERIALS AND METHODS

*Selection of patients and collection of clinical data.* From the hospital's central discharge register, we identified all patients discharged with a diagnosis of SLE<sup>4</sup> from January 2004 to May 2011. By linking with the register we identified 10 cases of IFI/fungemia among 309 patients admitted with SLE. Fungemia confirmation was based on a positive blood culture for fungi. IFI was deemed a fungal infection at sites other than skin, urine, or mucous membranes (histological diagnosis through biopsy or necropsy)<sup>5</sup>. We included fungemia with IFI because it is included as an invasive fungal disease by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the US National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group.

To identify factors associated with IFI, we performed a case-control study. For each case in which SLE and IFI were confirmed, 5 controls from our SLE cohort were selected. The next 5 hospital admissions with the diagnosis of SLE after 1 case (IFI and SLE) were matched as controls. The clinical data were reviewed and evaluated regarding the 1997 American College of Rheumatology (ACR) revised criteria for the classification of SLE<sup>4,6</sup> and IFI<sup>5</sup>. Cases and controls included men and women; pediatric cases as well as adults were included to evaluate age as a factor related to IFI. Patients were excluded if they did not fulfill the ACR criteria or if they had incorrect diagnosis registrations. Data retrieved from the medical records included age, sex, disease duration, laboratory test results [hematology, creatinine, albumin, C-reactive protein (CRP)], medical events (requiring hemodialysis and mechanical ventilation), disease activity (measured by SELENA-SLEDAI — Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index<sup>7</sup>), and treatment, particularly 1 month prior to fungal infection. These data were obtained at diagnosis of IFI for the cases. Data for the controls were obtained at admission (treatment and medical events included all medications and events received during the selected admission).

*Statistical analysis.* Nonparametric statistical analyses were performed; descriptive data are reported as median and interquartile range. Categorical measurements were compared using chi-squared or Fisher's exact test. All

analyses were performed using SPSS 15.0 (SPSS, Chicago, IL, USA). A level of  $p < 0.05$  was considered statistically significant.

## RESULTS

Ten patients fulfilled the ACR criteria for SLE and IFI<sup>4,6</sup>, then 50 SLE controls without IFI were selected. Characteristics of patients and controls are presented in Table 1. The statistically significant associated factors were requirement of mechanical ventilation, hemodialysis, levels of CRP, complement activity (CH50), and disease activity. Drugs associated with IFI were glucocorticoids (GC) in high doses, antibiotics, and mycophenolate mofetil (MMF). Thirty-five control patients (70%) were admitted for disease activity (18 with lupus nephritis, 11 neuropsychiatric SLE, 4 with hematologic disease activity, and 2 with diffuse alveolar hemorrhage). Fifteen patients were admitted for other causes [4 with pneumonia, 3 for surgical procedures, 2 seizures, 2 bacterial meningitis, 1 cellulitis, 1 diabetic ketoacidosis, 1 azathioprine-related pancytopenia, and 1 with pulmonary tuberculosis]. The distribution of causative organisms were 4 patients infected with

*Candida* spp., 2 *Cryptococcus* spp., 2 *Coccidioides immitis*, 1 patient with histoplasmosis, and 1 with both *Aspergillus* and *Mucor* spp. Patients with *Candida* spp. had disseminated invasive candidiasis; the other 6 patients also had disseminated fungal infections, including at least 1 of central nervous system, lung, liver, blood, and bone marrow (Table 2).

All patients with IFI and 20 (40%) controls received antibiotics; 11 controls (22%) and 2 patients with IFI were diagnosed as having bacterial infections (confirmed through cultures).

Concerning the drugs used to treat SLE in the previous month, doses of prednisone (or its GC equivalent) were higher in patients with IFI than in controls. Five out of 10 patients, and only 22% in the control group, were taking MMF.

IFI contributed to 7 deaths in this series. Only 7 out of 10 patients received antifungal therapy: 6 patients received amphotericin B or its liposome derivative, and the other patient received anidulafungin. Three patients did not receive any specific treatment, because their diagnosis of IFI was made postmortem and identified through necropsy studies.

Table 1. Main characteristics at admission of patients in the study. All data are median (interquartile range) unless otherwise indicated.

Characteristics	Patients with SLE, n = 10	Controls, n = 50	All, n = 60	p
Age, yrs	30.5 (29.75)	28.5 (13.75)	29 (15.25)	0.592
Women, n (%)	7 (70)	41 (82)	48 (80)	0.403
Duration of SLE, mo	27 (188.75)	13.5 (39)	16.5 (51)	0.118
Leukocytes $\times 10^3/\mu\text{l}$	4.1 (4.46)	7.2 (7.02)	6.3 (6.3)	0.059
Lymphocytes $\times 10^3/\mu\text{l}$	0.44 (0.51)	0.73 (0.69)	0.68 (0.70)	0.061
Neutrophils $\times 10^3/\mu\text{l}$	3.8 (4.22)	5.2 (5.84)	5.0 (5.3)	0.108
Hemoglobin, g/dl	9.0 (3.07)	9.5 (3.15)	9.5 (2.95)	0.677
Creatinine, mg/dl	2.8 (3.82)	0.9 (3.25)	1.1 (3.2)	0.190
Albumin, g/dl	2.9 (0.81)	3.0 (0.76)	2.9 (0.74)	0.147
CRP, mg/dl	16.3 (18.5)	1.3 (10.5)	1.7 (11.71)	0.002
CH50 units	10.5 (12.65)	21 (18.63)	20 (18.5)	0.014
Prednisone, n (%)	10 (100)	25 (50)	35 (58.3)	0.003
Prednisone > 0.5 mg/kg/day, n (%)	7 (70)	5 (10)	12 (20)	< 0.001
Cumulative dose of GC, g	2.2 (3.0)	0.1 (3.0)	0.2 (3.0)	0.003
SELENA-SLEDAI	14 (9.5)	8 (6)	8 (7.75)	0.004
DM2, n (%)	1 (10)	2 (4)	3 (5)	0.427
MV, n (%)	8 (80)	11 (22)	19 (31.7)	0.001
Antibiotics, n (%)	10 (100)	20 (40)	30 (50)	0.001
Hemodialysis, n (%)	5 (50)	7 (14)	12 (20)	0.021
Methotrexate, n (%)	3 (30)	12 (24)	15 (25)	0.700
Azathioprine, n (%)	3 (30)	13 (26)	16 (26.7)	1.00
MMF, n (%)	5 (50)	7 (14)	12 (20)	0.021
Antimalarial, n (%)	4 (40)	8 (16)	12 (20)	0.101
Cyclophosphamide, n (%)	3 (30)	8 (16)	11 (18.3)	0.371
Vitamin D, n (%)	3 (30)	10 (20)	13 (21.7)	0.675
Statins, n (%)	8 (80)	29 (58)	37 (61.7)	0.291
Rituximab, n (%)	2 (20)	4 (8)	6 (10)	0.259
mPDN, n (%)	5 (50)	15 (30)	20 (33.3)	0.278
Died, n (%)	7 (70)	9 (18)	16 (26.7)	0.002

SLE: systemic lupus erythematosus; CRP: C-reactive protein; GC: glucocorticoids; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; DM2: type 2 diabetes mellitus; MV: mechanical ventilation; MMF: mycophenolate mofetil; mPDN: pulse methylprednisolone.

Table 2. Clinical features of patients with invasive fungal infections (IFI).

History	Laboratory Tests	Therapy	IFI
Patient 1. Women, 32 yrs, 1 yr duration of SLE, required HD. Hospital admission for LN, fever. SELENA-SLEDAI 19, required MV	Cr: 2.8, WBC: 2.01, Lymps: 0.08, CRP: 16.4 mg/dl, CH50: 12	MMF, PDN 20 mg	Fungi: <i>Coccidioides immitis</i> . Localization: disseminated (necropsy). Tx: none, dead
Patient 2. Man, 16 yrs, duration of SLE 6 yrs, was under HD. Hospital admission: catheter-related fever. SELENA-SLEDAI 3	Cr: 8.09, WBC: 6.15, Lymps: 0.6, CRP: 0.55, CH50: 16	MMF, PDN: 30 mg	Fungi: <i>Candida sp.</i> Localization: blood. Tx: amphotericin
Patient 3. Woman, 29 yrs, duration of SLE 3 yrs. Hospital admission: diabetic ketoacidosis, DAH. SELENA-SLEDAI 10	Cr: 2.84, WBC: 2.4, Lymps: 0.72, CRP: 5.4, CH50: 8	PDN: 30 mg, mPDN, RTX	Fungi: <i>Mucor sp.</i> and <i>Aspergillus sp.</i> Localization: disseminated (necropsy). Tx: none, dead
Patient 4. Women, 27 yrs, duration of SLE 18 mo, required HD. Hospital admission: DAH; required MV, SELENA-SLEDAI 18	Cr: 3.8, WBC: 2.06, Lymps: 0.42, CRP: 24.3, CH50: 10	PDN 30 mg, CMP, mPDN	Fungi: <i>Cryptococcus sp.</i> Localization: disseminated, liver, bone marrow. Tx: amphotericin, dead
Patient 5. Woman, 32 yrs, duration of SLE 4 mo. Hospital admission: fever, pneumonia. Required MV, SELENA-SLEDAI 8	Cr: 0.93, WBC: 4.09, Lymps: 0.04, CRP: 16.25, CH50: 27	PDN 15 mg	Fungi: <i>Candida sp.</i> Localization: blood. Tx: amphotericin, dead
Patient 6. Woman, 51 yrs, duration of SLE 16 yrs. Hospital admission: DAH; Required MV, SELENA-SLEDAI 16	Cr: 2.81, WBC: 6.16, Lymps: 1.8, CRP: 30.5, CH50: 5	MMF, PDN 30 mg, RTX, mPDN	Fungi: <i>Coccidioides immitis</i> . Localization: disseminated (necropsy). Tx: none, dead
Patient 7. Man, 19 yrs, recent diagnosis of SLE because of NPSLE and pancreatitis. After he developed ARF, required HD and MV, SELENA-SLEDAI 18	Cr: 1.1, WBC: 6.16, Lymps: 1.8, CRP: 30.5, CH50: 3	PDN: 60 mg, CPM, mPDN	Fungi: <i>Candida sp.</i> Localization: blood. Tx: anidulafungin, dead
Patient 8. Woman, 22 yrs, new diagnosis of SLE, had LN and NPSLE. Even though had been receiving tx for short time (2 weeks), IFI diagnosed at admission. Required MV, SELENA-SLEDAI 29	Cr: 1.18, WBC: 1.86, Lymps: 0.33, CRP: 10.6, CH50: 4	PDN: 70 mg	Fungi: <i>Cryptococcus sp.</i> Localization: meningeal. Tx: receiving amphotericin
Patient 9. Woman, 51 yrs, duration of SLE 20 yrs. Hospital admission: pneumonia, meningitis. Required MV, SELENA-SLEDAI 12	Cr: 0.51, WBC: 7.54, Lymps: 0.68, CRP: 17.28, CH50: 20	MMF, PDN: 60 mg	Fungi: <i>Histoplasma capsulatum</i> . Localization: meningeal. Tx: amphotericin, dead
Patient 10. Man, 51 yrs, duration of SLE 16 yrs. Had LN, was under HD. Hospital admission: NPSLE. Required MV. SELENA-SLEDAI 9	Cr: 8.12, WBC: 20.7, Lymps: 0.21, CRP: 22, CH50: 11	MMF, PDN: 60 mg, CPM, mPDN	Fungi: <i>Candida sp.</i> Localization: blood. Tx: amphotericin, alive

SLE: systemic lupus erythematosus; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; HD: hemodialysis; LN: lupus nephritis; MV: mechanical ventilation; DAH: diffuse alveolar hemorrhage; ARF: acute renal failure; Cr: creatinine (mg/dl); WBC: leukocytes ( $\times 10^3/\text{mm}^3$ ); Lymps: lymphocytes ( $\times 10^3/\text{mm}^3$ ); CRP: C-reactive protein (mg/dl); CH50: complement activity (units); MMF: mycophenolate mofetil; NPSLE: neuropsychiatric SLE; MTX: methotrexate; AZA: azathioprine; PDN: prednisone (mg/day); CPM: cyclophosphamide; RTX: rituximab; mPDN: methylprednisolone pulse therapy; Tx: treatment.

A high level of CRP was a characteristic of our patients with IFI (Figure 1). We calculated a sensitivity of 74% and specificity of 70% of a CRP level  $> 10$  mg/dl for diagnosing IFI.

## DISCUSSION

Infection rates in patients with SLE appear to be more frequent than observed in other rheumatic diseases such as rheumatoid arthritis, a fact probably related to the distinctive characteristics of SLE such as hypocomplementemia, hypogammaglobulinemia, elevated cytokines, and the use of immunosuppressive therapy<sup>8,9</sup>. Bacterial infections are reported more often than fungal infections in patients with SLE<sup>3,10</sup>. Few case series have described the association between SLE and IFI<sup>3,8</sup>.

Our findings demonstrate that factors associated with IFI are treatment with MMF, antibiotics, high doses of GC, high disease activity, low CH50 levels, mechanical ventilation, and

hemodialysis. Some of these factors are also observed in patients with cancer, where associated factors agree with our findings, such as use of mechanical ventilation, dialysis, corticosteroids, and other immunosuppressive agents<sup>11</sup>.

Up to 90% of patients with SLE require GC for disease control<sup>12</sup>. GC have many complex quantitative and qualitative immunosuppressive effects that induce cellular immunodeficiency and increase host susceptibility to various viral, bacterial, fungal, and parasitic infections<sup>1</sup>. Our study describes the association of high doses of GC and IFI in patients with SLE.

MMF can inhibit B cell and T cell function, and it has been shown to modify dendritic cells and monocyte function. These factors might enhance the risk of infectious complications such as cytomegalovirus and BK virus<sup>13</sup>. Even though this drug is of frequent use in transplantation, and IFI is possible in those patients<sup>14</sup>, there are few studies about the association between MMF and fungal infections.

A high level of CRP is another of our findings. In other

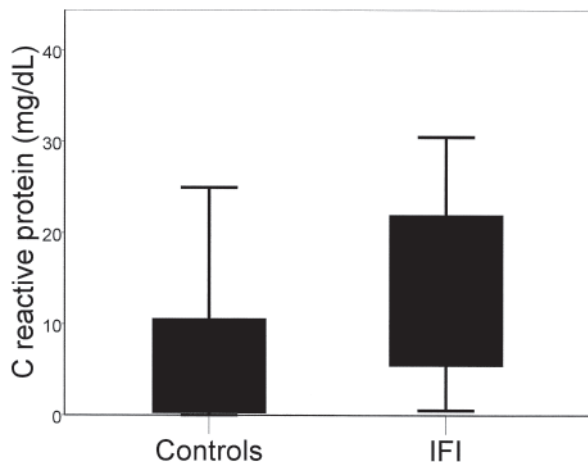


Figure 1. Box plot showing median, quartiles, and extreme values of C-reactive protein. IFI: invasive fungal infections.

studies, CRP has been reported as normal or with only modest elevation in patients with active SLE but without evidence of infection<sup>15</sup>. Moreover, CRP is a sensitive and specific marker for diagnosing bacterial infections in patients with SLE<sup>16</sup>. A level > 10 mg/dl in patients with SLE and the associated factors that we describe should alert rheumatologists to look for IFI.

Experimental studies in animals and observational studies in humans have shown that those treated with statins have a lower risk of sepsis and present more favorable outcome<sup>17,18</sup>. However, our results do not support the benefit of this drug to prevent IFI.

SLE is associated with a 2-fold to 5-fold risk of death compared with the general population; disease activity, infection, and accelerated atherosclerosis represent the main causes of death in SLE<sup>19</sup>. Mortality in our series was extremely high, similar to other studies that showed mortality of 50%<sup>3,20</sup>. IFI may explain the high rate of mortality in our study. We were not able to identify this fatal infection in 3 of our patients, and so they did not receive specific treatment (diagnosis was made through necropsy findings). Three patients also had diffuse alveolar hemorrhage, a condition also independently associated with high mortality<sup>21</sup>. We recognize that it is difficult to separate mortality related to disease activity from IFI itself.

Limitations of our study include that we did not measure the levels of the different components of complement pathways. This is a key factor that has been associated with infection in patients with SLE and immunoglobulin deficiency<sup>22</sup>. Another limitation is the number of patients, making it difficult to perform multivariate analysis. Moreover, management of all our patients included immunosuppressive drug combinations such as MMF and GC. One other limitation is that 10/309 patients may not reflect the true prevalence of IFI because the diagnosis requires biopsies in some cases; autopsies were not performed for all controls.

## REFERENCES

- Atzeni F, Bendtzen K, Bobbio-Pallavicini F, Conti F, Cutolo M, Montecucco C, et al. Infections and treatment of patients with rheumatic diseases. *Clin Exp Rheumatol* 2008;26:S67-73.
- Bouza E, Moya JG, Munoz P. Infections in systemic lupus erythematosus and rheumatoid arthritis. *Infect Dis Clin North Am* 2001;15:335-61, vii.
- Chen HS, Tsai WP, Leu HS, Ho HH, Liou LB. Invasive fungal infection in systemic lupus erythematosus: An analysis of 15 cases and a literature review. *Rheumatology* 2007;46:539-44.
- Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
- De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis* 2008;46:1813-21.
- Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.
- Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med* 2005;353:2550-8.
- Kim HJ, Park YJ, Kim WU, Park SH, Cho CS. Invasive fungal infections in patients with systemic lupus erythematosus: Experience from affiliated hospitals of Catholic University of Korea. *Lupus* 2009;18:661-6.
- Staples PJ, Gerding DN, Decker JL, Gordon RS Jr. Incidence of infection in systemic lupus erythematosus. *Arthritis Rheum* 1974;17:1-10.
- Al-Rayes H, Al-Swailem R, Arfin M, Sobki S, Rizvi S, Tariq M. Systemic lupus erythematosus and infections: A retrospective study in Saudis. *Lupus* 2007;16:755-63.
- Sipsas NV, Kontoyiannis DP. Invasive fungal infections in patients with cancer in the Intensive Care Unit. *Int J Antimicrob Agents* 2012 Feb 13. [E-pub ahead of print]
- Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 2000;43:1801-8.
- Ritter ML, Pirofski L. Mycophenolate mofetil: effects on cellular immune subsets, infectious complications, and antimicrobial activity. *Transpl Infect Dis* 2009;11:290-7.
- Charfeddine K, Zaghden S, Kharrat M, Kamoun K, Jarraya F, Hachicha J. Infectious complications in kidney transplant recipients: A single-center experience. *Transplant Proc* 2005;37:2823-5.
- Firooz N, Albert DA, Wallace DJ, Ishimori M, Berel D, Weisman MH. High-sensitivity C-reactive protein and erythrocyte sedimentation rate in systemic lupus erythematosus. *Lupus* 2011;20:588-97.
- Kim HA, Jeon JY, An JM, Koh BR, Suh CH. C-reactive protein is a more sensitive and specific marker for diagnosing bacterial infections in systemic lupus erythematosus compared to S100A8/A9 and procalcitonin. *J Rheumatol* 2012;39:728-34.
- Sun HY, Singh N. Antimicrobial and immunomodulatory attributes of statins: Relevance in solid-organ transplant recipients. *Clin Infect Dis* 2009;48:745-55.
- Viasus D, Gudiol C, Fernandez-Sabe N, Cabello I, Garcia-Vidal C, Císnal M, et al. Effect of statins on outcomes in immunosuppressed patients with bloodstream infection. *Eur J Clin Microbiol Infect Dis*

- 2011;30:77-82.
19. Ippolito A, Petri M. An update on mortality in systemic lupus erythematosus. *Clin Exp Rheumatol* 2008;26:S72-9.
  20. Weng CT, Lee NY, Liu MF, Weng MY, Wu AB, Chang TW, et al. A retrospective study of catastrophic invasive fungal infections in patients with systemic lupus erythematosus from southern Taiwan. *Lupus* 2010;19:1204-9.
  21. Martinez-Martinez MU, Abud-Mendoza C. Predictors of mortality in diffuse alveolar haemorrhage associated with systemic lupus erythematosus. *Lupus* 2011;20:568-74.
  22. Jesus A, Liphaut B, Silva C, Bando S, Andrade L, Coutinho A, et al. Complement and antibody primary immunodeficiency in juvenile systemic lupus erythematosus patients. *Lupus* 2011;20:1275-84.