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Patterns of Systemic Lupus Erythematosus in the Intensive Care Unit and Causes of Mortality

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Abstract. The aim of this study was to investigate the causes, clinical course and the outcome of critical illnesses requiring emergency admission to the intensive care unit in patients with Systemic Lupus Erythematosus. A retrospective study was conducted at King Abdulaziz University Hospital, Jeddah, in the western region of Saudi Arabia, which included all critically ill patients with Systemic Lupus Erythematosus who were admitted to the intensive care unit over a seven-year period. Their demographic features, causes of intensive care unit admission, duration of intensive care unit hospitalization and outcome were registered and compared statistically. A total of 30 patients were included in this study. The most common causes of admission were abnormal complete blood count (87%), fever (83%), renal involvement (80%), hypertension (60%), infections (53%), lung (50%), mucocutaneous (43%), musculoskeletal (30%), neuropsychiatric (27%), and cardiovascular (23%) involvement. Mortality rate was 40% and was significantly associated with septic shock (P 0.000), lung hemorrhage (P<0.02) and thrombocytopenia (P<0.05). The mortality rate in critically ill Systemic Lupus Erythematosus patients was high. Patients who had septic shock, lung hemorrhage and thrombocytopenia significantly increased the likelihood of dying.

Keywords: Systemic lupus erythematosus, Intensive care unit, Causes of mortality.

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Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem autoimmune disorder that provokes inflammation in various organs of the body. The inflammation is due to the production of antibodies that attack cells of host organs, including the skin, muscles, joints, blood, kidneys, and the brain. The disease persists for life and is characterized by sudden flare-ups, repeated life-threatening infections, mild-to-severe kidney impairments, repeated miscarriages, strokes, and, sometimes, permanent disability and death. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease. These include genetic, racial, hormonal, and environmental factors. The incidence of SLE also varies according to age, sex, and race. Globally, SLE primarily affects younger women; 9 of 10 patients with SLE are females between the ages of 15 and 45 years[1,2].

The disease often begins at menarche and many women with SLE experience sudden flare-ups during specific phases of the menstrual cycle or shortly after delivering a baby[1-3]. Although SLE is not prevalent in men, among patients who have the disease, renal, neurological, hematological and vascular outcomes are more severe in men than in women[4]. The pathogenesis of SLE is insidious and a definitive diagnosis may take up to 10 years, so organ damage is often severe by the time the diagnosis is confirmed.

Estimations of the exact incidence of SLE are variable. Some reports indicate that because of improved diagnostic measures, the incidence of SLE is increasing. For example, in a study covering a span greater than 40 years, Uramoto *et al.*[4] found that the pooled incidence of SLE had more than tripled from 1.51 per 100,000 during 1950 to 1979 to 5.56 per 100,000 during 1980 to 1992. In a recent review of 19 studies published from 1995 to 2000, Ruiz-Irastorza *et al.*[5] reported an even higher incidence rate: 7.3 per 100,000. The frequency of SLE is much higher among first-degree relatives of patients who have either SLE or other autoimmune disorders than among the general population. Many immune disturbances occur in SLE. Antinuclear antibodies (ANAs) are present in the serum in virtually all patients with active SLE, and antibodies to native Double Strand Deoxyribonucleic Acid (dsDNA) are relatively specific for the diagnosis of SLE. SLE is also classified as a Type III hypersensitivity reaction[6].

The major pathophysiological phenomenon in this type of hypersensitivity reaction is the formation of antigen-antibody complexes, called immune complexes. Immune complexes in SLE contain IgM, IgG, and IgA. Deposition of immune complexes is accompanied by the activation of the complement system, the very potent nonspecific defense mechanism involved in inflammation and infection. Complement proteins have a chemotactic affect on neutrophils, drawing these cells to the site of inflammation. In an attempt to eliminate the immune complexes, neutrophils release lysosomal enzymes, which damage local tissues. In SLE, the deposition of the immune complexes and subsequent complement activity initiate pathological changes. Immune complexes have a high affinity for vessel walls and the glomerular basement membrane of the kidneys. The changes caused by their deposition in these areas can progress and cause organ damage in such vital organs as the kidneys, lungs, and heart. Exacerbations in SLE requiring ICU admission may result from acute or persistent disease activity, the side effects of treatment, or both. The disease activity is directly associated with specific organ damage such as cardiovascular and cerebrovascular diseases, pulmonary hypertension, renal failure, and skin lesions.

Method

Study Design, Population and Setting

This was a retrospective study of the intensive care unit (ICU) at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia. The study included all patients with a diagnosis of SLE admitted to the ICU from September 1999 to August 2006. A total of 30 SLE patients out of 4,694 patients were admitted during that period (0.6%).

Data Collection and Statistical Analysis

Diagnosis of SLE was confirmed if the patient fulfilled at least four of the 1982 American Rheumatism Association revised classification criteria[2]. The following clinical and laboratory parameters were registered: demographic features, underlying diseases and associated manifestations of SLE, causes of admission, complete blood count, renal function tests, coagulation and autoimmune profiles, characteristics of lesions on chest radiographs, sites of infection and organisms cultured,

treatments administered during the patient's ICU stay, occurrence of complications, duration of ICU stay and outcome. The cause of ICU admission was defined as the major problem necessitating admission to the ICU. This was determined on the basis of clinical data. Cardiogenic pulmonary oedema is due to poor cardiac performance. Noncardiogenic pulmonary oedema is due to fluid overloading of a noncardiogenic cause. Renal involvement was defined, as urinary excretion of more than 500 mg protein/24 hours, cellular casts not attributable to infection, or abnormal histology on renal biopsy. Abnormal complete blood count was defined as hemolytic anemia or leucopenia ($< 4 \times 10^9$/l) or thrombocytopenia ($< 100 \times 10^9$/l) in the absence of offending drugs. Pneumonia was defined as new and persistent radiographic opacity, positive sputum culture and any three of the following body temperature above 38°C, white blood cell count above 15 × 10/l[4], increased airway secretions, or worsening gas exchange[7]. Acute respiratory distress syndrome (ARDS) was defined in accordance with the American-European Consensus Conference on ARDS[8].

Sepsis and septic shock were defined in accordance with the criteria of Bone and coworkers[9]. Hypertension (patient is known hypertensive or receiving antihypertensive agents or BP > 140/90 mmHg on more than one occasion), neuropsychiatric involvement was defined according to the American College of Rheumatology (ACR) revised criteria[10,11]; neurological involvement (headache, seizures, focal signs, strokes, chorea, aseptic meningitis, parkinsonism, peripheral neuropathy) and psychiatric involvement (depression, mania, delirium, dementia, cognitive difficulties)[10,11] .

Finally, patient outcome was classed as death while the patient was in the ICU or survival to discharge from the ICU.

Data analysis was done using statistical package for Social Sciences Software (SPSS)[12]. Mean ± SD was calculated for quantitative data and proportions for categorical variables. One-way analysis of variance (ANOVA) and 'Student's' *t*-test were used for comparing means of continuous variables. Proportions were compared by Chi-square test and Mantel-Haenszel test, if needed. Multiple logistic regression analysis was performed to test for the independent effect of different variables. Significance level was set at < 0.05 throughout the analysis.

Results

From September 1999 to August 2006, a total of 4,694 patients were admitted to the ICU. Of these, thirty SLE patients were included in the present study. They required 43 ICU admissions. There were 9 patients with more than one admission to the ICU including 5 patients with 2 admissions and 4 patients with 3 admissions. Age range was 9-46 years (24.4 ± 10.3) with a female predominance of 14:1. Their ICU duration was 2-55 days (15.5 ± 11.5). Table 1 shows the major causes of ICU admissions. The most common presentation during their ICU admission was abnormal complete blood count (26 [87%]); anemia was found in 12 patients, thrombocytopenia affected another 12 patients and another 2 patients had leukocytosis. 25 (83%) of the patients were febrile. Renal system involvement was seen in 24 (80%), and hypertension was present among 18 (60%). Infections were the cause of admission in 16 (53%). Respiratory system involvement was 15 (50%), mucocutaneous manifestation was found in 13 (43%), joints involvement in 9 (30%), and neuropsychiatry involvement in 8 (27%). Patients in the cardiogenic category were 7 (23%) and 5 (17%) with coagulopathy in the form of bleeding while 4 (13%) developed recurrent thrombotic episodes. 11 (69%) of infectious causes was pulmonary in origin and 9 (31%) were extra pulmonary (disseminated tuberculosis and septicemia). Respiratory system involvement was in the form of pneumonia with ARDS in 8 patients, lung hemorrhage in 3 patients, confirmed positive pleural effusion culture in 3 patients, and one patient with negative pleural effusion culture. For patients in the neurological category, repeated seizures were the most common cause of admission. Acute stroke (2 infarction and 2 intracranial bleeding) was the underlying diagnosis in 4 patients. Patients with cardiovascular involvement included 5 with pulmonary oedema (2 cardiogenic, 3 noncardiogenic), 1 with pericardial effusion and one with cardiac tamponade. Of those with bleeding diathesis, 3 had lung hemorrhage and 2 had intracranial bleeding (only 1 patient was on anticoagulant). Antinuclear antibodies (ANA) and anti-dsDNA were positive in 97%, and 60%, respectively. The anti-phospholipid antibodies were detected among five patients (17%).

Table 1. Reasons for admission of patients with systemic lupus erythematosus (SLE) to intensive care unit.

System involvement	Total number of patients N (100%)
Hematological system involvement	Yes 26 (87%) No 4 (13%)
Fever	Yes 25 (83%) No 5 (17%)
Renal system involvement	Yes 24 (80%) No 6 (20%)
Hypertension	Yes 18 (60%) No 12 (40%)
Infectious causes	Yes 16 (53%) No 14 (47%)
Respiratory system involvement	Yes 15 (50%) No 15 (50%)
Skin involvement	Yes 13 (43%) No 17 (57%)
Musculoskeletal system involvement	Yes 9 (30%) No 21 (70%)
Neuropsychiatry involvement	Yes 8 (27%) No 22 (73%)
Cardiovascular system involvement	Yes 7 (23%) No 23 (77%)
Bleeding diathesis	Yes 5 (17%) No 25 (83%)
Thrombosis	Yes 4 (13%) No 26 (87%)

As in Table 2, which represents the most common causes of mortality, the mortality rate was high (12 [40%]). Multivariate logistic regression analysis showed that the presence of septic shock, hemorrhagic lung, and thrombocytopenia increased the likelihood of dying and it was statistically significant (P-value 0.00, 0.02, 0.05), whereas other causes of ICU admissions had no influence.

Table 2. Causes of death for patients with systemic lupus erythematosus (SLE) in the intensive care unit and their significance to mortality rate.

Cause of death	Total number of patients N (100%)	Mortality		P-value
		Yes	No	
Total mortality	12 (40%)	12	18	
Septic shock	12 (40%)	10	2	0.00
Lung hemorrhage	3 (10%)	3	0	0.02
Thrombocytopenia	12 (40%)	8	4	0.05
Neuropsychiatry	8 (27%)	5	3	0.1
Respiratory system	15 (50%)	7	8	0.4
Hypertension	18 (60%)	8	10	0.5
Thrombosis	4 (13%)	1	3	0.5
Cardiovascular system	7 (23%)	2	5	0.5
Brain hemorrhage	2 (7%)	1	1	0.7
Renal failure	24 (80%)	10	14	0.7

Discussion

The number of SLE patients who required ICU admission was high 6/1000 compared to that in other studies[1,4,5]. This could be explained firstly by the fact that aggressive SLE is more common in women of reproductive age[1,2], and 93% of our patients were females with an age range of (24 ± 10). Secondly, the majority were non-white patients[1-3]; there were different races in our hospital and most of them were non-Caucasians (Asian and African in origin).

Factors that bring patients with SLE to the ICU; however, differs from those that contribute to mortality. In this study, cytopenia was the highest cause of ICU admissions (87%) of patients whether associated with fever (83%) or not; while some studies support this present study's findings that cytopenia is a leading cause of morbidity[13], other studies did not. Ansell *et al.*[14] found that infection followed by acute renal failure were the most common reasons of ICU admissions, while Thong *et al.*[15] found infection, hypotension due to sepsis and acute respiratory failure were the most common reasons for ICU admission. Fever can be a

sign of disease activity (47%) or as part of an infectious process (53%). Renal involvement (80%) was common among this present study's patients; kidney biopsy was done for half of them (Stages 3 and 4). Renal biopsy confirmed the presence of lupus nephritis, aids classification of SLE nephritis, and guides therapeutic decisions. Table 3 shows The World Health Organization (WHO) classification for lupus nephritis based on light microscopy, electron microscopy, and immunofluorescence findings[16]. Respiratory system infections affected 69% and this finding corroborates the earlier findings of previous studies[14,17,18].

Table 3. International Society of Nephrology 2003 revised classification of SLE nephritis.

Class I	Minimal mesangial	Normal light microscopy findings; abnormal electron microscopy findings
Class II	Mesangial proliferative	Hypercellular on light microscopy
Class III	Focal proliferative	<50% of glomeruli involved
Class IV	Diffuse proliferative	>50% of glomeruli involved; classified segmental or global; aggressively treated
Class V	Membranous	Predominantly nephritic disease
Class VI	Advanced sclerosing	Chronic lesions and sclerosis

ANA and anti-dsDNA titters were within expected percentages.

Although survival rates improved markedly during the past 5 decades, patients with SLE still die at a rate 3 to 5 times that of the general population[1,13,19,20]. A series of studies[21,22] of patients with SLE in general indicated distinct mortality patterns in SLE. Deaths that occurred within 5 years of diagnosis were due to active SLE and infection, whereas, those that occurred more than 5 years after onset were due to atherosclerotic complications, end-organ damage (renal, pulmonary) and treatment side effects. Mortality rate in this study was relatively high (40%) but it was less when compared with other studies (47%)[1,14]. The most important factors that influenced the occurrence of death were septic shock, lung hemorrhage and thrombocytopenia. These were documented by statistical calculations which illustrated significant P-values with the above three factors.

There are some limitations to the present study because of the relatively small number of patients included. Also, the retrospective

design and the study lacks some clinical and laboratory information. Further and larger prospective multicenter trial across the Kingdom of Saudi Arabia is recommended to evaluate the mortality rate and to focus on the role of teamwork (internist, rheumatologist, psychiatrist and specific ICU nursing care) in critically ill SLE patients and their effects in improving the outcome and the quality of patient's life from this serious illness.

Conclusion

The mortality rate in critically ill patients with SLE is high. There were significant causes of mortality in SLE patients admitted to ICU, which were not the most common causes for their ICU admissions.

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ملخص لدراسة وصفية لمرضى الذئبة الحمراء في العناية المركزة

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المستخلص. دراسة الحالات الحرجة بمرضى الذئبة الحمراء والذين تم علاجهم بالعناية المركزة، والبحث عن أهم أسباب الدخول للعناية المركزة، وما إذا كانت هذه الأسباب لها علاقة بزيادة نسبة الوفيات لديهم، أو أن هناك عوامل أخرى أدت إلى ذلك. تمت دراسة الحالات الحرجة بمرضى الذئبة الحمراء والذين تم علاجهم بالعناية المركزة في مستشفى جامعة الملك عبدالعزيز بجدة على مدى سبع سنوات، وتم إحصاء أهم أعراض وعلامات المرض عند دخولهم للعناية المركزة. ونتائج أهم الفحوصات التى أجريت لهم، ونسبة الوفيات لديهم والبحث عن أهم العوامل التي أدت إلى الوفاة ومقارنتها إحصائيًا. تمت دراسة (٣٠) حالة حرجة من حالات الذئبة الحمراء وكانت نسبة النساء (٩٣٪) وأهم أسباب دخولهم للعناية المركزة والمضاعفات التي حدثت لهم أثناء فترة وجودهم، وكانت نسبة الوفيات (٤٠٪)، وأهم الأسباب التي أدت بهم إلى الوفاة صدمة ناتجة عن تسمم الدم، ونزيف رئوي، ونقص الصفائح الدموية (٠,٠٠، ٠,٠٢، ٠,٠٥). ولم تكن هذه الأسباب من أهم أسباب دخولهم للعناية المركزة، بل الأسباب التي أدت إلى دخولهم للعناية المركزة متعددة، ونسبة الوفيات كانت مرتفعة (٤٠٪)، وكانت هناك أسبابًا لها علاقة مهمة بزيادة نسبة الوفيات، وهي تختلف عن أهم الأسباب التي دخلوا بها للعناية المركزة.