INFECTIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

H M L Oh, H H Chng, M L Boey, P H Feng

ABSTRACT

A prospective study was carried out on the occurrence of infections in 28 hospitalised systemic lupus erythematosus (SLE) patients. In 38 episodes of infection, 23 were bacterial (60.5%), 4 were viral (10.6%) and culture negative infections were present in 10 (26.3%). The most common isolated organisms were Staphylococcus aureus (30.4%), Salmonella species (21.7%), Pseudomonas species (13.0%), and Klebsiella species (13.0%). The cure rate was 94.7%. Death occurred in 2 patients. Lupus activity, impaired renal function, and cytotoxic therapy did not predispose to infection.

Keywords: *corticosteroid, immunoglobulins*

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INTRODUCTION

Infection is a frequent cause of morbidity and mortality in patients with SLE. There have been several studies evaluating the bacteriology and risk factors of infection in SLE[1-4]. A recent multicentre evaluation of 1,103 SLE revealed a mortality of 33% from infections[5].

PATIENTS AND METHODS

A prospective study was conducted on all SLE patients admitted to the Department of Medicine IV, Tan Tock Seng Hospital from September 1, 1988 to April 30, 1989. Patients were entered in the study if they had an admission diagnosis of infection or developed any infection during the course of their hospitalisation. All patients fulfilled the revised criteria for the diagnosis of systemic lupus erythematosus[6]. We recorded the demographic data, relevant past medical history, physical findings, laboratory data, hospital course, specific therapy and outcome.

Table I - Patient Characteristics

	No. of Patients (n=28)
Sex : Female : Male	25:3
Race : Chinese	22 (78%)
Malays	3 (11%)
Other races	3 (11%)
Mean age	31 years (range 15-45 years)
Mean duration of SLE	4.22 years (range 0.3-10 years)

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Table II - Sites of infection in SLE

Infections sites	No. of infection (n=38)
Skin and soft tissue	12 (31.6%)
Respiratory tract	11 (28.9%)
Bacteremia	5 (13.2%)
Urinary tract	3 (7.9%)
Gastrointestinal tract	2 (5.3%)
Peritoneum	2 (5.3%)
Bone and joints	2 (5.3%)
Ear	1 (2.6%)

Table III - Causative organisms in 38 episodes of infection in SLE patients

Organisms	No. of episodes	No. of isolates of specified pathogen
Bacteria +	23 (60.5%)	
Staphylococcus aureus		
Methicillin sensitive		6
Methicillin resistant		1
Salmonella species		5
Pseudomonas species		3
Klebsiella species		3
Escherichia coli		2
Proteus species		2
Mycobacterium tuberculosis		2
Others		4
Virus	4 (10.6%)	
Varicella zoster		4
Cytomegalovirus*		1
Protozoa	1 (2.6%)	
Pneumocystis carinii*		1
No Pathogens Isolated	10 (26.3%)	
Total	38	

\+ More than one organism may be isolated from the same anatomical site.

* Cytomegalovirus was isolated together with pneumocystis carinii during an episode of pneumonia.

The diagnosis of infection was established by clinical findings and a positive culture, biopsy or roentgenographic changes. The activity of SLE was assessed by the lupus activity criteria (LACC)[7].

Table IV - Characteristics of SLE patients with low serum immunoglobulins

Age/ Sex	Prior therapy				Total immunoglobulins			Total Urinary Protein (g/day)
	Prednisolone mg/day	MP (g)	CYC mg/day	Aza mg/day	IgG (N=7.6-16.0 g/L)	IgA (N=0.7-3.8 g/L)	IgM (N=0.3-1.6 g/L)	
39/F	12.5	-	75	-	11.65	2.05	0.21	Nil
38/F	7.5	-	-	-	5.65	3.10	0.90	Nil
38/F	20.0	-	1.0g) x 2 iv/mth) doses	-	5.61	0.95	0.09	0.9
31/F	30.0	1gx3	-	100	5.88	1.18	1.21	2.5
19/F	45.0	-	0.8g) x 2 iv/mth) doses	-	4.79	1.97	0.55	0.9
15/F	40.0	1gx3	-	-	5.16	1.16	0.25	1.7
29/F	7.5	-	-	-	6.61	1.58	0.26	2.0
30/F	45.0	-	-	-	15.86	0.09	0.80	Nil

MP : methylprednisolone CYC : cyclophosphamide Aza : azathioprine

Table V - Steroids and immunosuppressive therapy one month prior to admission

Drugs	No. of patients	No. of patients with active SLE disease
Prednisolone	17 (60.7%)	9
Prednisolone + cyclophosphamide*	7 (25%)	3
Prednisolone + methylprednisolone	1 (3.6%)	1
Prednisolone + methylprednisolone + azathioprine	1 (3.6%)	1
None	2 (7.1%)	0
Total	28	

* 4 patients received pulse i/v cyclophosphamide (mean 2.75 doses)
3 patients received oral cyclophosphamide

A patient was reported as having more than one infection simultaneously if each infection involved separate anatomical sites and showed different pathogenic organisms. Multiple pathogens isolated at any one time from a single anatomical site or one pathogen cultured at any one time from several anatomical sites were regarded as one infection only.

Culture negative infections were reported when a diagnosis was established by clinical findings and biopsy or roentgenographic changes with negative culture material. Clinical cure was defined as the disappearance of previously documented signs and symptoms of infection. Relapse was defined as recurrence of infection with an identical organism within 14 days of completion of treatment.

Significance testing between groups was done where applicable with Fisher's exact test.

RESULTS

During the study period, 38 episodes of infection occurred in 28 SLE patients during 30 hospital admissions. There were 25 female and 3 male patients, with a mean age of 31 years (15-45 years) (Table I). Patients with SLE had 180 admissions during the study period. The incidence of infection in SLE patients admitted to the hospital was 16.6%.

In the 38 episodes of infection, bacteria were isolated in 23 (60.5%), 4 were viral (10.6%), and 10 were culture negative (26.3%). Both *cytomegalovirus* and *pneumocystis carinii* were isolated during an episode of pneumonia. This same patient had concurrent *Salmonella* group B bacteraemia[8]. One patient had 4 episodes and 6 patients had 2 episodes of infection each. Five patients had polymicrobial infections.

The skin and soft tissues and respiratory tract were the most common sites of infection (Table II). The bacterial infections were due to gram-positive bacteria, namely *Staphylococcus aureus* (30.4%), and gram-negative bacteria namely *Salmonella* species (21.7%), *Pseudomonas* species (13.0%) and *Klebsiella* species (13.0%) (Table III).

The cure rate was 94.7%. Death occurred in 2 patients. One died from massive gastrointestinal bleed and another from acute pulmonary oedema. There were no relapses of infection.

RISK FACTORS

Total serum immunoglobulins were assayed in 14 patients. One patient had selective IgA deficiency, 7 had either low IgG or IgM levels or both and 6 patients had normal values (Table IV). Six of the patients with low IgG and/or IgM had lupus nephritis. However not all the patients were nephrotic.

Of the 4 patients who had leukopenia (WBC < 4000/mm^3), 2 had herpes zoster, one had herpes zoster and a chronic suppurative otitis media, and another had *Salmonella* group B infection. None of the 4 leukopenic patients were significantly neutropenic (that is absolute neutrophil count < 1,000/ul).

Six patients had serum creatinine more than 180 umol/l and 3 patients had diabetes mellitus. Eighteen patients (64.2%) had a low serum complements levels (CH50) at admission. Those patients with active lupus had a significantly lower level of CH50 compared with those with inactive lupus ($p < 0.05$). Fourteen patients (50%) had active disease at the time of infection (Table V). Of these 14 patients, 10 had bacterial infections, 2 had pulmonary tuberculosis, one had herpes zoster and one had herpes zoster and suppurative otitis media. Nine

Table VI - Prednisolone Dosage and Frequency of Infection

Average prednisolone dose mg/day	No. of infections
0	2 (5.3%)
1 - 10	7 (18.4%)
11 - 20	7 (18.4%)
21 - 30	8 (21.0%)
31 - 40	6 (15.8%)
41 - 60	8 (21.0%)

patients (32.1%) had pulse methylprednisolone, pulse or oral cyclophosphamide or azathioprine one month prior to the onset of infection (Table V). Of the 7 patients treated with cyclophosphamide, only 2 patients had leukopenia. Twelve patients (42.9%), who had been on steroids and immunosuppressive therapy, had quiescent lupus disease at the time of infection. The frequency of infection increased from 5.3% in the absence of steroid therapy to 21% in those on more than 40 mg of prednisolone per day. Twenty-two out of 38 episodes of infection (57.9%) occurred in those receiving more than 20 mg of prednisolone per day (Table VI).

DISCUSSION

The results of this study support the belief that corticosteroid therapy in patients with SLE predisposes to infection. The frequency of infections in this study does not appear to be related to the increasing corticosteroid doses. Ginzler et al and Staples et al, on the other hand, found the infection rate in lupus patients to increase with increasing doses of corticosteroids[1,4]. However, several other studies concluded. That steriod therapy per se was not a major factor in the development of infection[2,9].

Activity of SLE has been found to be a risk factor for infection in some but not all studies[3,10]. In our study, 50% of the patients had active lupus disease at the time of infection.

Immunosuppressive drugs have been used increasingly to treat patients with SLE. This study suggests that the use of pulse methylprednisolone and cytotoxic agents such as cyclophosphamide and azathioprine is not associated with an increased risk of infection in SLE patients. Other studies have suggested an association between the use of pulse methylprednisolone and cytotoxic chemotherapy in SLE patients and the increased risk of infections[11,12].

A low white cell count did not correlate with a risk of infection. The low levels of complement at admission is associated with an increased risk of infection. Ginzler found that uraemia was associated with a marked increase in infection rate[1]. However concomitant high dose steroids could have been responsible for the increased infection rate. Only 6 patients had impaired renal function in this study. The small number of patients and the lack of controls (non-infected SLE population) in this study limit the conclusions that can be drawn.

This study demonstrates the importance of common gram-positive and gram-negative bacterial infections which occurred in 60% of the patients. This is consistent with the findings of the study by Helmann et al[13]. Empiric treatment of a lupus patient with sepsis should include antibiotics effective against both gram-negative and gram-positive organisms especially *Staphylococcus aureus*.

The increased risk of infection may be linked to one or any impairments in the immune response. The immune abnormalities include abnormal leukocyte migration, opsonization, phagocytosis, immune complex clearance and immunoglobulin synthesis. Total immunoglobulins were assayed in 14 patients and 8 were detected to have low levels (one with selective IgA deficiency and seven with low IgG and/or IgM levels). Evaluation of the importance of decreased immunoglobulin levels in infections in lupus patients is therefore indicated.

We conclude that infection in SLE can be serious and life threatening. Lupus activity, impaired renal function and cytotoxic therapy did not appear to predispose SLE patients to an increased risk of infection. A low immunoglobulin level may be a contributing factor to the development of infection. Corticosteroid use especially in high doses has not been identified to be a major risk factor in the development of infection in SLE patients in this study.

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