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SPECTRUM AND OUTCOME OF INFECTIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Infections are responsible for 30% to 50% of the morbidity and mortality in patients with systemic lupus erythematosus (SLE), and have often been cited as the primary cause of death (34% to 66%).¹ This is due to impaired neutrophil, macrophage, T-cell and splenic function, complement abnormalities and defective humoral immunity.¹ The risk factors for infection in SLE include active lupus, renal insufficiency, proteinuria, low albumin, use of corticosteroid and immunosuppressive agent.²

This study describes the spectrum of infections in SLE and their association with the use of common immunosuppressants like corticosteroids and azathioprine.

All patients fulfilling the diagnostic criteria of systemic lupus erythematosus³ who were admitted to The Aga Khan University Hospital, a tertiary care referral center in Karachi, Pakistan, from January 1992 to January 2002 were included in this observational study.

Over a period of 10 years, 80 admissions (23.8%) were for management of 96 episodes of infections in 69 patients. There were 67 females and 2 males with a mean age of 30.9 years (range 8-65 years). The mean duration of lupus in these patients was 41.7 months (SD ± 57.84). Infections were diagnosed on the basis of clinical presentation, laboratory tests, and cultures of blood, urine, cerebrospinal fluid and other relevant samples and supported by radiological investigations. The mean duration of hospital stay for management of infection was 5.16 days (SD ± 5.24, range 1-25 days). Eleven patients (15.94%) had polymicrobial infections, and infections involving more than one site. The sites of infection are shown in Table I.

Bacterial infections accounted for more than 50% of all infectious episodes. *Staphylococcus (S.) aureus* was the commonest organism isolated, followed by *Escherichia coli* and *Klebsiella* spp. Four patients developed tuberculosis while receiving 10-30 mg/day of prednisolone; one had also received pulse therapy with methylprednisolone 3 months before developing TB.

Sepsis due to *Candida albicans* (3) and *Aspergillus flavus* (1) was seen in patients receiving 40-60 mg/day of prednisolone. These patients also had coexisting diabetes mellitus and renal failure; 2 out of 4 patients with fungal infections recovered.

Three patients had enteric fever and one had *Salmonella typhimurium* gastroenteritis. All were on 5-10mg of prednisolone per day for ≥ 2 months. Two of these patients were on azathioprine 100 mg/day for ≥ 6 months in addition to prednisolone.

The white blood cell count (WBC) was recorded for 12 patients out of 14 who were not on immunosuppressive therapy within three months of development of infection. The mean WBC count before admission was 6005/mm³, SD ± 1747, and at the onset of infection was 11,075/mm³, SD ± 8227 (mean difference 5070, SD ± 7610, C.I. 234.27-9905.73, p-value: 0.04, paired t-test).

Fourteen patients had leucopenia on admission (total white cell count <4000/mm³). Of these 2 had Herpes zoster, 2 had malaria, 2 had cholera, and 2 had *S. aureus* skin infection. Two patients had sepsis with *Candida* and BHS group A each. One patient was significantly leucopenic (WBC<1000mm³) with WBC count of 700/mm³ and absolute neutrophil count (ANC) of 343/mm³. This patient had meningitis with cerebrospinal fluid cultures positive for *Aspergillus flavus*.

The ESR was recorded only for 8 patients within the three months prior to admission. A significant difference was found in mean ESR before (30 mm/hr SD ± 13.0) and at the onset of infection in patients when the value was available for comparison (91.13, SD ± 40.25, mean difference 54.88, C.I. 21.21-88.54, p-value: 0.006).

In 55 out of 80 admissions (68.75%), patients were on steroid (oral prednisolone) therapy. The mean duration of steroid use was 3.38 months (SD ± 2.23). The maximum number of admissions for infections was seen in patients taking steroids for less than 6 months, 33/80 (41.25 %).

No significant association was found between the steroid dosage and number of admissions for infection. A significant association was found between steroids dose and duration of admission for infections; patients on higher doses of prednisolone (30-60mg per day) had significantly longer length of hospital stay as opposed to patients taking less than 30mg prednisolone per day (p-value 0.049 by one way ANOVA).

The mean duration of azathioprine therapy was 4.96 months (SD ± 1.96). The maximum number of admissions for

Table I: Sites of infection in SLE patients.

Infection sites	Number of infections (96)
Lungs and pleura	24
Skin and soft tissues	17
Sepsis/Bacteremia	16
Urinary tract	15
Gastrointestinal tract	8
Bone and joints	8
Central nervous system /meninges	6
Throat and ear	1
Endometrium	1

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infections was seen in patients taking azathioprine for less than 6 months (13/80, 16.25%) and 2 each for patients on therapy for 6-12 and 12-24 months.

No correlation was found between infection and dose and duration of azathioprine.

Fourteen patients (20.28%) were not on any immunosuppressive agents at the time of admission for infection.

Thirteen out of 69 patients (18.84 %) died during the course of infection. The rest were discharged home on appropriate antimicrobial therapy.

Most infections in the study patients were due to common bacteria like *Escherichia coli* and *Staphylococcus aureus*. However, some cases of tuberculosis, malaria, salmonellosis and cholera were also seen. Increased incidence of salmonellosis has been described in SLE⁵ and infections by non-typhoidal *Salmonella* occur mainly in those SLE patients who have lower levels of complement, splenic dysfunction and those receiving immunosuppressive therapy.⁶ Mycobacteria, esp. *M. tuberculosis* are important opportunistic infections in SLE patients, particularly in endemic countries.⁷ Serious mycobacterial infection necessitating hospitalization occurred in 4 patients and was caused exclusively by *Mycobacterium tuberculosis*, a reflection of disease endemicity.

Fungal infections occur frequently in SLE patients receiving high doses of corticosteroids or immunosuppressive therapy.⁸ Fungal infections accounted for 4% of all infectious episodes in our patients. *Aspergillus flavus* meningitis, a rare infection, was seen in a patient who was neutropenic and on high doses of corticosteroids. Herpes zoster, the most frequent viral infection reported in SLE^{8,9} occurs mainly in patients with previous histories of nephritis, hemolytic anemia, thrombocytopenia, and previous use of cyclophosphamide.¹⁰ Localized zoster accounted for 3% of all infections in our study. It has been described to occur during periods of disease quiescence and in patients receiving 20mg or less of prednisone per day¹⁰ as was seen in this study.

Parasitic infections, which have been described in SLE, include encephalitis caused by *Toxoplasma gondii* and disseminated strongyloidiasis and leishmaniasis.⁹ Three percent of all infections in the present series were due to parasites, which are generally not considered opportunistic, again suggesting local prevalence rather than profound disease-induced immunosuppression as the predominant factor.

The use of corticosteroids has been associated with increased occurrence of infections in patients with SLE.^{4,9} It is not clear, however, whether this risk relates to doses larger than 10 mg per day, incremental doses of corticosteroids, or the use of the intravenous route.⁴ Corticosteroids may not be "all bad" in terms of their effects on immune function in SLE.¹ Corticosteroids, by suppressing abnormally functioning cells, may actually improve the function of the rest of immune system. The dual role of corticosteroid treatment may explain why most studies have not found an adverse effect of

methylprednisolone pulse therapy on the risk for infection.¹ The role of azathioprine in predisposing to infection also remains unclear.

The outcome of infections in these patients was generally favorable and a significant majority (81.15%) was sent home after initial in-hospital management of their infection. Serious infections developed in patients with SLE of more than 3 years duration, most of whom were not taking more than 10mg/day of prednisolone for less than 6 months. Only a few patients were on concomitant high dose azathioprine. These observations suggest that in these patients, infections developed most likely as a consequence of immune abnormalities due to the disease itself with only a minor contribution from concomitant use of routine immunosuppressants used to control the disease. Use of higher doses of steroids did not appear to predispose to infections requiring hospitalization but did increase the length of hospital stay. Increased predisposition to infection was not seen in patients on high doses of azathioprine.

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