EXTENDED REPORT

Critical illness in systemic lupus erythematosus and the antiphospholipid syndrome

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Ann Rheum Dis 2002;**61**:414–421

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Accepted
7 December 2001

Systemic lupus erythematosus (SLE) is a chronic multi-system autoimmune disorder of unknown cause affecting mainly women of childbearing age. Recent data show that survival has increased¹ and this may be attributed to improved outpatient management of the disease and its complications. Prognosis is worse in patients with certain clinical characteristics, including renal disease,² neuropsychiatric features,³ and hypertension.⁴ Patients with SLE who have the antiphospholipid or Hughes' syndrome (APS) have been documented as having increased mortality rates independent of other variables.⁵

The outcome of critical illness in SLE and APS requiring intensive care unit (ICU) admission, however, is not well established. One report examined presenting features, prognostic factors, and outcome associated with the ICU. That retrospective study examined 30 patients in two South African teaching hospital ICUs between 1982 and 1993.⁶ Admissions were multifactorial and the prognosis poor, with a 53% ICU mortality. The presence of renal disease was the only preadmission factor predictive of a worse outcome. The effect of APS was not determined. We report the demographic, clinical, and laboratory features and outcome of 76 emergency admissions to the ICU by 61 patients with SLE and APS, in a specialist centre over a 15 year period from 1984 to 1998.

Objectives: To investigate the causes, course, and outcome of critical illness requiring emergency admission to the intensive care unit (ICU) in patients with systemic lupus erythematosus (SLE) or the antiphospholipid syndrome (APS), or both.

Methods: Critically ill patients with SLE or APS, or both, admitted to a London teaching hospital ICU over a 15 year period were studied. Demographic, diagnostic, physiological, laboratory, and survival data were analysed. Kaplan-Meier survival curves were constructed by age, time from first diagnosis of SLE, and time from first ICU admission. The log rank test and a backwards stepwise Cox regression were used to identify factors associated with reduced survival.

Results: Sixty one patients with SLE alone (39%) and/or APS (61%) required 76 emergency admissions to the ICU. Patients had high severity of illness scores (median APACHE II 22 (range 8–45)) and multiorgan dysfunction. The primary diagnoses for patients admitted were infection in 31/76 (41%), renal disease in 16/76 (21%), cardiovascular disease in 12/76 (16%), and coagulopathies in 11/76 (14%). The commonest secondary diagnosis was renal dysfunction (49%). Factors associated with an increased risk of death were cyclophosphamide before admission, low white cell count, and high severity of illness score. Before adjustment for these factors renal disease had a strong adverse effect on long term survival (analysis by age at diagnosis $p=0.005$, analysis by time since first ICU admission, $p=0.07$). After adjustment, infection at admission to ICU was associated with an increased ICU mortality ($p=0.02$) and was the cause of death in 13/17 patients who died in the ICU. Similarly, after adjustment, APS was associated with reduced ICU survival ($p=0.1$) and reduced long term ($p=0.03$) survival. Seventeen patients (28%) died in the ICU, and 31 patients (51%) had died by the last follow up. Median time from ICU admission to death was four years. Overall five year survival from the first ICU admission was 43%.

Conclusion: Critical illness requiring ICU admission may occur in patients with SLE and APS. In this study, ICU survival was better than previously described, but long term survival was poor. Cyclophosphamide administration, low white cell count, and high severity of illness score were associated with reduced survival. Before adjustment for these factors, only renal disease had an adverse effect on outcome but after adjustment, infection and APS reduced survival.

METHODS

All patients with SLE or APS, or both, requiring emergency admission to the ICU of St Thomas' Hospital over a 15 year period from January 1984 to December 1998 were included in the study, and data were collected prospectively for that period. A retrospective analysis of all admissions over the preceding 10 years was also performed: firstly, the ICU register was used to identify any patient with a diagnosis of SLE, vasculitis, connective tissue disease, or thrombophilia. Only patients having a diagnosis of SLE or APS made before, or during, admission were included in the study. Potential study patients were identified, the hospital number was obtained, and further data collected from the following sources: ICU notes and physiological data charts, hospital notes (both paper and microfiche), hospital notes from other hospitals, death certificates, postmortem results, and laboratory data. Only those patients who fulfilled the American Rheumatology

Abbreviations: ANA, antinuclear antibodies; APACHE, Acute Physiology and Chronic Health Evaluation (score); APS, antiphospholipid syndrome; ARDS, acute respiratory distress syndrome; CI, confidence interval; CRP, C reactive protein; ENA, extractable nuclear antigens; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; SLE, systemic lupus erythematosus; WCC, white cell count

Association criteria for the classification of lupus⁷ and those with APS were included in the study.⁸ Patients were recorded as having either primary APS (without SLE or other connective tissue disease) or secondary APS. Patients with possible catastrophic APS were identified retrospectively.⁹ In the absence of agreed diagnostic criteria for this newly described variant of APS, we judged which patients had the severest vasculopathy, multiorgan dysfunction, and haematological abnormalities. Their clinical and laboratory features are reported.

Data collection

The following information was obtained: date of birth, race, sex, duration of SLE and/or APS, time in hospital before ICU admission, time in the ICU, and whether admission was emergency or elective. Details of clinical, haematological, and serological features and treatment before hospital admission were also obtained. Previous clinical features included the presence of malar rash, photosensitive rash, discoid lupus, vasculitic rashes, alopecia, and Raynaud's phenomenon. Laboratory data collected included previous cytopenias; lupus anti-coagulant (determined by activated partial thromboplastin time and dilute Russell viper venom time in accordance with guidelines available at the time); anticardiolipin antibody (by enzyme linked immunosorbent assay (ELISA)); and serology, including antibodies to nuclear antigens (ANA, determined by indirect immunofluorescence), to double stranded DNA (anti-DNA, measured by both immunofluorescence and radio-immunoassay), and to extractable nuclear antigens (ENA, by counter-current immunoelectrophoresis) and levels of complement components C3 and C4.

The primary diagnostic reason for admission to the ICU was identified. However, many of the patients had multisystem disorders so "accompanying" diagnoses were also recorded. A diagnosis of infection was made in patients with clinical features of pneumonia, septicaemia, urinary tract infection, and other focal infections, only if there were clear physiological and laboratory data with appropriate radiological evidence to support the diagnosis. Microbiological confirmation was available in 78% of the diagnoses of infection. A primary diagnosis of renal disease was made only if patients required initiation of renal replacement treatment. An accompanying diagnosis of renal disease was made in the following: those normally requiring renal replacement and those with underlying renal disease confirmed by renal biopsy, preadmission proteinuria greater than 1 g/24 h, or a stable creatinine greater than 200 $\mu\text{mol/l}$. Patients were categorised as "cardiovascular" if they had cardiac arrest or circulatory collapse (not due to septic shock). A diagnosis of coagulopathy was used to describe any patient requiring management of haemorrhage, acute thrombosis, or disseminated intravascular coagulation. A small number of remaining diagnoses were assigned to a single group (neurological/other).

The clinical features and laboratory results obtained on admission to the ICU, including full blood count, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), biochemical profile, liver function tests, coagulation screen, arterial blood gases and, more recently, lactate levels, were documented. The requirement for mechanical ventilation, renal replacement treatment, anticoagulation, and antimicrobial treatment was recorded. A detailed record was made of patients' requirement for immunosuppressive treatment in the year before and during admission.

Severity of illness was determined from the Acute Physiology and Chronic Health Evaluation (APACHE II) score. The APACHE II score is a well validated and widely used tool for the assessment of severity of illness, weighted for age, sex, and previous morbidity.¹⁰ It is designed to predict risk of hospital death. Before 1989, APACHE II scores were not routinely recorded so they were calculated from ICU charts and records

Table 1 Characteristics of patients admitted to the ICU

Total number of patients	61
Age, median (range) (years)	33 (16–69)
Male:female	13:48
Caucasian:Asian:Afro-Caribbean	30:15:16
Duration of SLE at admission, median (range) (years)	6.4 (0.2–26.9)
SLE:SLE+APS:primary APS	24:36:1

retrospectively in patients admitted before this. Risk of hospital death was calculated from the APACHE II score. Deaths in the ICU and in hospital were recorded. Survival after discharge from hospital was ascertained from hospital records and by contacting the patient or their family doctor by telephone.

To examine the effect of APS, comparisons were made between those patients with APS and those with SLE alone. Five patients had clinical features strongly suggestive of APS, but confirmatory laboratory results were not available. After discussion with the editor and referees of the *Annals*, analyses were performed including and excluding these five patients.

Statistical analyses

Long term survival was compared between the clinical groups and by risk factors in three ways—according to age, time since diagnosis, and time since first admission to the ICU. Kaplan-Meier survival curves were calculated for each clinical group and were compared using the log rank test. As some risk factors were continuous variables, Cox proportional hazard regression was used to assess their relation to survival, for each of the three outcome variables. Each risk factor showing a relation ($p < 0.1$) to at least one of the survival variables was entered into a backwards stepwise regression for each of the three survival variables. Clinical groups were compared adjusting only for those risk factors that remained significant ($p < 0.05$) in the stepwise regression. Survival in the ICU was also compared between clinical groups using the log rank test and by risk factors using Cox regression. As there were fewer deaths in the ICU, only factors associated with ICU death in a univariate analysis were entered into a backwards stepwise regression. Clinical groups were compared for other categorical variables using the χ^2 test, and for age and APACHE II score using the Mann-Whitney U test.

RESULTS

Patient characteristics

Sixty five patients were identified as having SLE and/or APS before, or during, their first ICU admission. One patient (admitted for one day) was excluded from the analysis as inadequate data were available. A further three patients admitted for elective cardiovascular surgery were also excluded. Sixty one patients having 76 emergency admissions were analysed.

Table 1 reports the demographic and main clinical characteristics of the patients. Twenty four patients had SLE alone, 36 had both SLE and APS, and one patient had primary APS. The diagnosis of SLE had been established between one month and 26 years before admission: no patients were newly diagnosed as having SLE while in the ICU. APS was newly diagnosed definitively in the ICU in 12/36 (33%) patients with APS. Caucasians accounted for 30/61 (49%) of the patient cohort and Afro-Caribbeans for 16/61 (26%). Before admission, 15 patients were taking oral corticosteroids alone, 41 were taking oral corticosteroids and an additional oral agent (hydroxychloroquine or azathioprine). In total, 26 patients received pulsed IV cyclophosphamide the month before and/or

Table 2 Clinical and laboratory characteristics associated with SLE: number of patients (and total number for whom data available). ACR criteria shown in bold

Clinical/laboratory characteristics	Number of patients (total number for whom data available)
<i>Clinical features</i>	
Malar rash, discoid rash, photosensitivity, mouth ulcers, alopecia, Raynaud's phenomenon	55 (60)
Arthralgia	58 (60)
Renal disease v no renal disease	41 v 19 (60)
Biopsy proven lupus nephritis	28 (60)
Chronic RF not biopsy proven	4 (60)
Proteinuria	8 (60)
Chronic RF requiring RRT	9 (60)
Chronic RF not requiring RRT	20 (60)
Pericarditis	5 (60)
Pleurisy	25 (60)
Libman-Sachs endocarditis	4 (60)
Neurology (seizures/psychosis)	25 (60)
<i>Laboratory data</i>	
Haemolytic anaemia	2 (60)
Leucopenia	22 (60)
Lymphopenia	4 (60)
Thrombocytopenia	14 (60)
<i>Serology</i>	
ANA	58 (60)
dsDNA	47 (55)
ENA	36 (47)
Ro	22 (47)
La	6 (47)
RNP	15 (47)
Sm	14 (47)
Complement	
Low C3	33 (57)
Low C4	35 (56)

during the first ICU admission (15 before, eight before and during admission, and three during admission only).

Table 2 reports the clinical and laboratory features of the 60 patients with SLE requiring emergency admission (one patient had primary APS). Most had a history of arthralgia, rash, mouth ulcers, alopecia, or Raynaud's phenomenon. Renal disease occurred in 41/60 (68%) patients, of whom biopsy proven glomerulonephritis was recorded in 28 (68%). Leucopenia was recorded in 22/60 (37%). In patients whose serological results could be examined, ANA was positive in 58/60 (97%), and anti-DNA antibodies detected (by either immunofluorescence or radioimmunoassay) in 47/55 (85%). Antibodies to ENA were detected in 36/47 (77%) patients tested and were positive for Ro in 22 (47%), La in six (13%), RNP in 15 (32%), and Sm in 14 (30%).

A diagnosis of APS was made in 37 (61%) of the 61 patients; 36 with coexisting SLE and one with primary APS. Antiphospholipid antibody tests were positive in 32. Of the five patients lacking confirmatory antiphospholipid tests, four were negative on a single occasion but had clinical histories suggestive of APS: two with deep vein thrombosis and pulmonary embolism, one with Libman-Sachs endocarditis, and one with multiple arterial thromboses. The other patient was negative for antiphospholipid antibodies on several occasions but had severe coagulation problems with recurrent femoral thromboses. The analyses comparing SLE alone with patients with APS were performed both including and excluding these apparently antiphospholipid antibody negative patients. Of the 32 serologically confirmed cases, 20 patients were diagnosed before ICU admission, of whom 15 were anticoagulated with warfarin on admission to the ICU. One had stopped anticoagulation because of pregnancy and was admitted with

Figure 1 Frequency of diagnostic categories on admission for (A) primary and (B) accompanying diagnoses. CVS, cardiovascular; Inf, infection; Coag, coagulopathy; Neuro/other, neurological and other conditions.

bilateral renal vein thrombosis. The remaining 12 cases had not been diagnosed as having APS previously, and diagnosis was made during admission. Eight of these patients had a primary diagnosis of coagulopathy and two had had previous coagulopathy.

ICU admissions and management

Sixty one patients were admitted as emergencies on 76 occasions. Fifteen patients were admitted as emergencies twice, of whom three also had elective third admissions. In total, there were seven elective admissions over the 15 year period. Five such admissions were for cardiac valve replacement (four Libman-Sachs endocarditis, one mitral valve prolapse) and two were for haemofiltration in patients with chronic renal failure. Only the first emergency admissions were analysed, with elective and subsequent admissions excluded from survival analyses.

Length of ICU stay for emergency admissions was variable, with a median (range) of 3 (0–51) days. The median (range) length of stay in hospital before ICU admission was 1 (0–180) day, indicating that many patients were seriously unwell on admission to hospital and were transferred rapidly to the ICU.

Figure 1 shows the primary admitting and accompanying diagnoses in the 76 emergency admission episodes. Primary admitting diagnoses included infection in 31 (41%) admissions, renal disease in 16 (21%), cardiovascular 12 (16%), and coagulopathies 11 (14%). Renal impairment was the most frequently assigned, accompanying diagnosis, occurring in 49% of admissions. In total, 44/76 (58%) admission episodes had a renal diagnosis (either primary or accompanying). In 13 of these admission episodes patients had required previous dialysis for established chronic renal failure. Microbiological confirmation of the causative organism in cases of infection was obtained in 78%. Of the primary diagnoses of infection, 58% were septicaemia and 35% were pneumonia. The commonest organisms isolated were *Staphylococcus aureus* in 29% (one had methicillin resistance), with *Pneumococcus*, *Klebsiella*, and *E coli* each accounting for 10%. The coagulopathies included nine thrombotic, four haemorrhagic, and five pregnancy related episodes (thrombosis, haemorrhage, or pre-eclampsia).

Table 3 Management of 61 patients over 76 admissions and readmissions (number of admissions for which data available)

Management	Number
Mechanical ventilation	46 (75)
Renal replacement	
Haemofiltration	39 (75)
Dialysis	8 (75)
Inotropes	
Dopamine alone	22 (75)
Other inotropes ($\pm$ dopamine)	28 (75)
Total	50 (75)
Anticoagulation	34 (75)
Antimicrobial agents	66 (75)
Immunosuppression	
Corticosteroids	72 (75)
Cyclophosphamide	29 (74)
Plasmapheresis	11 (75)
Methotrexate	2 (74)
Immunoglobulin	1 (74)

Table 3 summarises the management of the 61 patients during 76 admissions. Mechanical ventilation was required in 46/75 (61%), inotropic support in 50/75 (67%), and renal replacement treatment in 47/75 (63%) patient admissions. Antibiotics were prescribed in 66/75 (88%) admissions, anticoagulants in 34/75 (45%), and corticosteroids in 72/75 (96%). Immunosuppression with IV cyclophosphamide was given in 11 (14%) during the first admission (and before admission in eight of these 11 patients), and three during subsequent admission. In addition, 15 patients received IV cyclophosphamide during the month before the first ICU admission (but not during admission). Plasmapheresis was used in 11/75 (15%) admissions. The only significant treatment difference between patients who had and did not have APS was anticoagulation (more common in APS, $p < 0.05$).

Severity of illness was assessed by the APACHE II score. The mean (standard deviation, range) APACHE II was 22.1 (8.9, 8–45) for the 61 first admissions. Subgroup analysis showed that the mean APACHE II score was 19 for long term survivors, 20 for ICU survivors, and 32 for ICU deaths. The mean risk of hospital death (standard error, SE) as calculated from the APACHE II score database, was 38.4 (3.6%). Actual hospital death rate and survival rates are reported below.

Long term survival

In total 31 patients had died at the time of last follow up, between September 1996 and November 1998. Of these 31, 13 died on first ICU admission, four on subsequent ICU admissions, and two in hospital after discharge from the ICU. The five year and 10 year survival rates from first ICU admission were 43% (95% confidence interval (CI) 28 to 57%) and

38% (22 to 53%) respectively. Median age at death was 46 years, median time from SLE diagnosis to death was 15 years, and median time from ICU admission to death was four years.

Risk factors considered as potentially influencing outcome were selected and analysed in the 61 patients by three survival variables (by age, by survival from diagnosis of SLE, and by survival from first ICU admission). Except where a lower sample size is shown data were obtained for all 61 patients. Table 4 shows the categorical risk factors and table 5 the continuous risk factors. Clinical subgroups analysed were renal failure (acute and chronic), infection, and APS. Analysis by age at diagnosis showed that acute and/or chronic renal failure was strongly associated with decreased life expectancy (log rank test $p = 0.005$, fig 2A). When the same analysis was used, infection on admission did not influence survival ($p = 0.76$, fig 3A), but there was an adverse effect of the combination of infection and/or renal disease ($p = 0.10$). Analysis by time since first ICU admission showed decreased survival with acute renal failure ($p = 0.07$, fig 2B) and chronic renal failure ($p = 0.07$). In this analysis there was an adverse influence of infection ($p = 0.06$, fig 3B), and the combination of infection and renal disease ($p = 0.04$).

Cyclophosphamide was given to 23 patients immediately before ICU admission. In general, patients received cyclophosphamide 500 mg IV every four weeks over six months, but there was variation in the dosing protocol over the 15 year period: dosing ranged between 250 mg and 750 mg and frequency ranged between weekly and monthly. Two patients received oral cyclophosphamide, 100–150 mg daily for up to two years. Eleven patients received cyclophosphamide during the first ICU admission. Cyclophosphamide treatment before admission was associated with increased risk of death as determined for all three outcomes (age at death, time since diagnosis of SLE, and time since first emergency ICU admission), as was a white cell count (WCC) below the reference range. Cyclophosphamide treatment during admission was associated with reduced age at death and reduced survival from diagnosis of SLE. The dose of steroid was associated with reduced survival from diagnosis, as was the use of inotropes. The other potential risk factors in tables 4 and 5, and also ethnic group, were not significantly related at the 10% level to any of the survival variables using Cox proportional hazard regression.

The variables identified above were entered into a backwards stepwise regression, using the Cox proportional hazard model, for each of the three survival variables. Table 6 shows the results obtained. Only two or three factors remained depending on the analysis: cyclophosphamide treatment during admission and APACHE II score when survival was analysed according to age; and APACHE II score and age at diagnosis for survival from the first ICU admission. All these relationships were significant ($p < 0.005$). The clinical groups (renal disease, infection, and APS) were analysed for survival, adjusting for the relevant risk factors in table 6. Only patients with APS were found to have reduced long term survival (by time from first ICU admission, $p = 0.03$).

Table 4 Univariate analysis of dichotomous risk factors in 61 patients on their first ICU admission analysed by time since first ICU admission, time since diagnosis of SLE, and by age

	No (%)	p Value for analysis from ICU admission	p Value for analysis by time from diagnosis	p Value for analysis by age
Second line oral immunosuppressants	32 (52)	0.39	0.27	0.99
Cyclophosphamide before admission	15 (25)	0.01	0.001	0.001
Cyclophosphamide before + during admission	26 (43)	0.12	0.08	0.003
WCC < 4	13 (21)	0.004	0.07	0.06
WCC > 9	26 (43)	0.86	0.52	0.79
ENA ever (n=48)	36 (75)	0.45	0.33	0.45
Inotropes	25 (41)	0.002	0.004	0.17

Table 5 Mean and variation of quantitative risk factors in 61 patients

	Mean	SD (range)	p Value for analysis from ICU admission	p Value for analysis by time since diagnosis	p Value for analysis by age
Age at diagnosis (years)	27.9	10.9 (9.1 to 68.1)	0.02	0.003	NA
APACHE II score	22.1	8.8 (8 to 45)	<0.001	0.001	0.001
Haemoglobin (g/l)	90	23 (50 to 157)	0.72	0.42	0.03
Platelets ($\times 10^9/l$)	170.5	111.9 (13 to 598)	0.57	0.97	0.12
ESR mm/1st h (n=61)	74.4	39.6 (2 to 162)	0.74	0.91	0.18
CRP mg/l (n=59)	87.5	90.6 (4 to 348)	0.90	0.85	0.75
pH (n=55)	7.32	0.12 (6.9 to 7.5)	0.47	0.63	0.96
Base excess (n=55)	-5.5	6.8 (-23 to 8.4)	0.48	0.79	0.86
Dose of prednisolone (mg)	20.0	17.4 (0 to 80)	0.08	0.04	0.59

Figure 2 Kaplan-Meier survival curves for patients with and without renal failure (A) by age and (B) by time since first ICU admission. **Figure 3** Kaplan-Meier survival curves for patients with and without infection on admission (A) by age and (B) by time since first ICU admission.

Survival in ICU

Overall, 17/61 (28%) patients died in ICU, 13 on their first admission. A further two patients died before hospital discharge (total hospital death rate 31%). Considering the first admissions only, median time in the ICU was four days (range <1–51). Table 6 shows the factors associated with ICU death. Haemoglobin, low WCC, base excess, APACHE II score, use of inotropes, and age at diagnosis were initially entered in the backwards stepwise regression analysis. As would be expected, APACHE II score was highly significantly associated with death in the ICU ($p < 0.001$). Both admission low WCC and haemoglobin were strongly and independently associated with death in the ICU ($p = 0.01$).

Renal failure, APS, and infection were not shown to influence ICU survival by univariate analysis and were not entered into the main backwards stepwise regression. However, after adjustment for factors that were associated with reduced ICU survival (haemoglobin, APACHE II score, and low WCC, table 6), infection was associated with an increased ICU death rate ($p = 0.02$). It was the cause of death in 13 of the 17 ICU deaths (76%). Of these 13 deaths, 10 had a

primary diagnosis of infection. Overwhelming septic shock caused four deaths within 48 hours of admission (two *Pneumococcus*, one *Staphylococcus*, and one *Klebsiella*). All 10 patients with primary infections who died had secondary acute renal failure. The remaining three patients who died had primary diagnoses of renal disease (two) and coagulopathy (one) but, nevertheless, infection was the ultimate cause of death (two *Pneumococcus*, one *Klebsiella*). Similarly, after adjustment, ICU survival in patients with APS was reduced with an adjusted death rate ratio of 3.56 (95% CI 0.80 to 15.77, $p = 0.1$). However, renal failure (acute and/or chronic) was only weakly associated with an increased rate of ICU death (rate ratio 1.63, 95% CI 0.35 to 7.58, $p = 0.53$).

Effect of APS

No significant differences were found between those having and not having APS by sex, race, age, ICU or hospital mortality, renal disease, severity of illness (APACHE II), or length of ICU stay. As discussed above, patients with APS had reduced ICU survival after adjustment for other factors (table 6, rate ratio 3.56, 95% CI 0.80 to 15.77, $p = 0.1$).

Table 6 Hazard ratios (95% confidence interval) for variables remaining significantly ($p < 0.05$) associated with survival in 61 patients, using backwards stepwise Cox proportional hazard regression. Rate ratio (RR) is the risk factor present compared with absent, or per unit increase for quantitative risk factors

Risk factor	Overall survival outcome variable			
	Survival from admission RR (95% CI)	Survival from diagnosis RR (95% CI)	Age RR (95% CI)	Survival to discharge from ICU Survival from admission RR (95% CI)
Previous cyclophosphamide	Eliminated	2.77 (1.26 to 6.09)	Eliminated	Not entered
Cyclophosphamide during admission	Eliminated	Eliminated	2.93 (1.34 to 6.40)	Not entered
APACHE score	1.16 (1.09 to 1.22)	1.06 (1.02 to 1.10)	1.07 (1.02 to 1.11)	1.16 (1.07 to 1.25)
Age at diagnosis	1.05 (1.02 to 1.09)	1.06 (1.02 to 1.09)	Not entered	Eliminated
Haemoglobin	Eliminated	Eliminated	Eliminated	1.61 (1.13 to 2.29)
Low WCC	Eliminated	Eliminated	Eliminated	8.33 (1.85 to 37.57)

Figure 4 Kaplan-Meier survival curves for patients with and without APS (A) by age and (B) by time since first ICU admission.

APS, when analysed by the log rank test, was not significantly associated with diminished long term survival (fig 4). However, when APS was analysed after adjusting for the relevant risk factors (table 6), patients with APS had reduced long term survival from diagnosis (rate ratio 1.91, 95% CI 0.86 to 4.24, $p = 0.11$) and reduced long term survival from first ICU admission (rate ratio 2.41, 95% CI 1.08 to 5.39, $p = 0.03$). Patients with APS were also shown to have a shorter survival time from first ICU admission after adjustment for haemoglobin, APACHE II score, and low WCC (hazard ratio 3.48, 95% CI 0.79 to 15.25, $p = 0.1$).

Retrospective analysis disclosed nine patients who might have had catastrophic APS and table 7 shows their important clinical and laboratory features. Infection was considered to be the precipitating cause in eight patients and five patients died

in ICU. Acute respiratory distress syndrome (ARDS) was present in seven, and acute renal deterioration seen in eight patients.

DISCUSSION

There is good evidence that long term survival of lupus patients is improving.¹¹ Ten year survival rates as high as 85% have been reported,¹² although these may reflect earlier diagnosis and the increased recognition of less severe disease, as well as improved patient management. Lupus patients with APS are reported to have higher mortality rates independent of these other variables.⁵ Outpatient management is usual in patients with lupus and the consequences of critical illness have not been as well documented as other prognostic factors.

Table 7 Table showing clinical features of patients with possible catastrophic APS, presence and absence of disseminated intravascular coagulation (DIC), possible precipitants and whether or not patient survived

Patient	Renal disease	CNS	CVS	ARDS	Limb infarctions	DIC	Platelet count/ $\times 10^9/l$	Other features	Possible precipitants	Died
1	Yes	No	?Pericarditis	Yes	Foot infarcts	Yes	33		Meningococcal septicaemia	No
2	Yes	Yes	No	Yes	No	Yes	30		Herpes simplex respiratory tract infection	Yes
3	No	Yes	?Pericarditis	No	Multiple leg infarctions	Yes	<100		<i>E coli</i> septicaemia	Yes
4	Yes	Yes	No	Yes	Toe infarcts	Yes	56	Spontaneous abortion	<i>E coli</i> septicaemia	No
5	Yes	No	No	Yes	No	No	<100		Staphylococcal septicaemia	No
6	Yes	Yes	No	Yes	No	Yes	31	Hepatic failure, hypoadrenal	<i>E coli</i> septicaemia	Yes
7	Yes	Yes	Yes	Yes	No	Yes	6	Gastritis, retinal haemorrhage	<i>E coli</i> septicaemia	Yes
8	Yes	Yes	No	Yes	No	Yes	<100		Staphylococcal septicaemia	Yes
9	Yes	Yes	No	No	Skin infarcts	Yes	71		Pre-eclampsia	No

The relation between APS and the development and outcome of critical illness is unknown.

Critical illness may intervene at any time throughout the course of lupus as a consequence of fluctuations in the disease process and of immunosuppressive or other iatrogenic interventions. In general rheumatology practice these episodes of critical illness are rare, but they affect women of child bearing age and have major social and economic consequences. This study is from a large tertiary referral centre for both SLE and APS. Although this will have influenced the results (owing to increased numbers of patients having severe disease), it has allowed the collection of sufficient data to perform multivariate analysis. The difficulty in collecting an adequate cohort of patients is reflected by the paucity of reported data describing the causes, prognostic indicators, and long term outcome of critically ill patients with SLE admitted to the ICU. There is only one other such publication of which we are aware.⁶ The authors reported a 53% mortality during or shortly after discharge of 30 patients admitted to two South African ICUs between 1982 and 1993, with a median length of stay of 13 days. Univariate analysis showed that renal disease alone affected long term survival. APS was not examined. In patients with chronic diseases like SLE, measurement of long term outcome is essential as health related quality of life may decrease in the long term. In an era of increasing awareness of high health expenditure, the impact of admission to the ICU on survival and subsequent quality of life needs to be examined.

In this study the short time in hospital before ICU admission and the high severity of illness score (APACHE II) show that the onset and severity of critical illness were rapid and dramatic. However, the median length of stay (four days) was shorter, and combined ICU and hospital mortality were substantially lower, than previously described.⁶ ICU mortality in our patients with SLE/APS was 28% and hospital mortality 31%. Using APACHE II scores, this mortality is similar to that expected in non-selected (that is, non-SLE) patients of similar age and severity of illness.¹⁰ This suggests that patients with SLE/APS do no worse than other critically ill young patients. In addition, ICU mortality fell from 37% (13/35) in the first 10 years to 12% (3/26) during the recent five years of our study. This decline in mortality may reflect both differences in severity of illness at admission and improved ICU management. Of interest, there was a high number of male patients (5:1) in this cohort of lupus patients compared with the usually quoted ratio of women to men of 9:1. This may be a chance finding, but it is in keeping with the view that male patients have a worse outcome.³ Another interesting observation is the distribution of antibodies against ENA: a high proportion (22/47 (47%)) had anti-Ro antibodies, compared with 25% of the "Euro-lupus" cohort.¹³ Possibly, this also reflects severe disease.

However, patients who survived to be discharged from hospital had a poor long term prognosis, particularly those with renal failure (fig 2), with a median time to death of four years from first ICU admission. A previous study of patients admitted to the ICU with systemic rheumatic diseases (including SLE) reported a favourable long term prognosis.¹⁴ This difference in findings may reflect the difference and severity of the underlying rheumatic illnesses. In this study the severity of underlying disease was reflected by the high proportion (24/61 (39%)) of patients receiving cyclophosphamide in the month before admission, compared with the general outpatient population. In this centre the point prevalence of cyclophosphamide administration is approximately 2% in lupus outpatients.

In this small cohort of patients reduced WCC was strongly associated with increased ICU mortality. This may reflect either severity of lupus or the use of immunosuppressive treatment, or both. Most patients admitted to the ICU had been receiving immunosuppressive treatment with corticosteroid and cytotoxic drugs, and it is now well established that

infection is a common cause of death in systemic rheumatic disease.¹¹ In a multicentre study examining the causes of death in SLE, 33% were due to sepsis,¹⁵ and a further study has shown infection to be associated with the use of corticosteroids and cytotoxic drugs within the preceding 12 weeks, even in the absence of leucopenia.¹⁶

Similarly, in this study, cyclophosphamide treatment at any stage was associated with increased risk of death for all three outcome variables (age, time since SLE diagnosis, and time since first ICU admission). The drug remained a significant adverse factor for survival by age and by time since SLE diagnosis when analysed by Cox proportional hazard regression. Whether these findings reflect adverse effects of the drug, or whether cyclophosphamide is simply a marker of severe lupus is unclear. The appropriate cyclophosphamide regimen for many of the manifestations of SLE remains to be established: the regimens used in this study highlight the empirical way in which it has been used.

Low haemoglobin and high APACHE II score were less strongly associated with reduced survival. This might be expected for APACHE II, which is a well validated measure of severity of illness,¹⁷ but has not hitherto been validated for lupus patients. That high APACHE II score was significantly associated with poorer outcome suggests it remains a useful tool, even in this highly selected group of patients.

Lupus renal involvement was present in a large proportion of patients before ICU admission, an observation consistent with severe underlying autoimmune disease. Glomerulonephritis had been histologically confirmed in 68% of the patients with renal disease. Furthermore, 49% of admission episodes required renal replacement treatment for acute or acute-on-chronic renal failure. Renal failure was associated with increased ICU death (rate ratio 1.63) when adjusted for APACHE II score, low WCC, and low haemoglobin, although this was not statistically significant. However, when infection occurred in patients with renal disease, there was a significant adverse effect on ICU survival ($p=0.03$). Long term life expectancy in patients with renal disease was also significantly reduced (by time since ICU admission, $p=0.04$).

Infection was the cause of death in 10 of the 13 patients who died on first ICU admission and it was shown to be a predictor of ICU mortality ($p=0.02$). Infection had a deleterious effect on long term survival (from first ICU admission, $p=0.06$), but this was not seen after adjustment for relevant risk factors. This may suggest that infection is a surrogate marker of low WCC or disease severity, or both. It is well established that mechanical ventilation is associated with an unfavourable prognosis, but the 35% death rate in mechanically ventilated patients was lower than that reported by others.^{6, 14} An increasing dose of corticosteroid and raised ESR also adversely affected outcome. These factors are likely to reflect high disease activity, immunosuppressive treatment, and potential risk of infective complications. In contrast with the study by Ansell *et al*,⁶ we found no ethnic group to be associated with increased risk of death. We have not objectively assessed quality of life after ICU admission, but from outpatient assessment and telephone contact we are aware that most hospital survivors are active and independent. Further assessment of quality of life is needed.

Thirty seven (61%) of this cohort of ICU patients had APS compared with the expected prevalence of approximately 30% reported in studies of outpatients.¹³ Possibly, APS predisposes to critical illness, but this will need confirmation by prospective studies. The effect of APS in critical illness has not been investigated before. No significant differences were found between patients with APS and SLE alone for sex, race, age, ICU or hospital mortality, renal disease, severity of illness (APACHE II), or length of ICU stay. APS was associated with increased rate of ICU death (rate ratio 3.56, $p=0.1$) when adjusted for haemoglobin, APACHE II score, and low WCC. Long term survival in patients with APS was reduced (analysis from first

ICU admission, rate ratio 2.41, $p=0.03$). This is in agreement with outpatient data, which suggest that patients with APS have increased mortality rates independent of other variables.⁵

Five patients did not have confirmatory antiphospholipid antibodies, although their absence in the acutely sick patient does not exclude a diagnosis of APS. Analysis of patient groups by assigning these five patients to the SLE group did not alter the adverse effect of APS on ICU survival (rate ratio 3.48, $p=0.1$). However, APS was not shown to influence survival from first admission when these five patients were analysed in the SLE alone patient group.

Catastrophic APS was identified retrospectively in nine patients. This is a variant of APS, whose description in the literature is based on a similar sized cohort of ICU patients world wide. The catastrophic APS was first recognised as an acute widespread non-inflammatory vaso-occlusive disease in 1991¹⁸ and named the following year when a study of a series of 10 patients was published.¹⁹ In contrast with the sporadic, large vessel thrombosis seen in APS, catastrophic APS presents acutely with multiorgan failure secondary to small vessel thrombotic vasculopathy.⁹ The male to female ratio is approximately 1:2. Death occurs in half the patients. The presence of anticardiolipin antibodies and/or lupus anticoagulant is the norm, though they may be absent. Possible precipitants include infection, drugs (thiazides, captopril, the oral contraceptive pill), and warfarin withdrawal.⁹

In conclusion, critically ill patients with lupus and APS had ICU and hospital mortality rates lower than previously reported (28% and 31%, respectively),⁶ which were comparable with ICU patients with similar severity of illness scores.¹¹ However the long term outlook of ICU survivors is poor, with a median survival time of four years. This suggests severe, ongoing, autoimmune disease. Low WCC at admission was strongly associated with poor ICU survival. There was reduced ICU and long term survival in patients with APS. A number of other factors including renal disease and infection were associated with reduced long term survival, the former in agreement with the previous study.⁶ This suggests that after ICU admission, patients with SLE and APS should be monitored closely.

ACKNOWLEDGEMENTS

FMK Williams is supported by the Arthritis Research Campaign. We thank Dr DF Treacher for his helpful advice.

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