

An Audit of Patients with Rheumatic Disease Requiring Medical Intensive Care

B Y H Thong,*^{MBBS, MRCP (UK)}, D Y H Tai,**^{FAMS, MRCP (UK), EDIC}, S K Goh,***^{FAMS, MRCP (UK), M Med (Int Med)},
A Johan,****^{FAMS, MRCP (UK), FCCP}

Abstract

Introduction: Medical intensive care for patients with rheumatic disease is usually complicated by significant morbidity and mortality. The aims of this study were to examine the reasons for admission, the outcomes of these patients and the possible prognostic factors in an Asian cohort. **Materials and Methods:** This was a retrospective study of the case records of 29 admissions to the medical intensive care unit (MICU) of Tan Tock Seng Hospital (TTSH) from August 1999 to August 2000. **Results:** There were 28 patients admitted, of whom 1 had a repeat admission. The majority of these patients were young (mean age 38.9 ± 16.3 years) and 71.4% were females. Twenty patients (71.4%) had systemic lupus erythematosus (SLE). The main reasons for admission were infection/ sepsis syndrome ($n = 18$), hypotension ($n = 16$) and acute respiratory failure ($n = 14$). The observed in-hospital mortality was 64.3%, which was higher than the predicted risk of hospital death of 47.3%. Infection contributed to 55.6% of deaths. The patients who died had a longer mean duration of the rheumatic disease, higher APACHE II scores, higher rates of hypertension and hyperlipidaemia, higher doses of steroid and immunosuppressive therapy and more organ failures. Renal failure and acute respiratory distress syndrome were the two most common organ failures in patients who died. **Conclusion:** Many of our critically-ill patients with rheumatic disease were young females with good functional status. Despite the high mortality, they should be aggressively treated because infection and acute respiratory failure are potentially reversible.

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Key words: APACHE II, Immunocompromised, Infection, Prognostic factors, Systemic lupus erythematosus

Introduction

Patients with rheumatic disease are often immunocompromised as a result of either their disease or treatment. They may become ill either from a flare of their autoimmune disease or from complications of treatment, at times requiring intensive care. Intensive care for these patients is usually prolonged, complicated by nosocomial infections and organ failures, and hence utilise many resources. There are few overseas studies of patients with rheumatic disease requiring medical intensive care¹⁻⁶ and none from Asian countries.

The aims of this study were to examine the reasons for admission to medical intensive care unit (MICU), the outcomes of these patients and the possible prognostic factors in an Asian cohort.

Materials and Methods

The clinical charts and medical records of all patients

with rheumatic disease admitted to the MICU of Tan Tock Seng Hospital, a tertiary referral centre for rheumatology, from 1 August 1999 to 31 August 2000 were reviewed retrospectively. Patients admitted to the coronary care unit, surgical and neurosurgical ICUs were excluded. The rheumatological diagnoses were made according to the accepted classification criteria for the respective rheumatic diseases.

The reasons for admission to intensive care were classified as follows:

- (1) rheumatic disease flare, defined as a non-infectious complication directly attributable to systemic rheumatic disease;
- (2) infection, defined by microbiologically documented processes (bacteriological and opportunistic) or by sepsis syndrome using the criteria proposed by Bone et al.⁷ Briefly, sepsis syndrome represents a systemic response to infection and is defined as hypothermia

* Registrar

Department of Rheumatology, Allergy & Immunology

** Consultant and Director, Medical Intensive Care Unit

*** Consultant

Department of General Medicine

**** Consultant

Department of Respiratory Medicine

Tan Tock Seng Hospital

Address for Reprints: Dr Bernard Thong Yu Hor, Department of Rheumatology, Allergy & Immunology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.

E-mail: bernard_thong@notes.ttsh.gov.sg

- (temperature $<36^{\circ}\text{C}$) or hyperthermia (temperature $>38^{\circ}\text{C}$), tachycardia (>90 beats/min), tachypnoea (>20 breaths/min), clinical evidence of an infection site, and with at least one end organ with inadequate perfusion or dysfunction expressed as altered cerebral function, hypoxaemia ($\text{PaO}_2 <75$ mmHg), elevated plasma lactate, or oliguria (urine output <30 ml/h or 0.5 ml/kg body weight/h without corrective therapy);
- (3) hypotension/ shock (systolic blood pressure <90 mmHg and/or diastolic blood pressure <60 mmHg with signs of organ hypoperfusion);
- (4) acute respiratory failure ($\text{PaO}_2 <60$ mmHg or $\text{PaCO}_2 >50$ mmHg);
- (5) acute renal failure defined as a rapidly rising plasma urea and creatinine or oliguria (urine volume <400 ml/d or <30 ml/h or 0.5 ml/kg body weight/h);
- (6) neurological change (change in sensorium, coma, seizures, paralysis).

The patient's health status 3 months before admission was assessed according to Berdit's classification:⁸

- good health with no limitation of mobility;
- mild limitation of mobility, such as dyspnoea climbing one flight of stairs;
- severe restriction of mobility, such as inability to walk more than 2 blocks;
- patient bedridden or institutionalised.

The APACHE (Acute Physiology and Chronic Health Evaluation) II score and risk of hospital death (R)⁹ for individuals/ groups were calculated. Other factors evaluated included the average length of MICU stay, duration of various intensive care therapies (mechanical ventilation, inotropic support, dialysis and plasmapheresis), types of immunosuppressive therapy for the 2 months prior to admission, medical co-morbidities (diabetes mellitus, hypertension and hyperlipidaemia) and the types of infections acquired either from the community or during hospitalisation.

The organ failures were classified as:

- acute renal failure defined as a rapidly rising plasma urea and creatinine or oliguria (urine volume <400 ml/d or <30 ml/h or 0.5 mg/kg body weight/h);
- acute respiratory distress syndrome (ARDS);¹⁰
- disseminated intravascular coagulation;
- heart failure;
- acute liver failure;
- stroke which could be either cerebral infarction or intracranial haemorrhage.

The outcome measures were in-MICU and in-hospital mortality.

Results

There were 28 patients with a total of 29 admissions to

the MICU during the study period. Twenty patients (71.4%) were female and 8 (29.6%) were male. The mean age of all patients was 38.9 ± 16.3 years (range 18 to 77 years). The mean age of the females was 36.8 ± 15.5 years (range 18 to 77 years) and the males was 34.3 ± 11.7 years (range 22 to 55 years). The racial distribution was 19 (67.9%) Chinese, 4 (14.3%) Malays, 2 (7.1%) Indians and 3 (10.7%) of other racial denominations (2 Indonesians and 1 Gurkha).

Twenty patients (71.4%) had systemic lupus erythematosus (SLE), 3 (10.7%) rheumatoid arthritis (RA) and 5 (17.9%) other rheumatic diseases; the latter include 2 dermatomyositis, 1 primary Sjogren's syndrome, 1 relapsing polychondritis and 1 diffuse scleroderma. The average duration of the rheumatological disease since diagnosis was 43.7 ± 58.6 months (range 1 to 360 months).

The mean Berdit's health score prior to MICU admission was 1.7 ± 1.0 and APACHE II score was 24.0 ± 9.5 (range 9 to 45).

The main reasons for MICU admission are shown in Table I.

There were 18 (62.1%) admissions for infection/sepsis syndrome. Of the 16 (55.2%) admissions for hypotension, 12 were due to sepsis, the commonest being pneumonia (66.7%). Acute respiratory failure accounted for 14 (48.3%) admissions, of which half were due to pneumonia. Five admissions (17.2%) were for flare of the underlying rheumatic disease, of which 3 were associated with pneumonia. Fifteen (51.7%) admissions were for a combination of (2 or more of the above) reasons, the commonest being septic shock.

The mean length of ICU stay was 5.5 ± 3.7 days (range 1 to 16 days). Twenty-six (89.7%) admissions required mechanical ventilation (either invasive or non-invasive) with the mean duration of 84.2 ± 84.3 hours (range 2 to 240 hours). Twenty admissions (70.0%) required inotropic support with a mean duration of 46.1 ± 62.1 hours (range 3 to 240 hours). Two patients required dialysis for acute renal failure from sepsis. One patient with SLE required plasmapheresis for pulmonary haemorrhage.

For the 2 months prior to the MICU admission, 20 patients had been on corticosteroids >7 mg/d with a mean daily dose of 36.2 ± 19.6 mg (range 8.5 to 67.5 mg). Fifteen

TABLE I: REASONS FOR MICU ADMISSIONS

Reason for admission	Number (%)
Infection/sepsis syndrome	18 (62.1)
Hypotension	16 (55.2)
Acute respiratory failure	14 (48.3)
Flare of rheumatic disease	5 (17.2)
Neurological	4 (13.8)
Others	2 (6.9)

patients had, in addition, been on disease-modifying anti-rheumatic drugs (DMARDs) or other immunosuppressive therapy which included azathioprine (n = 5, mean daily dose 77.5 mg, range 50 to 125 mg/d), hydroxychloroquine (n = 4, mean daily dose 325 mg, range 200 to 400 mg/d), a combination of azathioprine and hydroxychloroquine (n = 1), methotrexate (n = 2, mean dose 10 mg/week) and mycophenolate mofetil (n = 1, mean daily dose 1312.5 mg).

Two patients with SLE were given pulse methylprednisolone 1 g per day for 3 days followed by pulse intravenous cyclophosphamide 500 to 600 mg during the 10 to 14 days prior to MICU admission, 1 of whom was pancytopenic on admission to MICU. Both patients died from *Klebsiella pneumoniae* septicaemia. Three other patients were given monthly intravenous cyclophosphamide during the 2 months prior to the MICU admission, the mean dose of which was 683 mg (range 550 to 800 mg). Only 3 patients had defaulted treatment during the 3 months prior to admission.

Community-acquired or nosocomial infections were common in MICU patients. The sources of infection are listed in Table II. Seventeen patients had bacteria isolated from blood specimens (10), endotracheal tube/tracheostomy aspirates (6), bronchoalveolar lavage (1), pleural effusion (2), joint effusion (2), urine (2) and wound swab (2). There

were equal numbers of Gram-positive and Gram-negative infections. One patient each had *Mycobacterium tuberculosis* complex (MTC) isolated from respiratory and wound cultures respectively. One patient had *Pneumocystis carinii* pneumonia, one probable cytomegalovirus (CMV) hepatitis based on biochemical hepatitis and evidence of high CMV antibody titres, and another had disseminated varicella. Neither fungi nor salmonella were isolated from any of the patients. The organisms isolated are shown in Table III.

Fifteen deaths (53.6%) occurred in the MICU and there were altogether 18 in-hospital deaths (64.3%). Infection contributed to 55.6% of all deaths. The other causes of death are listed in Table IV. The characteristics of the survivors and non-survivors are shown in Table V. The patients who died had a longer mean duration of the rheumatic disease, higher mean APACHE II score, higher rates of hypertension and hyperlipidaemia, higher rates and doses of steroid and immunosuppressive therapy, and more organ failures. The survivors had a longer mean duration of ICU stay and mechanical ventilation compared to the non-survivors and this may have been due to earlier death in the non-survivors. The mean duration from MICU admission to death in non-survivors was 4.6 ± 2.9 days compared to the mean duration of 6.7 ± 4.7 days from MICU admission to discharge for survivors.

Seventeen (60.7%) patients had at least one organ failure during the admission, of which 82.4% (14/17) died. Fourteen (77.8%) of the non-survivors had at least one organ failure, of which 7 had acute renal failure (38.9%) and 5 had ARDS (27.8%). Among the 12 SLE patients who died, 10 had clinical or biopsy-proven class IV or class V nephritis, 4 of whom developed acute renal failure at the time of death due to concomitant sepsis. Three SLE patients with ARDS at the time of death had concomitant pneumonia and 1 had pulmonary haemorrhage.

During the study period, there were 2 patients with SLE and 3 with RA, not from our MICU cohort, admitted to the

TABLE II: SOURCES OF INFECTION

Source of infection	Number (%)
Pneumonia	12 (66.7)
Septic arthritis	1 (5.5)
Infective endocarditis	1 (5.5)
Infected ulcer	1 (5.5)
Haemorrhagic varicella	1 (5.5)
Unknown	2 (11.3)

TABLE III: CAUSATIVE ORGANISMS IN 18 EPISODES OF INFECTION

Organism	Number
Gram positive	
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	3
Methicillin-sensitive <i>Staphylococcus aureus</i> (MSSA)	4
Streptococcus	2
Gram negative bacilli	
<i>Klebsiella spp.</i>	3
<i>Escherichia coli</i>	3
Others	3
<i>Mycobacterium tuberculosis</i>	2
<i>Pneumocystis carinii</i>	1
Varicella-zoster virus	1
Cytomegalovirus	1

TABLE IV: CAUSES OF DEATH

Cause of death	Number (%)
Infection	7 (38.9)
Disease	
Flare	2 (11.1)
Progression	2 (11.1)
Infection & active disease	3 (16.7)
Atherosclerosis	
Coronary artery disease	2 (11.1)
Cerebral infarct	1 (5.5)
Ruptured hepatic artery aneurysm	1 (5.5)

TABLE V: CHARACTERISTICS OF SURVIVORS AND NON-SURVIVORS

Characteristic	Survivors (n = 10)	Non-survivors (n = 18)
Age (years) *	37.9 ± 17.8	40.5 ± 15.8
Sex		
Female	8 (80.0%)	13 (72.2%)
Male	2 (20.0%)	5 (27.8%)
Race		
Chinese	4 (40.0%)	15 (83.2%)
Malay	3 (30.0%)	1 (5.6%)
Indian	1 (10.0%)	1 (5.6%)
Others	2 (20.0%)	1 (5.6%)
Rheumatic disease		
SLE	8 (80.0%)	12 (66.7%)
RA	1 (10.0%)	2 (11.1%)
Others	1 (10.0%)	4 (22.2%)
Duration of rheumatic disease (months)	43.7 ± 53.5	66.8 ± 89.9
Reason for admission		
Infection/sepsis syndrome	6 (60.0%)	10 (55.6%)
Hypotension	5 (50.0%)	8 (44.4%)
Acute respiratory failure	7 (70.0%)	6 (33.3%)
Flare of rheumatic disease	2 (20.0%)	3 (16.7%)
Neurological	1 (10.0%)	4 (22.2%)
APACHE II score*	21.8 ± 7.8	26.1 ± 9.7
SLE	21.4 ± 8.6	27.8 ± 10.7
RA	NA	30.0 ± 5.7
Others	NA	18.8 ± 3.9
Berdit score*	1.4 ± 0.7	1.9 ± 1.1
Risk of hospital death, R*	40.8 ± 25.1	53.3 ± 27.8
Length of stay (days)*	6.7 ± 4.7	4.6 ± 2.9
Mechanical ventilation (hours)*	94.0 ± 90.9	69.6 ± 72.3
Inotropic support (hours)*	48.3 ± 36.0	54.3 ± 69.8
Comorbidity		
Diabetes mellitus	1 (10.0%)	2 (11.1%)
Hypertension	1 (10.0%)	4 (22.2%)
Hyperlipidaemia	1 (10.0%)	4 (22.2%)
Treatment		
Prednisolone > 7 mg/d	5 (50.0%)	13 (72.2%)
Dose (mg/d)*	27.8 ± 21.5	39.9 ± 19.3
Other immunosuppressants	3 (30.0%)	10 (55.6%)
No. of organ failure		
0	7 (70.0%)	4 (22.2%)
1	2 (20.0%)	5 (27.8%)
2	1 (10.0%)	9 (50.0%)

* Results reported as mean ± sd.

NA: Not applicable as there was only 1 patient.

coronary care unit (CCU) for acute myocardial infarction or unstable angina. They all had other coronary risk factors including hypertension, hyperlipidaemia, chronic smoking and corticosteroid use. One patient had diabetes mellitus. All 5 patients had angiographic evidence of coronary artery disease, with 2 requiring coronary artery bypass surgery and 1 angioplasty. There were no patients outside

our MICU cohort, admitted to the neurology, neurosurgical or surgical intensive care units during this period.

Discussion

There were only a few studies of critically ill patients with rheumatic diseases requiring medical intensive care. The main findings from these studies are summarised in Table VI.

The first large series was reported by Godeau et al.¹ This was a study of 69 patients with rheumatic disease over 10 years, mean age 53 ± 17 years, of whom the majority had SLE (23.2%), necrotising vasculitis (27.5%) and RA (27.5%). Of these patients, 37.7% were admitted for infection and 27.5% for disease flare. Infection was the main cause of death in 82.6% of patients. The in-ICU mortality was 33% and in-hospital mortality was 42%. The mean simplified acute physiological score (SAPS) was 12 ± 5.5, the score in those who died was 15 ± 5.2, versus 9.9 ± 4.7 for survivors and this was a statistically significant prognostic factor. Long-term follow-up showed 83% survival at a mean of 38 months (range 2 months to 9 years) after the ICU admission.

In 1997, Godeau et al.² reported on the short and long term outcomes of a larger cohort of 181 patients admitted to ICUs. These patients were studied over 12 years from 4 teaching hospitals. Their mean age was 57 ± 17 years, the in-ICU mortality was 33%, in-hospital mortality was 43% and the estimated 5-year survival for discharged patients was 69%. Factors that were found to be significantly associated with in-hospital mortality apart from the SAPS included the reason for admission, prior health status and corticosteroid administration.

Bouachour et al.³ compared 18 patients with rheumatic disease newly diagnosed in the MICU versus 70 patients previously diagnosed requiring MICU care. They found that the SAPS, the number of acute organ system failure and iatrogenic complications were the main prognostic factors. The in-hospital mortality was not influenced by age or systemic rheumatic disease. However, age >60 years was a prognostic factor significantly associated with increase in long-term mortality.

In Ansell et al.'s study⁴ on 30 critically ill patients with SLE where the median age of 29 years was much younger, lupus nephritis was a pre-treatment factor predicting poor outcome. The median APACHE II score for all patients was 18 and the in-ICU mortality was 46.7%. The only other large ICU cohort studied using APACHE II was by Kollef and Enzenauer⁵ where there were 48 ICU admissions for 36 patients with rheumatic disease. Half of the admissions had rheumatoid arthritis and 16.7% had SLE. The mean APACHE II scores were significantly higher for non-survivors (27.5) compared to survivors (14.8) ($P < 0.0001$).

TABLE VI: PREVIOUS STUDIES ON MICU PATIENTS

Year	Author	Sample	Age (years)	Severity Score	Mortality in-ICU	Mortality in-hospital	Long-term survival
1992	Godeau et al	n = 69 SLE = 16 RA = 19 Vasculitis = 19	mean = 53 ± 17	mean SAP all = 12 ± 5.5 alive = 9.9 ± 4.7 dead = 15 ± 5.2	33%	42%	83% 2 mo to 9 yr
1996	Ansell et al	n = 30 (SLE)	median = 29	median APACHE II = 18 (range 8 to 42)	46.7%	—	—
1996	Bouachour et al	n = 88 Gp I/II* = 18/70 SLE = 3/12 Vasculitis = 6/12 RA = - /31 PM = - /4 IBD = 4/5 Misc = 5/6	—	mean SAPS II = 14 ± 8	37.5%	—	—
1997	Godeau et al	n = 181 SLE = 37 RA = 60 Vasculitis = 29	mean = 57 ± 17	mean SAPS II alive = 11 ± 6 dead = 17 ± 9	33%	43%	69% 5 yr
2000	Pourrat et al	n = 33	mean = 47 ± 22	mean SAPS II = 47 ± 22	30.3%	—	—
2001	Thong et al	n = 28 SLE = 20 RA = 3 Others = 5	mean = 38.9 ± 16.3	mean APACHE II all = 24.0 ± 9.5 alive = 21.8 ± 7.8 dead = 26.1 ± 9.7	53.6%	64.3%	—

* Gp I = rheumatic disease diagnosed in ICU, gp II = rheumatic disease previously known and treated.

The in-ICU mortality was 22.9%. However, neither of these papers reported the predicted mortality.

Pourrat et al⁶ reported 39 patients with systemic rheumatic diseases admitted to 2 ICUs over 7 years. The mean age was 50 ± 21 years, with the commonest reason for admission being acute respiratory failure (33%), followed by infection (33%) and disease flare (26%). Although the mean SAPS II score was high (47 ± 22), the in-ICU mortality was 30.3%, of which 60% was from infection.

Infection remains a frequent problem in patients with rheumatic disease and this accounted for 55.6% of our deaths. The incidence of infections was 16.6% of SLE admissions in an earlier local study by Oh et al.¹¹ Infection as the leading cause of death parallels Koh et al's earlier study of patients with SLE in Singapore,¹² where 40.3% of deaths were due to infection and 44.8% were due to SLE. Infection was also the commonest cause of death in Mok et al's southern Chinese population of lupus patients.¹³ However, there were 2 deaths in SLE patients in our cohort from atherosclerotic disease (coronary artery disease) at 12 and 96 months from the onset of SLE compared to none in Koh's study.

The mortality (more than 50% both in-MICU and in-hospital) in our Asian cohort is higher than that in previous studies on ICU patients. Infection risk may be related to the degree of immunosuppression, in particular, higher prednisolone dose, pulse methylprednisolone and cyclophosphamide as explored in previous literature.¹⁴ Bacterial infections were common whilst opportunistic and Mycobacterial infections were uncommon. The pattern of infections was similar to that in earlier ICU studies as well as our earlier local series except that none of the patients in our study developed salmonella infections.

Disease flare was a less common cause of death, as in previous ICU studies. There were 4 deaths principally from flare of the rheumatic disease or its progression. Two SLE patients died of pulmonary haemorrhage, one patient with scleroderma died from sudden cardiac death, probably from pulmonary hypertension and a patient with dermatomyositis died of respiratory failure from progressive pulmonary fibrosis.

There were a few differences between our cohort and previous ICU cohorts. Seventy-five per cent of our cohort had SLE. Patients were also generally younger with a mean

age of 38 years compared to previous studies where the mean or median age was in the 50s. However, there are no studies comparing the age-adjusted mortality of patients with SLE to those with other rheumatic diseases. Most of the previous studies used SAPS for prognostication, hence the APACHE II scoring in our study is not comparable. The in-ICU and in-hospital mortality were also much higher than that reported in previous MICU studies. This could be due to a higher proportion of SLE in our cohort, and more complex and severe rheumatic disease requiring more immunosuppressive therapy. The higher observed mortality compared to the predicted mortality may be due to the latter not being a very sensitive prognostic indicator in most rheumatic diseases, given their progressive multi-system involvement. None of the other studies computed the predicted mortality.

The non-survivors had a longer mean duration of rheumatic disease, higher mean APACHE II score, higher rates of hypertension and hyperlipidaemia, higher rates and doses of steroid and immunosuppressive therapy, and more organ failures compared to the survivors. However, the number of patients in each group was too few for any tests of statistical significance to be meaningful. Prospective studies are needed to evaluate the effects of these as prognostic factors on the patient outcomes.

Conclusion

Our Asian cohort comprised predominantly young females with SLE and good functional status. However, they had high severity scores, possibly contributed by chronic illness and immunosuppressive therapy. The most common reasons for admission to the MICU were septic shock and acute respiratory failure. More than 50% of the patients admitted to the MICU ultimately died, with infection accounting for more than 50% of the deaths. Despite the high mortality, these patients should be aggressively treated, as infection and acute respiratory failure are potentially reversible. Prospective studies are needed to fully evaluate the impact of these prognostic factors on patient outcomes.

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