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Outcome of children with systemic rheumatic diseases admitted to pediatric intensive care unit: An experience of a tertiary hospital

Sulaiman M Al-Mayouf^{a,*}, Rehab Fallatah^a, Mohammed Al-Twajery^a, Tareq Alayed^b, Abdullah Alsonbul^a

^a Pediatric Rheumatology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

^b Pediatric Intensive Care Unit, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

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ABSTRACT

Objective: To report the outcome of children with rheumatic diseases admitted to pediatric intensive care unit (PICU) in a tertiary hospital.

Methods: Database from PICU and pediatric rheumatology section used to retrieve all candidate patients admitted to PICU from June 2000 to December 2017. Medical records of all enrolled patients reviewed for diagnosis, organ involvement, reason of PICU admission, the length of stay, and outcome.

Results: Twenty-five patients (17 female, 8 male) with total of 41 admissions identified. The median PICU stay was 13.5 days (range, 3–24). The most frequent diagnoses were systemic lupus erythematosus (SLE) (48%), followed by systemic vasculitis (16%). Most admissions were from the medical ward (68.3%), while 24.4% from the emergency room. The main reason of PICU admission was a disease flare or related complications (48.8%), followed by infection (34.2%). Fifty one percent of the admissions were due to respiratory dysfunction, 46% required non-invasive respiratory support while 38% was in need for mechanical ventilation. During PICU stay, anti-microbial agents used 90.3%, immunosuppressive treatment adjustment 75.6%, anti-hypertensive 24.4% and vasopressors 12.2%. Twelve patients (48%) fully recovered and 40% partially recovered while three patients died during their PICU stay. The causes of death were macrophage activation syndrome complicated by sepsis in two patients and advanced pulmonary hypertension in one patient.

Conclusion: Our data showed that children with rheumatic diseases, particularly SLE, are mostly admitted to PICU with serious disease exacerbation or severe infection. To improve the outcome, early diagnosis of critical condition and proper intervention are fundamental in reducing mortality.

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1. Introduction

Childhood rheumatic diseases comprise a heterogeneous group of uncommon diseases which are categorized under autoimmune and autoinflammatory conditions [1–3]. These diseases have multisystem involvement with a variety of clinical manifestations which represent diagnostic and therapeutic challenges. Patients with systemic lupus erythematosus (SLE), systemic juvenile

idiopathic arthritis (sJIA), and systemic vasculitis are at high risk of frequent disease flares. Furthermore, they are immunocompromised due to the altered function of the adaptive and innate immune system in addition to the need of immunosuppressive treatment [4–6]. Children with rheumatic diseases may require hospitalization at the first assessment or during the disease course due to either disease flare, disease related complications, or incidental infection. Furthermore, seriously sick patients need admission to the pediatric intensive care unit (PICU).

The mortality of adult patients with systemic rheumatic diseases admitted to the intensive care unit is high, both during their stay in the intensive care unit and afterwards. The prognosis related to the age, poor prior chronic health status, earlier critical care unit admission, infection, and immunosuppressive treatment [7–9]. Unfortunately, the available published data about children with

* Corresponding author. Rheumatology, Department of Pediatrics, King Faisal Specialist Hospital and Research Center, Alfaisal University, Po Box 3354, Riyadh, 11211, Saudi Arabia.

E-mail address: mayouf@kfshrc.edu.sa (S.M. Al-Mayouf).

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rheumatic diseases admitted to intensive care unit is very limited [10,11]. Furthermore, we are not aware about any published data from the Middle East. The aim of this study was to report the indications and outcome of children with rheumatic diseases who required admission to the PICU of a tertiary hospital.

2. Methods

A retrospective cross-sectional study including all consecutive children with rheumatic diseases admitted to PICU at King Faisal Specialist Hospital and Research Centre (KFSH&RC), Riyadh, Saudi Arabia between June 2000 and December 2017. The diagnosis of rheumatic diseases was made by the standard classification criteria of these diseases and coded according to ICD-9. Database from PICU and pediatric rheumatology sections were used to retrieve all children with rheumatic diseases admitted to PICU. All included patients who were admitted under the care of pediatric rheumatology service and younger than 14 years at the time of PICU admission. It is worth mentioning that as per our hospital policy, those who exceed 14 years of age transferred to the adult rheumatology care to provide ongoing and comprehensive clinical care. The diagnoses of included patients were made by pediatric rheumatologists. Furthermore, those who were seen by rheumatology service as a consultation without confirmed rheumatic diseases were excluded. Medical records of all enrolled patients were reviewed for diagnosis, age at the onset of the disease, organ involvement, interval duration prior to PICU admission, immunosuppressive treatment prior to PICU admission and the indication for PICU admission. Furthermore, all patients were also reviewed for the length of stay, intervention and treatment during PICU stay and outcomes. Disease duration was calculated since the onset of first symptom related to the disease and the interval duration prior to PICU admission calculated from the diagnosis until PICU admission. Outcome was assessed in the view of the disease related mortality and morbidity and the impact on the patient after discharge from PICU. The outcome was defined as either recovery, partial recovery from the indication of PICU admission, or death.

Variables measured in interval scales were described as the mean $\pm$ standard deviation (SD), when variables had a normal distribution. When there was a non-normal distribution, the value was expressed as the median. Comparison of normally distributed continuous variables between groups was made using Student *t*-test and Chi-square test for categorical variables. Factors associated with outcome were assessed by a univariate approach using the Fisher's exact test. The following factors were assessed for an association with outcome: diagnosis, organ involvement, disease duration, prior immunosuppressive treatment, and length of stay in PICU. For all analysis, *P* value of <0.05 was considered significant.

Ethics committee of the Research Affairs Council at KFSH&RC approved the study protocol under RAC# 2171 096.

3. Results

A total of 41 PICU admissions for 25 patients (17 female, 8 male) with systemic rheumatic diseases were enrolled. Twenty-eight (68.3%) admissions were from the medical ward, while ten (24.4%) admissions from Emergency department and three (7.3%) were direct admissions from other hospitals. There were seven patients who had two or more PICU admissions; of whom four SLE patients admitted repeatedly to PICU due to refractory hypertension due to severe glomerulonephritis. One patient with sjIA complicated by macrophage activation syndrome (MAS), one juvenile dermatomyositis (JDM) patient with severe interstitial lung disease and one patient with juvenile systemic hyalinosis with dilated cardiomyopathy had multiple admissions.

Table 1 shows the demographic data, frequency of diagnoses, and organ involvement prior to PICU admission. The median age at PICU admission was 11.0 years (range, 1–14) and the median PICU stay was 13.5 days (range, 3–24). The most frequent diagnoses were SLE (52%) followed by systemic vasculitis (16%) including polyarteritis nodosa (PAN), severe Henoch-Schonlein purpura (HSP). The lungs and kidneys were the most frequently affected organs during the disease course prior to PICU admission. The majority of patients received immunosuppressive drugs and corticosteroids before PICU admission. Twenty-two patients received prednisone, low dose (<0.5 mg/kg/day) was used most frequently (76.8% of patients) with a mean dose of 8.4 ± 3.0 mg daily. Methylprednisolone pulses were giving to 15 patients during the acute disease flare. Eight patients commenced cyclic cyclophosphamide infusion ($500\text{--}750$ mg/m²) every month for six doses then every three months for another six doses, two of them received rituximab infusion (375 mg/m²), while four patients treated with mycophenolate mofetil (600 mg/m²/day). Three patients were on oral cyclosporine (5 mg/kg/day), subcutaneous methotrexate injection (15 mg/m²/week), two of them received anakinra (1 mg/kg/day) and one patient was on tocilizumab (12 mg/kg every two weeks).

The reasons for PICU admissions comprised of disease flare or related complications and severe infection. Few patients were admitted because of both disease flare and concurrent infection. Twenty-four admissions (58.5%) were due to disease related either a flare or complications. Most SLE patients required admission to PICU because of refractory hypertension associated with renal impairment secondary to glomerulonephritis. Two PAN patients admitted to PICU with severe hypertension and interstitial lung disease while two patients with HSP had severe gut involvement manifested by massive lower gastrointestinal tract bleeding and gut perforation. All three patients with JDM had severe interstitial lung disease complicated by air leak with pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema and required prolonged mechanical ventilation while MAS was the reason of admission for patients with sjIA. In contrast, infection was the cause in 17 (41.5%) admissions either documented or suspected infections. There were 13 admissions with documented infections; five patients had more than one infection. Pneumonia was the most frequent infection followed by bacteremia. The isolated organisms included staphylococcus aureus, streptococcus pneumoniae, streptococcus pyogenes, *Escherichia coli* and pseudomonas. Three patients had fungal infection with candida and aspergillus. Furthermore, four patients admitted with negative culture septic shock.

Table 2 shows the characteristics of the PICU stay and offered treatment and surgical intervention.

During the PICU stay, antimicrobial agents were the most frequently used medication followed by antihypertensive and vasopressors. Treatment of the underlying diseases was modified as needed, 23 patients have required higher dose of prednisone with a mean dose of 12.3 ± 5.3 mg daily and 19 patients were in need of immunosuppressive treatment adjustment. Twenty-one admissions (51.2%) were due to respiratory dysfunction; 46% of them required non-invasive respiratory support while 38% was in need for mechanical ventilation. Fifteen out of the 25 (60%) patients underwent 22 surgical intervention (ten central line insertion, four chest tube insertion, two pericardiocentesis, two lumbar punctures, one each required tracheostomy, fundoplication aorto-femoral graft and aneurysm resection, leg fasciotomy) and one patient required renal replacement therapy.

Twenty-two patients improved and discharged from the PICU and then from the hospital; 12 patients fully recovered, and 10 patients partially recovered. The condition of three out of the 25 (12%) patients deteriorated and eventually died during their PICU

Table 1

Demographic data, diagnoses and organ involvement of the 25 patients prior to PICU admission.

Total PICU admission	41
Age at diagnosis of rheumatic disease (years), median, range	7.6 (2.5–13.1)
Disease duration (years), median, range	6.7 (1.5–10.2)
Follow up duration (years), median, range	3.6 (1.4–7.3)
Disease interval prior PICU admission (months), median, range	18.3 (3–30)
Underlying disease	Number (%)
Systemic lupus erythematosus	13 (52)
Systemic vasculitis	4 (16)
Juvenile dermatomyositis	3 (1)
Juvenile idiopathic arthritis	2 (8)
Others ^a	2 (8)
Organ involvement prior PICU admission	Number (%)
Renal	13 (52)
Respiratory	12 (48)
Cardiovascular	10 (40)
Neurological	10 (40)
Musculoskeletal	7 (28)
Skin	5 (20)
Gastrointestinal	4 (16)
Medications prior PICU admission	Number (%)
Corticosteroids	23 (92)
Immunosuppressive agent	24 (96)
Antimicrobial agent	17 (68)
Antihypertensive agent	13 (52)

^a One juvenile systemic hyalinosis, one patient with macrophage activation syndrome.**Table 2**

Characteristics and outcome of PICU stay.

Age at PICU admission (years), median, range	11.0 (1–14)
Duration of PICU stay (days), median, range	13.5 (3–24)
Treatment during PICU stay	
Medications	
Antimicrobial agents	90.3
Immunosuppressive treatment adjustment	75.6
Antihypertensive agents	24.4
Vasopressors agents	12.2
Respiratory support	
Non-invasive support	46
Mechanical ventilation	38
Surgical intervention	
No. patients, (%)	15 (60)
No. procedures per total admissions, (%)	22 (53.7)
Outcome	
Alive patients, number, (%)	22 (88)
Fully recovered, number, (%)	12 (48)
Partially recovered, number, (%)	10 (40)
Deaths, number, (%)	3 (12)

stay. The cause of death was MAS complicated by sepsis in two patients and one patient died due to advanced pulmonary hypertension. In univariate analysis, severe interstitial lung disease requiring mechanical ventilation and frequent PICU admission were associated with poor outcome and mortality ($P < 0.05$). The association of the length of stay in PICU with the poor outcome was not statically significant ($P = 0.06$). Other variables including gender, diagnosis, disease duration and immunosuppressive treatment were not associated with the mortality (Table 3).

4. Discussion

Patients with rheumatic diseases may require PICU admission throughout their disease course due to disease flare associated with life-threatening conditions including multi-organ dysfunction or serious infections [12,13]. The outcome of patients admitted to critical care unit could be predicated based on the values of the severity scores. Acute Physiology and Chronic Health Evaluation

(APACHE) II score and Pediatric Risk of Mortality (PRISM) III are frequently used [11,14].

In general, data about the clinical features, outcomes and prognostic contributions of the underlying diseases in critically ill-children with rheumatic diseases admitted to critical care unit are scarce. To our knowledge, this study is the first report from Middle East. This study described the clinical characteristics, outcome of children with rheumatic diseases admitted to PICU in a tertiary referral hospital. Our findings are comparable to the available data from the largest cohort of children with rheumatic diseases admitted PICU. In line with previous reports, our findings were compared with a cohort of 90 patients, their age at first PICU admission was up to 17.4 years [11]. The cut off age at 14 years instead of higher probably underestimated the frequency of PICU admission in our cohort. Similarly, to our cohort, patients with SLE and systemic vasculitis constituted most of the enrolled patients. Also, the main indications for PICU admission were comparable, a flare and exacerbation of the underlying disease was the most common cause [11]. In cohort, most patients were diagnosed with the underlying disease few months before PICU admission, this may underscore the severity and complexity of the underlying diseases or poor compliance to the maintenance treatment. The second common reason for PICU admission was infection, namely sepsis and pneumonia. Serious and frequent infections requiring PICU admission may reflect the immunocompromised status of those patients either due to the underlying immunedysregulation or the intensity of immunosuppressive treatment. It is not unusual that the admission to critical care unit occurs years after the diagnosis [15].

Our patients had longer duration of PICU stay than the previous report cohort. It is possible that the refractory MAS and the need for prolonged mechanical ventilatory support due to complicated interstitial lung disease in our cohort are related in part to the long duration of PICU stay. while others had refractory cases of MAS. Ideally, when patients admitted to PICU, APACHE II and PRISM III score should be considered. These parameters have good prediction of mortality and outcome in PICU [18,19]. Due to the long period and the retrospective nature of our study, it was difficult retrieving the essential data for calculation of APACHE II and PRISM III for

Table 3

Univariate analysis of variables associated with the mortality.

Variables	OR (95% CI)	P value
Diagnosis	1.05 (0.98–1.12)	NS
Gender	1.52 (0.43–5.21)	NS
Interstitial lung disease requiring mechanical ventilation	9.1 (2.4–34.2)	<0.05
Frequent PICU admissions ^a	8.3 (2.7–24.3)	<0.05
Disease duration	1.01 (0.97–1.05)	NS
Previous immunosuppressive treatment	1.18 (0.36–3.45)	NS
Length of stay in PICU	5.4 (2.1–13.6)	0.06

OR = odds ratio, CI = confidence interval, NS = not significant.

^a More than two admissions.

most of the enrolled patients. Unfortunately, these parameters were not considered in our analysis.

The mortality rate in this study based on the deaths during the PICU admission is low. Two of the three deaths were attributed to MAS and serious infection. MAS associated with sJIA and SLE remains one of the common causes of admission to PICU and increased mortality [16,17]. This emphasizes the challenge in differentiating infection and other serious diseases complications from the clinical spectrum of the underlying rheumatic diseases.

In our cohort, severe lung disease requiring mechanical ventilation and the frequent admission to PICU have significantly contributed to the mortality. Most of our patients improved and discharged from PICU and later from the hospital in a stable condition. A recent study reported a higher mortality rate than the global PICU population; 18 out of 90 patients admitted to PICU died, of which 17 deaths happened during PICU stay. However, their patients had higher severity of illness at the time of admission to PICU based on PRISM III; most of the deaths were due to infection¹¹.

The mortality rate for all patients in PICU at KFSRC-RC, Riyadh is about 8%, while the overall mortality rate in our study is 12%, which is lower than the formerly reported rate [11]. Though, it is difficult to attribute the mortality rate in our cohort to a single reason. However, it is worth mentioning that the Pediatric Early Warning System (PEWS) applied in our hospital for many years. Pediatric Rapid Response Team (PRRT) identifies and assess in transferring unstable patients before their deterioration to PICU for observation and possible critical care management. Implantation of PEWS and PRRT assisted in recognizing and early intervention of critically ill-children, eventually reducing length of stay in PICU and mortality rate [20].

The retrospective design, the small sample and lack of the severity scores of illness when patients admitted to the PICU are considerable limitations in our study. Thus, all reported findings in this work should interpret in the light of these limitations. A multicenter study is the ideal to overcome the low number of patients. Hopefully, this study will be the first step for further study.

We conclude that children with rheumatic diseases, particularly SLE are mostly admitted to PICU with serious disease exacerbation or severe infection. To improve the outcome, early recognition and diagnosis of critical conditions and proper therapeutic intervention are fundamental in reducing mortality.

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