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ORIGINAL RESEARCH

Patients with Primary Immunodeficiencies in Pediatric Intensive Care Unit: Outcomes and Mortality-Related Risk Factors

Çağlar Ödek · Tanıl Kendirli · Figen Doğu · Ayhan Yaman · Göksel Vatansever · Funda Çipe · Şule Haskoloğlu · Can Ateş · Erdal İnce · Aydan İkincioğulları

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Abstract
Purposes The aims of this study were to review the frequency, characteristics, and the clinical course of primary immunodeficiency (PID) patients admitted to pediatric intensive care unit (PICU) and attempt to identify factors related with mortality that might predict a poor outcome.
Methods We performed a retrospective review of children with PID aged 1 month to 18 years and admitted to PICU from January 2002 to January 2012 in our tertiary teaching children's hospital.
Results There were a total of 51 patients accounting for 71 admissions to the PICU. The most common diagnosis was severe combined immunodeficiency. Respiratory problems were the leading cause for admission. A total of 20 patients received hematopoietic stem cell transplantation. Immune reconstitution was achieved in 9 (45 %) patients and eight of them did survive. In all 56 % of all admission episodes resulted in survival. Risk factors for mortality included requirement of mechanical ventilation ($P<.001$), number of organ system failure ($P=.013$), need for renal replacement therapy ($P<.001$), use of inotropes ($P<.001$), higher Pediatric Logistic Organ Dysfunction (PELOD) score ($P=.005$), and length of PICU stay ($P<.001$).
Conclusions This is the first study regarding the outcome and mortality-related risk factors for PID patients requiring PICU admission. We suggest that PICU management is as important as early diagnosis and treatment for these patients. Prediction of those at risk for poorer outcome might be beneficial for accurate intensive care management and survival.

Keywords Primary immunodeficiency · hematopoietic stem cell transplantation · pediatric intensive care unit · multiple organ failure · renal replacement therapy · mechanical ventilation

Introduction

Primary immunodeficiencies (PIDs) are inherited disorders characterized by poor or absent function in one or more components of the immune system. There is a wide spectrum of clinical manifestations like autoimmunity, allergy, and cancer but increased susceptibility to serious, recurrent, and unusual infections are the hallmark of PID [1–4]. Early diagnosis and accurate treatment are crucial for preventing morbidity and mortality. Despite advances in treatment, many patients suffer from serious complications associated with chronic infections, end-organ damage, and hematopoietic stem cell transplantation (HSCT) [5]. Patients have high rates of pediatric intensive care unit (PICU) admissions related to these complications but limited data are available.

We conducted this retrospective study to determine the frequency, characteristics, and the clinical course of PID patients who were admitted to PICU over 10 years. We also questioned whether identifying factors related with mortality and PICU outcome would be beneficial for physicians. We

Ç. Ödek · T. Kendirli · A. Yaman · G. Vatansever · E. İnce
Department of Pediatrics, Division of Pediatric Critical Care, Ankara University Faculty of Medicine, Ankara, Turkey

F. Doğu · F. Çipe · Ş. Haskoloğlu · A. İkincioğulları
Department of Pediatrics, Division of Pediatric Immunology and Allergy, Ankara University Faculty of Medicine, Ankara, Turkey

C. Ateş
Department of Biostatistics, Ankara University Faculty of Medicine, Ankara, Turkey

Ç. Ödek (✉)
Çocuk Yoğun Bakım Bilim Dalı, Ankara Üniversitesi Tıp Fakültesi Cebeci Hastaneleri, 06100Dikimevi, Ankara, Turkey
e-mail: odek@ankara.edu.tr

aimed to emphasize the importance of PICU management for PIDs.

Patients and Methods

Patient Population

Our institution is a tertiary teaching children's hospital with a 6-bed PICU capacity. During the study period our PICU had approximately 160–250 admissions per annum, with patients ranging in age from 1 month to 18 years. We performed a retrospective review of children aged 1 month to 18 years who were diagnosed with PID and required PICU admission at our institution between January 2002 and January 2012. All patients met the diagnostic criteria of PID defined by European Society for Immunodeficiencies (ESID) and Pan-American Group for Immunodeficiency (PAGID) [6]. Patients were included if they were admitted to PICU for a problem related to PID. PICU admission was determined by the requirement of mechanical ventilation, renal replacement therapy (RRT), inotrope infusions or observation for a potential deterioration in the clinical course. Patients were excluded if they were admitted to PICU for problems unrelated to their diagnosis of PID.

Data Collection

Approval for the study was obtained from the Medical Ethics Committee of Ankara University Faculty of Medicine before data collection began. The following data were obtained from electronical records and paper charts: patient age, sex, diagnosis, reason for admission to PICU, Pediatric Risk of Mortality III-24 (PRISM III-24) [7] and Pediatric Logistic Organ Dysfunction (PELOD) scores [8], number of organ system failures at the time of admission, length of PICU stay, PICU management, and outcome. Data also included the history of HSCT, donor type, source of stem cells, conditioning regimen, and cytomegalovirus (CMV) viral load. A positive result for CMV viremia was accepted as >400 copies/μL and identified with polymerase chain reaction.

Statistical Analysis

In order to test whether the data were normally distributed, the Kolmogorov-Smirnov and Shapiro Wilk tests were used. Homogeneities of variances were tested by Levene test. According to results Mann Whitney *U* test for continuous variables and chi-square test for categorical variables were used to evaluate differences between groups. Frequencies (percentages), medians (minimum-maximum), and means (±SD) were given as descriptive statistics. Statistical analyses were performed by using SPSS 15.0 for Windows and *P* value less than 0.05 were considered as statistically significant.

Results

Patients' Characteristics

During the study period, 821 patients with PID (Table I) were admitted to the pediatric immunology and allergy department and a total of 51 (6 %) patients required 71 episodes of admission to PICU (3.7 % of a total of 1,890 patients admitted to PICU over 10 years). We could not find the data of PICU management (ventilation support, inotropes, and RRT) and the number of organ system failures at admission in six episodes therefore these variables were analyzed over 65 episodes of admission. Forty (78 %) of 51 patients had 1 PICU admission each, while 7 had 2 admissions, 3 had 3 admissions and 1 patient had 9 admissions.

The median age at admission was 12 months (2 months–18 years). In all, 27 (53 %) were male. Age and sex were not significantly associated with mortality. Fifty-four (76 %) out of 71 PICU admissions were for patients with combined immunodeficiencies (CIDs). There was no significant difference in underlying diagnosis between survivors and non-survivors. Diagnoses and overall PICU outcome are given in Table II according to the 2011 update of International Union of Immunological Societies (IUIS) PID classification [9, 10].

Sixty-eight PID patients received allogeneic HSCT during the study period. Twenty (51 %) out of 39 CID patients admitted to PICU received HSCT. The rest of our CID patients could not receive HSCT because they were too unwell to undergo transplant or they did not have any matched donors. Sixteen patients were admitted to PICU following HSCT and

Table I Diagnoses of all primary immunodeficiency patients followed-up during the study period

Diagnosis	*N=821
Combined immunodeficiencies	142 (17,3 %)
- Severe combined immunodeficiency (SCID)	64 (45 %)
- Other combined immunodeficiencies	78 (55 %)
Predominantly antibody deficiencies	462 (56.2 %)
Well-defined syndromes with immunodeficiency	92 (11.3 %)
Diseases of immune dysregulation	35 (4.2 %)
Congenital defects of phagocyte number, function, or both	55 (6.7 %)
Defects in innate immunity	8 (1 %)
Autoinflammatory disorders	4 (0.5 %)
Complement deficiencies	9 (1.1 %)
Unclassifiable immune deficiencies	14 (1.7 %)

*N indicates total patient number

Table II Diagnoses of primary immunodeficiency patients admitted to pediatric intensive care unit and overall outcome

Diagnosis	All patients, *N=51	Survivors, *N=20
Combined immunodeficiencies	39 (76 %)	14 (36 %)
T-B- SCID	17 (44 %)	6 (35 %)
T-B + SCID	9 (23 %)	5 (55 %)
Omenn syndrome	5 (13 %)	1 (20 %)
DNA ligase IV deficiency	1 (2.5 %)	0
MHC class II deficiency	4 (10 %)	0
Hyperimmunglobulin M syndrome	1 (2.5 %)	1 (100 %)
Other combined immunodeficiencies	2 (5 %)	1 (50 %)
Predominantly antibody deficiencies	3 (6 %)	2 (67 %)
CVID	2 (67 %)	2 (100 %)
Selective IgA deficiency	1 (33 %)	0
Congenital defects of phagocyte number, function, or both	2 (4 %)	1 (50 %)
Chronic granulomatous disease	2 (100 %)	1 (50 %)
Diseases of immune dysregulation	3 (6 %)	1 (33 %)
ALPS	3 (100 %)	1 (33 %)
Complement deficiencies	1 (2 %)	1 (100 %)
C2 deficiency	1 (100 %)	1 (100 %)
Well-defined syndromes with immunodeficiency	3 (6 %)	1 (33 %)
AT	1 (33 %)	0
WAS	2 (67 %)	1 (50 %)

PICU indicates pediatric intensive care unit, *CVID* common variable immunodeficiency, *ALPS* autoimmune lymphoproliferative syndrome, *AT* ataxia telangiectasia, *WAS* Wiscott-Aldrich syndrome

**N* indicates patient number

other four received HSCT during their PICU stay. The timing of PICU admissions in the post-HSCT period were ranged between 7 and 97 days after transplantation. Cyclosporin A has been the agent of choice for graft versus host disease (GvHD) prophylaxis in nine transplantations. Eight (40 %) patients received a myeloablative conditioning regimen with busulphan and cyclophosphamide. CMV reactivation, B + SCID phenotype, and unstable clinical status were the main criteria for unconditioned transplant. Immune reconstitution was achieved in 9 (45 %) patients and eight of them did survive. One patient died because of complications related with GvHD at day +103 after transplantation. Other deaths occured in the first 100 days after HSCT. Immune reconstitution did not happen in five patients and could not be evaluated in six patients because they died too early to evaluate. Immune reconstitution was significantly associated with mortality ($P<.001$). HSCT characteristics are summarized in Table III.

Reason for Admission

In all, 52 (73 %) admission episodes were for respiratory problems (pneumonia, acute respiratory distress syndrome defined by the criteria that were recommended by the American-European Consensus Conference on acute respiratory distress syndrome [11], pleural effusion, pulmonary edema, and respiratory arrest) eight were for sepsis and septic shock, two were for intractable diarrhea and hypovolemic shock, eight were for neurological problems (seizures or encephalopathy) and one was for elective post-operative admission following osteomyelitis surgery. Reason for admission was not significantly associated with mortality.

PICU Management

PICU management of the patients are summarized in Table IV. All patients were scored with PRISM III-24 and PELOD. Median PRISM III-24 scores were 5.5 (0–19) and 7 (0–18) in survivors and non-survivors respectively. Median PELOD scores were 1 (0–22) in survivors and 10 (0–21) in non-survivors. There was a significant difference in PELOD score between survivors and non-survivors ($P=.005$).

A total of 65 admissions (91 %) were for support of at least one organ system, while six admissions were for observation for potential deterioration. Respiratory failure was seen in 50 (77 %) of the 65 episodes. The mean number of organ system failure is 1.82 ± 0.98 in survivors and 2.41 ± 1.04 in non-survivors. There is a significant difference in the number of organ system failures between survivors and non-survivors ($P=.013$).

Patients required mechanical ventilation in 46 (71 %) episodes. Non-invasive ventilation, invasive ventilation, high frequency oscillatory ventilation or combination of these were the types of ventilation supports used. There is a significant difference in requirement of mechanical ventilation between survivors and non-survivors ($P<.001$). Median duration of mechanical ventilation is 6 (1–103) days for survivors and

Table III The characteristics of patients those received hematopoietic stem cell transplantation

Patient number	Gender	Diagnosis	Donor type	Stem cell source	GvHD prophylaxis	Conditioning regimen	CMV viremia	Immune reconstitution[a]	Survivors
1	F	T-B- SCID	H	PB	CsA	Bu/Cy	−	+	+
2	F	T-B- SCID	H	PB	CsA	Bu/Cy	−	+	+
3	M	T-B- SCID	H	PB	CsA	Bu/Cy	−	Not evaluated	−
4	F	T-B- SCID	H	PB	CsA	Bu/Cy	−	Did not happen	−
5	F	T-B- SCID	MS	BM	−	−	+	+	+
6	M	T-B- SCID	MS	BM	CsA	Bu/Cy	+	Did not happen	−
7	M	T-B- SCID	H	PB	CsA	−	+	Not evaluated	−
8	M	T-B- SCID	H	PB	−	−	+	Did not happen	−
9	M	T-B + SCID	H	PB	CsA	Bu/Cy	+	+	+
10	M	T-B + SCID	MF	BM	−	−	−	Not evaluated	−
11	M	T-B + SCID	MF	BM	−	−	−	+	+
12	M	T-B + SCID	MS	PB	−	−	+	+	+
13	M	T-B + SCID	MF	PB	−	−	−	+	+
14	F	T-B + SCID	H	PB	−	−	+	Did not happen	−
15	F	Omenn S	MS	BM	CsA	Bu/Cy	+	+	+
16	M	Omenn S	H	PB	CsA	Bu/Cy	+	Did not happen	−
17	M	Omenn S	MF	BM	−	−	−	Not evaluated	−
18	M	Omenn S	H	PB	−	−	+	Not evaluated	−
19	F	DNA ligase IV def	MF	BM	−	−	−	Not evaluated	−
20	F	MHC class II def	MF	BM	CsA	Bu/Cy	+	+	−

F indicates female, *M* male, *H* haploidentical, *MS* matched sibling, *MF* matched family, *PB* peripheric blood, *BM* bone marrow, *CsA* cyclosporine, *Bu* busulphan, *Cy* cyclophosphamide

[a] Immune reconstitution was assessed by lymphocyte phenotyping and functional assays after engraftment

11 (1–42) days for non-survivors. Duration of ventilation support was not related with survival.

Of the 65 episodes, patients required 1 inotrope in 9 (14 %), 2 inotropes in 11 (17 %), 3 inotropes in 8 (12 %), and 4

Table IV Pediatric intensive care unit management

PICU management	Survivors, *N=38	Non-survivors, *N=27	**P
PRISM III-24	5.5 (0–19)	7 (0–18)	.435
PELOD	1 (0–22)	10 (0–21)	.005
Number of organ system failures	1.82±0.98	2.41±1.04	.013
Ventilation support	19	27	<.001
NIV	3	–	
NIV + IV	2	–	
IV	14	17	
IV + HFOV	–	10	
Duration of ventilation support (days)	6 (1–103)	11 (1–42)	.299
RRT	1	10	<.001
Peritoneal dialysis	1	10	
Inotropes	5	24	<.001
1	2	7	
2	1	10	
3	2	6	
4	–	1	
Length of PICU stay (days)	6 (1–103)	13 (1–43)	<.001

PICU indicates pediatric intensive care unit, *PRISM III-24* Pediatric Risk of Mortality III-24 score, *PELOD* Pediatric Logistic Organ Dysfunction score, *NIV* non-invazive ventilation, *IV* invazive ventilation, *HFOV* high frequency oscillatory ventilation, *RRT* renal replacement therapy

*N indicates the number of PICU admission episodes and analyzed over 65 episodes because of missing data in six episodes

**P value less than 0.05 were considered as statistically significant

inotropes in 1 episode. In 36 episodes, patients did not require inotrope infusion. There is a significant difference in the number of inotrope infusions between survivors and non-survivors ($P<.001$).

Renal replacement therapy was performed in 11 (17 %) episodes. Peritoneal dialysis was chosen as RRT modality in all patients. There is a significant difference in requirement of RRT between survivors and non-survivors ($P<.001$).

Outcome

Median length of PICU stay were 6 (1–103) days in survivors and 13 (1–43) days in non-survivors. There was a significant difference in duration of PICU stay between survivors and non-survivors ($P<.001$).

In all, 40 (56 %) episodes resulted in survival. A total of 20 children (39 %) survived to discharge from PICU. Of those who died, 26 (51 %) deaths occured during the first admission, four deaths occured during the second admission and one death occured during the third admission. One child survived nine admissions. There was no significant difference between the number of admissions required and survival. The causes of death are summarized in Table V.

Discussion

To our knowledge, this is the first study specifically regarding the outcome and the mortality-related risk factors for children with PID requiring PICU admission. In all, 9 % of the PID patients required intensive care unit admission. Because of the pre-existing severe infections, organ damage and complications related with HSCT, it was 29 % in the patient group who underwent HSCT. Our findings were similar to the previous studies [12, 13].

Age, sex, and underlying diagnosis were not significantly associated with mortality. Previous studies showed that patients younger than 6 months of age have more frequent PICU admissions and less survival because severe forms of PID like SCID and Omenn syndrome usually present early in life [5]. Similar to these reports, 54 (76 %) episodes of our 71 PICU admissions were for patients with CID and 56 % of them were younger than 6 months of age. It is well known that patients with CID, especially Omenn syndrome patients [14], have the worst outcome compared to other PIDs due to the severity of manifestations and infections. Twenty-five (64 %) of 39 CID patients did not survive but this finding did not reach to a statistical significance. This could be due to our heterogenous patient population. However, the overall 56 % survival rate is quite striking.

Reason for PICU admission was not significantly associated with mortality. Respiratory problems were the leading cause for admission. This is not surprising because respiratory failure due to severe infections are common [15]. Al-Herz et al. showed that sepsis and pneumonia were the most common causes of death in PID patients [5]. Need for intubation and mechanical ventilation was shown to be the most common cause of PICU admission in children following HSCT for PID and other non-malignant disorders [13].

Previous reports showed that relative mortality risk was high for patients who required ventilation support in PICUs [16]. We observed that requirement for mechanical ventilation was significantly associated with mortality. It is well documented that the prognosis of the immunocompromised patients with respiratory failure severe enough to require ventilation support is poor. The risk of death is higher especially if the patient had CMV pneumonia [17]. Eleven (28 %) of our CID patients had CMV pneumonia and 81 % of them did not survive. Avoiding intubation and mechanical ventilation is a major goal in the management of respiratory failure in immunocompromised patients because they are predisposed to secondary bacterial infections and ventilator-associated pneumonia (VAP). Six of our intubated CID patients developed VAP and all these six admissions resulted in death. Three of our

Table V The causes of death and underlying diagnoses

The cause of death	Underlying diagnosis	*N=31
Septic shock + MODS	Combined immunodeficiencies	12
	Diseases of immune dysregulation	2
	Congenital defects of phagocytes	1
Pneumonia + ARDS		
- CMV	Combined immunodeficiencies	9
- Bacterial	Combined immunodeficiencies	2
GvHD related complications	Combined immunodeficiency	1
Myocarditis	Predominantly antibody deficiency	1
Intracranial hemorrhage	Wiscott-Aldrich syndrome	1
Massive gastrointestinal hemorrhage	Combined immunodeficiency	1
Massive pulmonary hemorrhage	Ataxia telengiectasia	1

MODS indicates multiple organ dysfunction syndrome, *ARDS* acute respiratory distress syndrome, *CMV* cytomegalovirus

**N* indicates patient number

patients (2 CIDs, 1 ataxia telengiectasia) who were managed by non-invasive ventilation did survive (Table IV). Non-invasive ventilation might be a successful treatment option for these patients who are at an early stage of hypoxemic respiratory failure [18].

Multiple organ failure (MOF) is defined by failure of at least two organ systems. There is an association between the increasing number of organ failures and PICU mortality [19]. There was a significant difference in number of organ failures between survivors and non-survivors. We observed that requirement for 1 or more inotrope infusions for cardiovascular instability is significantly associated with mortality. Timely use of RRT might be life saving in critically ill children [20]. It is recognised that there is a significant association between renal failure requiring RRT and death [13]. Fluid overload due to acute kidney injury or failure is associated with impared oxygenation and morbidity [21]. Similar to previous reports, renal failure requiring RRT was associated with poorer outcome in our study.

PELOD is the most frequently used score aiming to describe the severity of cases of MOF. The relationship between mortality and number of dysfunctioning organs is stronger than that with presence or absence of MOF [22, 23]. We observed that there was a significant difference in PELOD score between survivors and non-survivors. PRISM III-24 score is unique in that it can predict both mortality and length of stay in PICU [23] but there was no significant difference in PRISM III-24 scores between survivors and non-survivors.

The treatment of PID is complex and generally involves both supportive and definitive strategies. HSCT can be curative for PID, has improved the survival rate of PID patients [24], and is the only curative therapy for SCID [25]. It is very important to perform HSCT before the patient develops complications related to the disease. Children with SCID who are healthy at the time of transplant and who have HLA-matched donors are expected to have a better than 90 % chance of long term survival [26]. In the absence of a matched family donor, haploidentical transplantation from parental donors represents an available option and offers a high chance of cure [25, 27]. There were no significant differences in donor type, source of stem cells, GvHD prophylaxis, and conditioning regimen between survivors and non-survivors in our study.

Despite recent advances in HSCT techniques, many patients suffer from HSCT related complications and require intensive care support. These patients need high dependency level care which can be provided by pediatric HSCT wards but admission to PICU is required when the need for invasive ventilation, inotrope and RRT occurs [13]. The need for ventilation support, RRT, and presence of MOF were significantly associated with mortality in our study. Although there is no literature available specifically regarding the outcome for children with PID requiring intensive care following HSCT, Cole et al. showed that the outcome for children undergoing HSCT for PIDs (92 % of the study population were diagnosed with PIDs) and other non-malignant conditions who require intensive care admission is worse than for those who do not require this support (survivals were 38 % and 96 % respectively) [13] . Survival for HSCT patients admitted to PICU was 8/20 (40 %), compared with 47/48 (98 %) for those who were never admitted to PICU. All these findings may be useful when counselling families whose child with PID deteriorated and required PICU admission.

The present study has some limitations. The major limitation was the small size of this single-center study, which may pose barriers to the generalization of the results. The study design was retrospective and some of the data were missing. It is possible that these limitations could have some impact on our findings. But this is the first study regarding the outcome and mortality-related risk factors for PID patients requiring intensive care admission and the results are encouraging. Prospective validation of our predictive model with larger numbers and at multiple institutions would improve its utility.

Conclusions

Patients with PID had high rates of PICU admission. Respiratory failure was the most common reason for PICU admission. Length of PICU stay, higher PELOD score at the time of admission, MOF, requirement of mechanical ventilation, RRT, and inotropes are associated with mortality. Immune reconstitution after HSCT was significantly associated with mortality. With adequate support, 56 % of all admission episodes resulted in survival. We suggested that PICU management is as important as early diagnosis and accurate treatment for these patients.

Conflict of Interest The authors declare that they have no conflict of interest.

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