Immunomodulator use in paediatric severe sepsis and septic shock

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ABSTRACT

Introduction: The use of drugs that modulate the immune system during paediatric severe sepsis and septic shock may alter the course of disease and is poorly studied. This study aims to characterise these children who received immunomodulators and describe their clinical outcomes.

Methods: This is a retrospective chart review of patients with severe sepsis and septic shock admitted into the paediatric intensive care unit (PICU). Clinical, haematological and outcome characteristics of patients with or without exposure to immune-modulating drugs were compared. Primary outcome was PICU mortality; secondary outcomes were 28-day ventilator-free days (VFD) and intensive care unit-free days (IFD). Univariate and multivariable analyses were performed for these outcomes.

Results: A total of 109 patients with paediatric severe sepsis or septic shock were identified. Of this number, 47 (43.1%), 16 (14.7%) and 3 (2.8%) patients received systemic corticosteroids, intravenous immunoglobulins and granulocyte colony stimulating factor, respectively. Patients who received immune-modulating drugs were more likely to require invasive ventilation (38/54 [70.4%] versus 26/55 [47.3%], $P=0.019$) compared to those who did not. PICU mortality was indifferent between the 2 groups (20/54 [37.0%] vs 11/55 [20.0%], $P=0.058$) even after accounting for chronic complex conditions and admission organ dysfunction (PELOD score) (adjusted odds ratio 1.90, confidence interval [0.72–5.01], $P=0.193$). However, VFD (19.5 [0–28] vs 25 [12–28] days, $P=0.038$) and IFD (15 [0–24] vs 22 [9–26] days, $P=0.024$) were decreased in the immunomodulator group compared to the non-immunomodulator group.

Conclusion: Immune-modulating drugs were frequently used in paediatric severe sepsis and septic shock. Patients who received these drugs seemed to require more PICU support. Further studies are required to examine this association thoroughly.

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INTRODUCTION

Paediatric sepsis is one of the main causes of childhood mortality.¹ Globally, paediatric severe sepsis and septic shock accounts for 6.2% to 23.1% of paediatric intensive care unit (PICU) admissions, and mortality rates can be as high as 21.3% in North America and Europe to 50.0% in Asia.²⁻⁴ Of particular concern are the outcomes in the increasing number of children with significant comorbidities such as malignancy, or those with chronic organ impairment

who survive into later years and pose new considerations to the management of severe sepsis and septic shock.⁵⁻⁷

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.⁸ This definition recognises the role of the host immune response to an infection. Sepsis is thought to be driven by an initial hyper-inflammatory response followed by an immunosuppressive phase. However, recent studies have shown a shift towards a new paradigm, where a prolonged inflammatory and anti-inflammatory state

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CLINICAL IMPACT

What is New

- Our report shows frequent exposure to immune-modulating drugs in children with severe sepsis and septic shock.
- The reactive increase in white cell indices expected during the course of sepsis is absent in children exposed to immune-modulating drugs.
- Exposure to immune-modulating drugs during paediatric severe sepsis and septic shock is associated with greater duration of invasive mechanical ventilation and paediatric intensive care stay.

Clinical Implications

- Exposure to immune-modulating drugs during paediatric severe sepsis and septic shock is associated with worsened clinical outcomes and warrants further study.

occurring simultaneously is driven by a dysfunctional innate and suppressed adaptive immunity, which together results in persistent organ injury and death.^{9–11} Therefore, it has been theorised that immunotherapy holds promise in modulating the immune system. However, the use of immunotherapy in treating sepsis has been met with mixed results.^{12,13} Recent clinical trials involving corticosteroids showed mixed results regarding mortality and hospitalisation.^{14,15} A Cochrane review on intravenous immunoglobulin (IVIG) revealed mortality benefit in adults with sepsis but not in neonates.¹⁶ Statistically proven mortality benefit has yet to be found with the use of granulocyte-colony stimulating factor (GCSF), interferon-gamma, interleukin-7 and anti-PD1 (programmed cell death protein 1) in sepsis.^{17–20}

While several studies have been conducted in the paediatric setting, these have largely involved limited sample sizes with inconclusive results.^{21–23} Nevertheless, we suspect these therapies are often utilised in the management of paediatric sepsis and septic shock.²⁴ In this study, we review cases of paediatric severe sepsis and septic shock in our institution to determine the characteristics of patients who concurrently received immune-modulating drugs, particularly corticosteroids, IVIG and GCSF, and examine their outcomes.

METHODS

This is a retrospective cohort study conducted in the PICU of KK Women's and Children's Hospital, a university-affiliated tertiary hospital in Singapore. This

study was approved by the SingHealth Centralised Institutional Review Board (reference number: 2016/2171) and a waiver of consent was granted.

Patients were identified based on their discharge diagnosis from hospital-wide electronic medical databases. Patients aged 0 to 18 years admitted to the PICU between 1 January 2010 and 31 October 2017 were included upon meeting the diagnostic criteria for paediatric severe sepsis or septic shock as defined by the International Pediatric Sepsis Consensus Conference.²⁵ The use of corticosteroids, GCSF, IVIG, plasma exchange or other biologic drugs at the time of PICU admission for sepsis, regardless of indication, was considered to play a direct role on the immune system and categorised in the immunomodulator group. Patients who did not meet the above criteria were placed under the non-immunomodulator group.

Demographic, clinical, microbiological and detailed treatment data were obtained from electronic medical records. Significant chronic comorbidities were defined by the complex chronic conditions list of diseases.²⁶ Complex chronic conditions refer to a list of medical conditions that can be reasonably expected to last at least 12 months (unless death intervenes) and to involve either several organ systems or at least 1 organ system severely enough to require specialty paediatric care and probably some period of hospitalisation in a tertiary care centre.²⁶ Severity of illness scores, Pediatric Index of Mortality (PIM) 2 score and the Pediatric Logistic Organ Dysfunction (PELOD) score were obtained on PICU admission.^{27–29} Organ dysfunction was defined based on the International Pediatric Sepsis Consensus Conference definition.²⁵ Day 1 of severe sepsis and/or septic shock was defined as the day the patient fulfilled the criteria for severe sepsis or septic shock in the PICU. 28-day ventilator-free days (VFD) is defined as days alive and free from invasive mechanical ventilation up to 28 days—this is to account for early deaths.³⁰ Similarly, 28-day intensive care unit-free days (IFD) is defined as days alive and discharged from the PICU up to 28 days.

Statistical analysis

We compared patients in 2 groups: the immunomodulation group and non-immunomodulation group. Clinical characteristics were compared between the 2 groups. Haematological markers across the first 7 days of sepsis including the total leukocyte, lymphocyte, neutrophil and platelet counts were also compared between the 2 groups. The primary outcome of this study was PICU mortality. Secondary outcomes included VFD and IFD. Categorical and continuous variables were expressed as counts (percentages) and median (interquartile range),

respectively. The Fisher's exact test and Wilcoxon rank sum test were used to compare categorical and continuous variables, respectively. Multivariable logistic regression for the primary outcome was performed with a priori determined covariates: presence of chronic complex conditions, organ dysfunction (summarised as the PELOD score) and the use of immunomodulators. Association from logistic regression was characterised as odds ratio (OR) with corresponding 95% confidence intervals (CI). The logistic regression was repeated, excluding patients exposed to immunomodulators for autoimmune or immune related indications, as a sensitivity analysis. Secondary outcomes were also analysed with respect to immunomodulator versus non-immunomodulator groups. Analysis was performed on STATA software version 15.1 (StataCorp, College Station, US). All tests were 2-tailed and P value <0.05 was accepted as statistically significant.

RESULTS

There were 109 patients who met the criteria for paediatric severe sepsis or septic shock (Table 1). Clinical characteristics were similar between the immunomodulator and non-immunomodulator groups in terms of age, presence of complex chronic conditions, PIM2, PELOD scores and source of sepsis on admission. The most common source of sepsis was pneumonia (59/109, 54.1%), followed by gastrointestinal (16/109, 14.7%) and musculoskeletal (8/109, 7.3%) (Table 2). Sepsis from a single aetiological agent was most commonly bacterial (28/109, 25.7%), followed by viral (25/109, 22.9%). Co-infections were present in 19 (17.4%) patients and no identifiable aetiological agent was found in 32 (29.4%).

Immunomodulating therapies, regardless of indications, were used in 54 (49.5%) patients. Systemic corticosteroid was the most common immunomodulator (47/109, 43.1%), followed by IVIG (16/109, 14.7%) and GCSF (3/109, 2.8%). One patient who fulfilled the criteria for severe sepsis also received therapeutic plasma exchange. There were no patients who concurrently received chemotherapy or biologics during the course of sepsis in the PICU. The clinical indications for use of these therapies are summarised in Table 3. The median total white cell count was lower in the group receiving immunomodulators throughout the first 7 days of study (except on day 2, which did not reach statistical significance) (Fig. 1A). The trend of total white cell count was also observed to increase across the 7 days in those without exposure to immunomodulators, but this was not seen in those on immunomodulator group. A similar trend was seen in the

absolute neutrophil and lymphocyte counts, especially toward the end of the 7 days (Figs. 1B and 1C). There was no difference in the platelet count over the 7 days of sepsis between the 2 groups (Fig. 1D).

Despite having similar admission characteristics, patients in the immunomodulation group required greater PICU support compared to those in the non-immunomodulation group, including invasive ventilation (38/54, 70.4% vs 26/55, 47.3%; $P=0.019$) and inotropes (41/54, 75.9% vs 32/55, 58.2%; $P=0.067$), though this did not reach statistical significance. Ventilator- and ICU-free days were also reduced in the immunomodulator group (20 [0–28] vs 25 [12–28]; $P=0.038$ and 15 [0–24] vs 22 [9–26]; $P=0.024$, respectively). In this sepsis cohort, a total of 31 deaths (28.4%) occurred. PICU mortality was higher among patients receiving immunomodulating therapy compared to patients who did not receive it (20/54 [37.0%] vs 11/55 [20.0%]; $P=0.058$), although this was not statistically significant (Table 1). Significantly greater number of patients with malignancy received immunomodulator therapy as compared to those who did not (14/54 [25.9%] vs 3/55 [5.5%]; $P=0.004$). After accounting for complex chronic conditions and admission organ dysfunction (PELOD score), exposure to immunomodulator therapy was not associated with an increase in PICU mortality (adjusted odds ratio 1.90 (95% confidence interval 0.72–5.01); $P=0.193$) (Table 4). In the sensitivity analysis excluding patients exposed to immunomodulators for autoimmune or immune related indications, the results were similar.

DISCUSSION

Our report shows frequent exposure to immunomodulating drugs in children with severe sepsis and septic shock. This group of children seem to require greater PICU support including mechanical ventilation and inotropes. After adjusting for complex chronic conditions and admission organ dysfunction, immunomodulators were associated with an almost 2-fold increased mortality, though this did not achieve statistical significance due to the small cohort size. A reactive and expected increase in white cell indices was observed in children with severe sepsis and septic shock. However, this was absent in those receiving immunomodulators.

The use of immunomodulators may inherently bias towards a group of patients with underlying immunological defects (e.g. malignancies, chemotherapy and autoimmune disease), though in the logistic regression model, these conditions were accounted for. In our cohort, 17 patients had malignancy and 3 patients had haematological disease, for which 14 patients and

Table 1. Characteristics of patients who received immune modulating therapy

	Immune modulation (n=54)	No immune modulation (n=55)	All (N=109)	P value
Age, median (IQR), years	9.3 (1.4–13.0)	9.4 (0.4–13.1)	9.4 (2.4–13.0)	0.952
Male sex, no. (%)	22 (40.7)	29 (52.7)	51 (46.8)	0.251
Weight, median (IQR), kg	24.7 (12.7–37.8)	24.4 (11.2–40.0)	24.4 (11.5–40.0)	0.971
CCC, no. (%)	31 (57.4)	23 (41.8)	54 (49.5)	0.127
Malignancy	14 (25.9)	3 (5.5)	17 (15.6)	0.004
Haematology-Immunology	2 (3.7)	1 (1.8)	3 (2.8)	0.618
PIM 2, median (IQR)	3.3 (1.3–7.1)	3.5 (1.2–9.6)	3.4 (1.3–8.9)	0.854
PELOD, median (IQR)	13 (11–22)	11 (10–21)	12 (10–21)	0.123
Source of sepsis, no. (%)				0.603
Pneumonia	26 (48.2)	31 (56.4)	57 (52.3)	
Central nervous system	4 (7.4)	3 (5.5)	7 (6.4)	
Musculoskeletal	6 (11.1)	2 (3.6)	8 (7.3)	
Gastrointestinal	7 (13.0)	10 (18.1)	17 (15.6)	
Blood stream	4 (7.4)	2 (3.6)	6 (5.5)	
Others	7 (13.0)	7 (12.7)	14 (12.8)	
Bacteraemia, no. (%)	12 (22.6)	11 (19.6)	23 (21.2)	0.815
Source control, no. (%)	4 (7.4)	7 (12.7)	11 (10.1)	0.527
Inotropes, no. (%)	41 (75.9)	32 (58.2)	73 (67.0)	0.067
Non-invasive ventilation, no. (%)	13 (24.1)	18 (32.7)	31 (28.4)	0.397
Invasive ventilation, no. (%)	38 (70.4)	26 (47.3)	64 (58.7)	0.019
Duration of invasive ventilation, no. (%), days	3 (0, 6)	0 (0, 4)	2 (0, 5)	0.134
VFD, median (IQR), days	19.5 (0–28)	25 (12–28)	23 (0–28)	0.038
Multorgan dysfunction, no. (%)	51 (94.4)	46 (83.6)	97 (89.0)	0.124
ECMO, no. (%)	6 (11.1)	3 (5.5)	9 (8.3)	0.320
Mortality, no. (%)	20 (37.0)	11 (20.0)	31 (28.4)	0.058
ICU LOS, median (IQR), days	5 (2–11)	3 (1–7)	4 (2–9)	0.076
IFD, median (IQR), days	15 (0–24)	22 (9–26)	21 (0–25)	0.024
Hospital LOS, median (IQR), days	15 (7–29)	10 (5–19)	12 (6–22)	0.146

CCC: complex chronic conditions; ECMO: extra-corporeal membrane oxygenation; ICU: intensive care unit; IFD: 28-day intensive care unit-free days; IQR: interquartile range; LOS: length of stay; PELOD: Pediatric Logistic Organ Dysfunction; PIM: Pediatric Index of Mortality; VFD: 28-day ventilator-free days

Categorical variables are reported as count (percentages) and continuous variables are reported as median (IQR)

P values in bold are significant

2 patients, respectively received immunomodulator therapy. In the same way, patients with significant organ dysfunction at PICU admission who were likely to bias the outcome negatively were also accounted for. Nevertheless, our study seems to suggest that

immunomodulator therapy was associated with an almost 2-fold increase in mortality, although this was statistically not significant. A prospective study with a larger sample size would provide a clearer association and determination of statistical significance.

Table 2. Aetiologic agents involved in paediatric severe sepsis and septic shock

Source of sepsis	None (n=32)	Single aetiologic agent			Co-infection			
		Bacteria (n=28)	Virus (n=25)	Fungi (n=5)	Bacteria and virus (n=9)	Bacterial and fungi (n=3)	Virus and fungi (n=6)	Bacteria, virus and fungi (n=1)
Pneumonia	15	13	16	3	4	1	6	1
Genito-urinary	0	1	0	0	1	0	0	0
Central nervous system	0	2	4	0	1	0	0	0
Musculoskeletal	4	4	0	0	0	0	0	0
Gastrointestinal	5	2	3	1	3	2	0	0
Blood stream	0	6	0	0	0	0	0	0
Others	2	0	2	1	0	0	0	0
No primary source	6	0	0	0	0	0	0	0

Table 3. Indications for immune-modulating therapy

Immune modulating therapy	Indication	Patients, no.
Systemic corticosteroids (n=47)	Septic shock	26
	Respiratory disease	11
	Pulmonary hemosiderosis	
	Pulmonary fibrosis	
	Asthma	
	ARDS	
IVIg (n=16)	Airway oedema	
	Premedication for blood transfusion (or other drugs)	5
	Others	5
	Takayasu arteritis	
	Hypoglycaemia	
	Acute necrotising encephalomyelitis	
	Autoimmune haemolysis	
	Resistant mycoplasma infection	
	Infection	10
	Severe sepsis	
GCSF (n=3)	Influenza encephalitis	
	Toxic shock syndrome	
	Myocarditis	
	Adenovirus infection	
	Immunoglobulin replacement	3
	Post HSCT	
Therapeutic plasma exchange (n=1)	Primary immunodeficiency	
	Haemophagocytic histiocytosis	
	Autoimmune disease	3
	Takayasu arteritis	
GSCF (n=3)	Kawasaki disease	
	Autoimmune haemolysis	
	Severe neutropenic sepsis	3
Therapeutic plasma exchange (n=1)	Post-chemotherapy	
	Haemophagocytic histiocytosis	
Autoimmune haemolysis		1

ARDS: acute respiratory distress syndrome; GCSF: granulocyte-colony stimulating factor; HSCT: haematopoietic stem cell transplant; IVIG: intravenous immunoglobulin

Fig. 1. Trend of haematological markers across first 7 days of sepsis in patients with and without immunomodulator therapy.

(A) Total white cell count trend.

(B) Absolute neutrophil count trend.

(C) Absolute leukocyte count trend.

(D) Platelet count trend.

Table 4. Multivariable logistic regression for paediatric intensive care unit mortality

Covariate	Univariate			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
CCC	2.86	1.19–6.88	0.019	2.16	0.80–5.82	0.127
PELOD	1.11	1.05–1.16	<0.001	1.10	1.05–1.16	<0.001
Immuno-modulation	2.35	0.99–5.57	0.051	1.90	0.72–5.01	0.193

Replacing “CCC” with “malignancy” generated similar results

CCC: complex chronic conditions; CI: confidence interval; OR: odds ratio; PELOD: Pediatric Logistic Organ Dysfunction

The majority of immunomodulator use consisted of systemic corticosteroids (47/54, 87.0%). Though indications for the use of corticosteroids, in our cohort, were largely adrenal suppression and respiratory, corticosteroids have myriad effects on other systems and have been associated with hyperglycemia, impaired wound healing, hospital acquired infections, as well as increased organ failure and mortality.^{31,32} In addition, corticosteroids also contribute to the development of

myopathy^{33,34} and can prolong the duration of invasive ventilation and hospitalisation.³⁵ These negative effects may have contributed as a cause for the increased mortality, and decreased VFD and IFD observed in our cohort, however, due to the retrospective design, only an association can be made. The Stress Hydrocortisone in Pediatric Septic Shock (SHIPSS) trial specifically seeks to determine if adjunctive hydrocortisone will significantly reduce the proportion of children with

septic shock from death or subsequent poor quality of life (clinicaltrials.gov NCT03401398). The outcome of this randomised controlled, double-blinded study is anticipated to provide a definitive answer to the current gap in knowledge on the effect of corticosteroids in sepsis.

Mortality benefit was found in adult patients with sepsis who were treated with IVIG.³⁶ These effects may be attributed to IVIG's role in immunoglobulin replacement and its potential effects on B cells, T cells, antibodies, complement pathways and cytokines in adult neuromuscular disorders and immune neuropathies.³⁷ However, a meta-analysis evaluating the effects of IVIG in neonatal infections found no mortality benefit.³⁸ Our paediatric cohort may not be directly comparable to either the adult nor neonatal population; however, our data suggest a tendency to poorer outcomes in patients who receive drugs that have an immunomodulating effect including IVIG. A reduction in the overall white cell count has also been described in patients from other studies receiving IVIG consistent with a reduction in both absolute neutrophil count and absolute lymphocyte count (ALC); however the mechanism was described as multifactorial^{39,40} and not fully understood.²² The reduction in ALC may also be contributed by the suppressive effects of corticosteroids on ALC.^{41,42} The overall reduction of white cell differentials may also be a reflection of the biphasic sepsis response, whereby patients who survive the initial hyper-inflammatory phase enter a protracted hypo-inflammatory phase characterised by persistent inflammation and immune suppression.^{43,44} Immune cell depletion in this phase is driven by caspase-mediated apoptosis.⁴⁵ Compromise in innate defences^{46,47} and T cell exhaustion⁴⁸ contribute to a state of malfunctional immune tolerance and susceptibility to further infections and mortality.⁴⁴

There are several limitations in this study's findings. Firstly, due to the small sample size, we could not establish an association between mortality and immunomodulation therapy despite an almost 2-fold increase in mortality, nor perform additional subanalysis (e.g. to examine each immune-modulator therapy separately). The current sample size of 109 achieves only 66% power to detect a difference in mortality of 20% between the 2 groups, using the two-sided Fisher's exact test and assuming a significance level as 5%. A prospective study design with a larger cohort (n=182) is recommended to address these limitations and adequately power the study ($\beta=80\%$) to detect a mortality difference.

We also were unable to determine causation between the use of immunomodulation and worsened primary and

secondary outcomes given the retrospective nature of this study. Indications for these immunomodulation therapies were also heterogenous and physician dependent. Lastly, other important variables such as malnutrition that may have affected the immune system were not accounted for.

CONCLUSION

Exposure to immune-modulating drugs during paediatric severe sepsis and septic shock is associated with higher use of invasive ventilation and less IFD and VFD. A reactive and expected increase in white cell indices was observed during the course of sepsis; however, this was absent in children receiving immunomodulators. A prospective study is recommended to further determine the effectiveness of immune-modulating therapy on primary and secondary outcomes in severe sepsis and septic shock in the paediatric population.

Disclosures

There are no affiliations or financial involvement with any commercial organisations in this study. An abstract of the current work has been presented at the 6th SG-ANZICS Asia Pacific Intensive Care Forum 2019.

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