

# Inotropes, Absolute Monocyte Counts and Survival of Children with Septic Shock

I DELGADO, KLE HON, A RASZYNSKI, BR TOTAPALLY

## Abstract

**Background:** Monocytes play important role in immune modulation during sepsis. Monocyte dysfunction is known to affect the outcomes in septic patients. The current study evaluates the association between inotrope usage, absolute monocyte count and survival of critically ill children with septic shock. **Methods:** Charts of all children who received vasoactive medications during one calendar year and admitted to a paediatric intensive care unit (PICU) were reviewed. Children with immunodeficiency, cardiogenic shock, and post-operative conditions were excluded. Data collected included total and absolute blood cell counts, serum electrolytes, dosages of inotropes, use of supportive measures, outcomes, paediatric index of mortality (PIM-2) scores, and PICU length of stay. Daily laboratory values were collected for 5 days from the start of vasoactive support. Data from children who survived were compared with those expired. **Main Results:** Records of 26 children who were admitted to PICU with septic shock were analysed. The mortality rate was 15.4%. These children received multiple supportive therapies including insulin (23%), hydrocortisone (42%), nitric oxide (15%), diuretics (61.5%), blood products (77%), ventilator support (85%), sedatives and analgesics (89%), and paralytics (61.5%). There were no significant differences in their use, minimum and maximum absolute monocytes counts, length of stay, PIM-2 score, and cumulative inotropic score between those who survived versus those who expired. All 4 patients who died received more than one vasoactive medication on day 1 of septic shock compared to only 10 (45%) among those who survived ( $p < 0.05$ ). Lower proportion of survivors received inotropic support for  $\geq 5$  days (27% vs 75%;  $p = 0.03$ ). The relative risk of death if epinephrine was used on first day is 7.7 [95% CI (1.6-36.0),  $p = 0.0099$ ]. The change in absolute monocyte count (max-min count) was lower in those who survived (733 vs  $1293 \times 10^9/\text{dL}$ ;  $p < 0.05$ ). **Conclusion:** Epinephrine and the number of inotrope use on first day are associated with non-survival. Absolute monocyte count fluctuation is less among children who survived septic shock compared to those who die with septic shock.

**Key words** Child; Inflammation; Monocyte; Sepsis; Shock

Division of Critical Care Medicine and Miami Children's Hospital, Miami, FL 33155, United States of America

I DELGADO MD  
A RASZYNSKI MD  
BR TOTAPALLY MD

Herberth Wertheim College of Medicine, Florida International University, Miami, FL 33199, United States of America

A RASZYNSKI MD  
BR TOTAPALLY MD

Department of Paediatrics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong

KLE HON (韓錦倫) MD

Correspondence to: Dr BR TOTAPALLY

Received February 24, 2015

## Introduction

Sepsis is defined as a serious medical condition characterised by a whole-body inflammatory state (called a systemic inflammatory response syndrome or SIRS) and the presence of a known or suspected infection.<sup>1</sup> The body may develop this inflammatory response to microbes in the blood, urine, lungs, skin, or other tissues. Septic shock is a serious medical condition due to decreased tissue perfusion and oxygen delivery as a result of infection and sepsis.<sup>1-3</sup>

Sepsis can cause multiple organ dysfunction syndrome and death.<sup>1-3</sup> Its most common victims are children, immunocompromised individuals, and the elderly, as their immune systems cannot deal with the infection as effectively as those of healthy adults.

Outcome of patients with sepsis may depend upon the balance of pro- and anti-inflammatory responses. Initial pro-inflammatory response followed by compensatory anti-inflammatory response syndrome (CARS) follow an insult from infection.<sup>4</sup>

Cellular elements in the blood play an important role in the defense against microbes. Absolute neutropenia has long been recognised as a risk factor for nosocomial sepsis in children. A recent study demonstrated that critically ill children with prolonged lymphopenia are more likely to develop nosocomial infection.<sup>5</sup> The authors have concluded that prolonged lymphopenia and apoptosis-associated depletion of lymphoid organs play a role in nosocomial sepsis-related death in critically ill children.<sup>5</sup>

Activated monocytes release large amounts of TNF- $\alpha$ , which can be considered as the principal mediator that sets the septic response.<sup>6</sup> Monocytes are known to play an important role in CARS with reduced HLA-DR expression during immune suppression or immune paralysis.<sup>4</sup> It has been suggested that a defective adaptive immune response contributes to sepsis-associated immuno-suppression or immune paralysis. Although there is a lot of published literature regarding the role of monocytes in pathogenesis of sepsis, it is mostly centered on mediator production and the expression of HLA-DR from monocytes. The role of absolute peripheral blood monocyte count or the association of absolute monocyte count to outcome of patients with sepsis is not known. The aim of the present study is to evaluate the association of inotrope use, absolute monocyte counts and outcomes of critically ill children with septic shock.

## Methods

The charts of all children who received vasoactive medications during one year and admitted to the PICU, Miami Children Hospital, Florida were reviewed. Data were collected from various databases including hospital administrative database, patient care database, and VPS<sup>LLC</sup> database, a paediatric critical care patient database with standardised, validated and reliable clinical data. Children with immunodeficiency, cardiogenic shock (after CPR, near drowning etc.), post-operative conditions (e.g. spinal surgery), and patients under 1 month of age were excluded. Children who received dopamine of <5 mcg/kg/min for less than 12 hours were also excluded. Data collected included, demographic data, daily complete blood counts (CBC) and absolute counts, serum electrolytes, dose of vasoactive medications, use of supportive measures, outcomes, paediatric index of mortality (PIM-2), and PICU length of stay. Daily lab values close to 8 AM were collected for 5 days from the start of vasoactive support.

*Septic shock* was defined in this study as a child with sepsis and needing at least one inotrope to support cardiovascular function.<sup>7</sup>

*Inotropic score* was calculated using the formula: dopamine ( $\mu\text{g}/\text{kg}/\text{min}$ ) x 1 + dobutamine ( $\mu\text{g}/\text{kg}/\text{min}$ ) x 1 + milrinone ( $\mu\text{g}/\text{kg}/\text{min}$ ) x 15 + epinephrine ( $\mu\text{g}/\text{kg}/\text{min}$ ) x 100 + nor-epinephrine ( $\mu\text{g}/\text{kg}/\text{min}$ ) x 100 + vasopressin (munits) x 100.<sup>8</sup>

*Statistical analyses:* Data from children who survived were compared with those expired. The binary data were analysed using Chi-square test and continuous data were analysed using either t-test (parametric data) or Mann-Whitney-U test (non-parametric data). A *p* value <0.05 was considered significant. The Miami Children Hospital Institutional Review Board approved this retrospective cohort review.

## Results

Charts of 26 children with septic shock who were treated in the PICU were reviewed. Patients who received vasoactive medication infusions for cardiogenic shock (e.g. after cardiac arrest or drowning), after prolonged surgery (e.g. spinal surgery), children with immunodeficiency (e.g. oncologic patients), and patients who received only dopamine of <5 mcg/kg/min for less than 12 hours were excluded.

There were 8 (30.8%) females in the group. The median age of the study population was 5.63 years with inter-quartile range (IQR) of 1.76 to 9.93 years. The average age was  $6.94 \pm 6.04$  years. The median weight of the patients was 18 kg (IQR=13.1 to 33 Kg) with the average weight of  $25.6 \pm 22.9$  kg.

These children received multiple supportive therapies including, insulin (23%), hydrocortisone (42%), nitric oxide (15%), diuretics (61.5%), blood products (77%), ventilator support (85%), sedatives and analgesics (89%), and paralytics 61.5%). Four of the 26 patients with septic shock died (mortality rate of 15.4%). There were no significant differences in their use of supportive therapies among those who survived compared to those expired (Table 1).

**Monocyte counts:** Absolute minimum and absolute maximum counts were higher among children who died compared to those who survived, although not reached statistical significance at 5% level (Table 2). The variation in the monocyte count during the five days of starting inotropic support was significantly higher among children who died. Platelet counts and other white cell counts are given in Table 2.

**Inotropic support:** Nine patients (34.6%) received inotropic support for  $\geq 5$  days. Significantly lower proportion children received inotropic support for  $\geq 5$  days among who survived (27% vs 75%;  $p=0.03$ , one tail). Only

one child died after receiving inotropic support for a day. The median duration of inotropic support among the groups was 3 and 5 days (data collection was limited to 5 days). Total inotropic support (cumulative score) during 5 days was not significantly different between two groups (132 vs 150).

**Table 1** Type and rate of supportive care received in children with septic shock. The data are presented as numbers (%)

Supportive Care	Survivors (n=22)	Expired (n=4)	Total (n=26)
Insulin infusion	5 (22.7)	1 (25)	6 (23)
Hydrocortisone	9 (40.9)	2 (50)	11 (42.3)
Nitric oxide	3 (13.6)	0 (0)	3 (11.5)
Diuretics	13 (59.1)	3 (75)	16 (61.5)
Fluid boluses	19 (86.4)	4 (100)	23 (88.5)
Blood products	18 (81.8)	2 (50)	20 (76.9)
Ventilator assistance	18 (81.8)	4 (100)	22 (84.6)
Sedatives/analgesics	20 (90.9)	3 (75)	23 (88.5)
Paralytics	13 (59.1)	3 (75)	16 (61.5)

There were no statistical differences in the rates of supportive care received based on the outcome (survival vs expired). Data were analysed using Chi-square or Fisher Exact test.

**Table 2** Absolute white blood cell counts, PICU length of stay, and PIM-2 risk of mortality in patients with septic shock. Data are presented as mean  $\pm$  SD

	Survivors (n=22)	Expired (n=4)	Total (n=26)	Significance
Minimum monocyte count	313 $\pm$ 286	399 $\pm$ 271	327 $\pm$ 281	NS
Maximum monocyte count	1047 $\pm$ 698	1693 $\pm$ 580	1146 $\pm$ 711	NS
Monocyte count variation (max-min)	733 $\pm$ 628	1293 $\pm$ 465	819 $\pm$ 632	<0.05 (one tail)
Minimum lymphocyte count	963 $\pm$ 844	1577 $\pm$ 994	1069 $\pm$ 864	NS
Maximum lymphocyte count	1601 $\pm$ 1388	2676 $\pm$ 1991	1773 $\pm$ 1504	NS
Minimum neutrophil count	5416 $\pm$ 6136	6086 $\pm$ 2203	5670 $\pm$ 5653	NS
Maximum neutrophil count	11822 $\pm$ 7988	11745 $\pm$ 1507	11813 $\pm$ 7562	NS
Minimum platelet count	171 $\pm$ 98	161 $\pm$ 122	169 $\pm$ 99	NS
PICU LOS (days)	23 $\pm$ 26	5.6 $\pm$ 3.3	20.3 $\pm$ 24.3	NS
PIM-2 - risk (%)	7.2 $\pm$ 5.2	12.6 $\pm$ 8.1	8.0 $\pm$ 5.9	NS
Total IS	133 $\pm$ 247	150 $\pm$ 79	135 $\pm$ 229	NS

Units in  $\times 10^9/\text{dL}$

PICU=paediatric intensive care unit; LOS=length of stay; PIM-2= paediatric index of mortality; NS=not significant; IS=inotropic score.

All 4 patients who died received more than one vasoactive medication on day 1 of septic shock compared to only 10 (45%) among those who survived ( $p<0.05$ ; Fisher's Exact test with normal approximation). Various vasoactive medications used on first day of septic shock management are given in Table 3. The relative risk of death if epinephrine was used in first day is 7.7 [95% CI (1.6-36.0),  $p=0.01$ ].

## Discussion

We have reviewed 26 children with septic shock. These children were previous healthy and had no prior history of immunodeficiency before the episode of sepsis. In this cohort, the mortality with septic shock was 15.4% compared to an overall published mortality of 24% in children with severe sepsis admitted to PICU.<sup>9</sup> The study by Markovitz et al also included neonates as well as children with oncological problems.<sup>9</sup> The overall mortality for septic shock was similar to a recently published large PICU series.<sup>10</sup>

Most of the patients in our cohort died relatively early in their PICU course with an average LOS in PICU of 5.4 days compared to those who survived the event. It is known that early deaths with sepsis are mostly due to overwhelming inflammatory response and late deaths are due to CARS and immune paralysis.

Apoptosis is important in the pathogenesis of sepsis. The affect of apoptosis may dependent up on the type of cells involved and also timing of apoptosis.<sup>11</sup> It has been shown

that lymphopenia and lymphocyte apoptosis is associated with prolonged immunosuppression and increased nosocomial infections and death.<sup>5</sup> This usually causes secondary infections and late deaths after sepsis. In contrast, Giamarellos-Bourboulis et al<sup>12</sup> have shown that an early increase in the apoptosis of blood monocytes is associated with improved survival of patients with sepsis. This may mean, decreased peripheral monocyte count early in the course of sepsis may be beneficial, presumably by reducing the pro-inflammatory response. This effect was still present until 5 days after the onset of septic shock.<sup>12</sup> In contrast, decreased expression of HLA-DR on monocytes later in sepsis has shown to increase mortality.

Monocytes are peripheral blood antigen-presenting cells. Monocytes present antigens through the expression of HLA receptors leading to the production of pro-inflammatory cytokines.<sup>13</sup> Current theory of sepsis syndrome is that sepsis manifestations are due to an over production of inflammatory mediators from monocytes after they come in contact with microbial cell wall components.<sup>14</sup> Hence, monocytes play an important role both in genesis of inflammatory syndrome of sepsis through over-production of mediators and immunosuppression through functional deficiency of monocytes later in course by development of CARS.<sup>15</sup> This study shows that low initial monocyte count and decreased fluctuations in monocyte count are associated with a better outcome.

Our study shows a utilisation of several supportive cares indicative of their sickness and the rate of utilisation was no different in the two groups. Length of stay in PICU was lower, although not statistically significant, in patients who died compared to those who survived. It is consistent with our explanation that these patients died early in the course of fulminant sepsis, hence had lower length of stay. PIM-2 risk of mortality was non-significantly higher among those who died. PIM-2 tends to be lower in previously healthy children who died with fulminant sepsis.<sup>2,3</sup> The major limitation of the present study is the small sample size. A longer study duration will be necessary to confirm some of the observations in this study.

In the present cohort, about 54% needed more than one inotrope with all children who died eventually received more than one inotrope. As expected, dopamine was most commonly used inotropic medication followed by nor-epinephrine. This is consistent with recommendations in sepsis guidelines.<sup>16-19</sup>

**Table 3** Vasoactive medications used during the first day of cardiovascular support in children with septic shock. The data are presented as numbers (%)

Vasoactive medication	Survivors (n=22)	Expired (n=4)	Total (n=26)
Dopamine	18 (82)	4 (100)	22 (85)
Dobutamine	1 (4.5)	0 (0)	1 (3.9)
Epinephrine*	1 (4.5)	2 (50)	3 (11.5)
Nor-epinephrine	10 (45.5)	1 (25)	11 (42.3)
Milrinone	3 (13.6)	1 (25)	4 (15.4)
Vasopressin	2 (9.1)	0 (0)	2 (7.7)

\* $p=0.05$

Relative risk of death if epinephrine was used on first day is 7.7 [95% CI (1.6-36.0),  $p=0.01$ ]

In conclusions, there was trend towards lower absolute monocyte count in survivors of early septic shock and less variation in the monocyte count during first five days was associated with better survival. Further studies are needed to evaluate the use of this as a marker of overwhelming inflammatory state in children with sepsis.

## Conflict of Interest

None

## References

- American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:864-74.
- Hon KL, Poon TC, Wong W, et al. Prolonged non-survival in PICU: does a do-not-attempt-resuscitation order matter. *BMC Anesthesiol* 2013;13:43.
- Hon KL, Fu A, Leung TF, et al. Cardiopulmonary morbidity of streptococcal infections in a PICU. *Clin Respir J* 2015;9:45-52.
- Haveman JW, Muller Kobold AC, Tervaert JW, et al. The central role of monocytes in the pathogenesis of sepsis: consequences for immunomonitoring and treatment. *Neth J Med* 1999;55:132-41.
- Felmet KA, Hall MW, Clark RS, Jaffe R, Carcillo JA. Prolonged lymphopenia, lymphoid depletion, and hypoprolactinemia in children with nosocomial sepsis and multiple organ failure. *J Immunol* 2005;174:3765-72.
- Cavaillon JM, Adib-Conquy M. Monocytes/macrophages and sepsis. *Crit Care Med* 2005;33(12 Suppl):S506-9.
- Goldstein B, Giroir B, Randolph A; International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;6:2-8.
- Rosenzweig EB, Starc TJ, Chen JM, et al. Intravenous arginine-vasopressin in children with vasodilatory shock after cardiac surgery. *Circulation* 1999;100(19 Suppl):II182-6.
- Markovitz BP, Goodman DM, Watson RS, Bertoch D, Zimmerman J. A retrospective cohort study of prognostic factors associated with outcome in pediatric severe sepsis: what is the role of steroids? *Pediatr Crit Care Med* 2005;6:270-4.
- Schlapbach LJ, Straney L, Alexander J, et al. Mortality related to invasive infections, sepsis, and septic shock in critically ill children in Australia and New Zealand, 2002-13: a multicentre retrospective cohort study. *Lancet Infect Dis* 2015;15:46-54.
- Moraes TJ, Downey GP. Death of the septic monocyte: is more better? *Crit Care* 2006;10:146.
- Giamarellos-Bourboulis EJ, Routsis C, Plachouras D, et al. Early apoptosis of blood monocytes in the septic host: is it a mechanism of protection in the event of septic shock? *Crit Care* 2006;10:R76.
- Krakauer T, Oppenheim JJ. IL-1 and tumor necrosis factor-alpha each up-regulate both the expression of IFN-gamma receptors and enhance IFN-gamma-induced HLA-DR expression on human monocytes and a human monocytic cell line (THP-1). *J Immunol* 1993;150:1205-11.
- Power C, Fanning N, Redmond HP. Cellular apoptosis and organ injury in sepsis: a review. *Shock* 2002;18:197-211.
- Ward NS, Casserly B, Ayala A. The compensatory anti-inflammatory response syndrome (CARS) in critically ill patients. *Clin Chest Med* 2008;29:617-25, viii.
- Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39:165-228.
- Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.
- Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;36:296-327.
- Parker MM, Hazelzet JA, Carcillo JA. Pediatric considerations. *Crit Care Med* 2004;32(11 Suppl):S591-4.