

# The Utilization of the Surviving Sepsis Campaign Care Bundles in the Treatment of Pediatric Patients with Severe Sepsis or Septic Shock in a Resource-Limited Environment: A Prospective Multicenter Trial

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## Abstract

**Background:** Sepsis is a common condition affecting the lives of infants and children worldwide. Although implementation of the surviving sepsis campaign (SSC) care bundles was once believed to be effective in reducing sepsis mortality rates, the approach has recently been questioned. **Methods:** The study was a prospective, interventional, multicenter trial. Infants and children aged 1 month to 15 years in seven different large academic centers in Thailand who had been diagnosed with severe sepsis or septic shock. They were given treatment based on the SSC care bundles. **Results:** A total of 519 children with severe sepsis or septic shock were enrolled in the study. Among these, 188 were assigned to the intervention group and 331 were recruited to the historical case-control group. There were no significant differences in the baseline clinical characteristics. The intervention group was administered a significantly higher fluid bolus than was the control group ( $28.3 \pm 17.2$  cc/kg vs.  $17.7 \pm 10.6$  cc/kg;  $P = 0.02$ ) with early vasopressor used ( $1.5 \pm 0.7$  h) compared to control group ( $7.4 \pm 2.4$  h,  $P < 0.05$ ). More importantly, our sepsis mortality reduced significantly from  $37\% \pm 20.7\%$  during the preintervention period to  $19.4\% \pm 14.3\%$  during the postintervention period ( $P < 0.001$ ). **Conclusion:** Our study demonstrated a significant reduction in sepsis mortality after the implementation of the SSC care bundles. Early diagnosis of the disease, optimum hemodynamic resuscitation, and timely antibiotic administration are the key elements of sepsis management.

**Keywords:** Decrease in mortality, multicenter, pediatric, septic shock, severe sepsis, surviving sepsis campaign care bundles

## INTRODUCTION

Sepsis is a common clinical condition with a significant impact on health-care resources and expenditures. According to the WHO estimates, sepsis accounts for 60%–80% of pediatric mortality per year.<sup>[1-3]</sup> In addition, it is responsible for approximately 20% of admissions to intensive care units and remains the leading cause of morbidity and mortality in pediatric intensive care units (PICUs) worldwide.<sup>[3,4]</sup> Surviving sepsis campaign (SSC) statistics indicates a sepsis mortality rate between 30% and 50% with the rate being higher in the developing countries.<sup>[5,6]</sup> Such high mortality rates and the increasing number of patients with severe sepsis or septic shock require changes in the current management protocols. In 2002,

the American College of Critical Care Medicine for the first time published clinical practice parameters for the hemodynamic support of pediatric and neonatal septic shock. Han *et al.* later reported that early diagnosis and aggressive resuscitation of pediatric-neonatal septic shock by community physicians could bring about better outcomes and save more lives.<sup>[6,7]</sup>

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Early diagnosis and effective resuscitation and treatment are very important approaches to sepsis reversal in both children and adults. Our previous report demonstrated that applying the SSC care bundles was able to reduce morbidity and mortality rates in children.<sup>[7]</sup> Sankar *et al.* reported the benefit of using intermittent superior vena cava oxygen saturation (SCVO<sub>2</sub>) monitoring early goal-directed therapy (EGDT) in the management of children with sepsis in a single-centered resource-limited study.<sup>[8]</sup> Recently, large adult randomized controlled trials in the Western world have reported similar outcomes in protocolized and usual care for septic shock.<sup>[9-11]</sup> They compared early goal-directed sepsis combined with protocol-based therapy with the other without protocol (usual care). However, such results may not apply directly to children in resource-limited countries. Thus, the purpose of our study is to determine the clinical effectiveness of the application of SSC care bundles in treating children with severe sepsis or septic shock in a resource-limited environment.

## METHODS

We prospectively employed an intervention study in seven PICUs of university and large provincial referral hospitals in a resource-limited environment from January 2013 to December 2014. The study was approved by the Institutional Review Board and Joint Research Ethics Committees of the hospitals. In addition, informed consent was acquired before the commencement of the research in an interventional group. An educational program addressing the importance of early diagnosis, therapeutic intervention, quality indicators, and data collection was run for those hospitals through a protocol based on the SSC care bundles.<sup>[12,13]</sup> This particular program helps each center to improve the guideline compliance and efficacy of sepsis management.

Patients aged between 1 month and 15 years had been diagnosed with severe sepsis or septic shock<sup>[14]</sup> and admitted to the participating hospitals' pediatric ward and then to their PICU or directly to their PICU during 2013–2014 (interventional group) without exclusion criteria as the following:

1. Cyanotic heart disease with clinical heart failure
2. Patients with multiorgan failure
3. Patients with severe congenital anomaly or end-stage tumor/terminal illness or during 2010–2012 (historical match-control group) were consecutively recruited into our study using the Society of Critical Care Medicine's criteria.<sup>[11]</sup> The PICU attendings, fellows, and managing nurses were simultaneously notified of the enrolled cases. Clinical data, including age, sex, admission date, the time of diagnosis before PICU admission, location, the time of antibiotic administration, the length of stay, and Pediatric Risk of Mortality (PRISM) and Pediatric Logistic Organ Dysfunction (PELOD) scores, were collected. The participants' blood was drawn at the time of diagnosis and kept for further analysis. Once a patient met the inclusion criteria, an acute intervention (resuscitation care bundle), including hemodynamic resuscitation, was performed to achieve

adequate tissue perfusion within 3 h. This was followed by basic laboratory work, such as blood culture collection and antibiotic administration. Inotropic or vasopressors drugs were administered early if clinically indicated. In addition, hydrocortisone was also given if catecholamine-resistant shock was suspected. Postacute intervention was due to be completed within 24 h (treatment care bundle).

## Statistical analysis

Data are presented as mean  $\pm$  standard deviation or the median (interquartile range), depending on the normality of their distribution. If the data were normally distributed, a Student's *t*-test was performed to draw comparisons. Otherwise, a Wilcoxon rank-sum (Mann–Whitney) test was run. In addition, a Fisher's exact test was conducted to compare proportion variability. Furthermore, a multivariate logistic regression analysis was carried out to determine the correlations between different risk factors and mortality. All tests of significance were two-tailed with  $P < 0.05$  being considered statistically significant. All statistical analyses were performed using the software SPSS, version 16 (Chicago, IL).

## RESULTS

In this study, a total of 519 children were recruited. Among these, 188 were enrolled in the intervention group and 331 were recruited to the historical control group. There was no significant difference in the baseline clinical characteristics [Table 1]. In the intervention group, 108 (57.4%) were male and 80 (42.6%) were female with the mean age (m) of  $84.1 \pm 62.1$ . In the control group, 164 (49.5%) were male and 167 (50.4%) were female with the mean age (m) of  $76.7 \pm 63$ . As for the intervention group, 146 (77.6%) had underlying diseases apart from sepsis. The most common was hematologic malignancy (78, 44.5%), followed by congenital anomaly (17, 9%), chronic liver disease (9, 4.7%), and neurological disorder (8, 4%). Hematologic malignancy was significant higher in interventional group compare to control [Table 2]. In addition, 100 (53.1%) in this group developed a respiratory failure and required mechanical ventilation that significantly higher than those in the control group [ $P = 0.03$ ; Table 1]. The mean initial PRISM III and PELOD scores were not significantly different between the two groups. In the interventional group, fever was the most common presentation (178, 95%). The initial arterial pH was significantly lower in the nonsurvival group than in the survival group ( $7.3 \pm 0.1$  vs.  $7.4 \pm 0.1$ ,  $P = 0.04$ ). The initial oxygen index was  $9.7 + 7.6$ , and the PaO<sub>2</sub>/FiO<sub>2</sub> ratio was  $215.1 \pm 85.1$ . The initial positive inspiratory pressures for those mechanically ventilated were not significantly different ( $20.8 \pm 7.5$  CmH<sub>2</sub>O for the intervention group vs.  $22.78 \pm 6.9$  CmH<sub>2</sub>O for the control group). There was no significant baseline in underlying disease between two groups except for hematologic malignance [Table 2].

## Primary outcomes

After full implementation of the SSC care bundles, we found a significant reduction in the septic shock mortality rates

**Table 1: Comparison of baseline clinical characteristics between the intervention group and the control group**

|                       | Treatment            |                 | P      |
|-----------------------|----------------------|-----------------|--------|
|                       | Intervention (n=188) | Control (n=331) |        |
| Gender, n (%)         |                      |                 |        |
| Male                  | 108 (57.4)           | 164 (49.6)      | 0.08   |
| Female                | 80 (42.6)            | 167 (50.4)      |        |
| Age (month)           | 84.14±62.15          | 76.76±63.88     | 0.2    |
| BMI                   | 17.11±4.29           | 16.76±4.48      | 0.5    |
| PRISM                 | 9.6±4.61             | 11.3±8.66       | 0.1    |
| PELOD                 | 18.5±10.4            | 16.5±9.5        | 0.2    |
| BT (°C)               | 38.8±1.2             | 38.7±1.2        | 0.4    |
| RR (min)              | 48.5±14.1            | 45.1±16.2       | 0.3    |
| SBP (mmHg)            | 85.3±17.1            | 84.9±19.7       | 0.2    |
| HR (min)              | 162.6±28.4           | 161.8±27.2      | 0.4    |
| On MV (n=214), n (%)  | 100 (53.1)           | 170 (51.3)      | 0.3    |
| iPIP (mmHg)           | 20.86±7.53           | 21.78±6.97      | 0.2    |
| A-line insertion      | 107 (56.9)           | 115 (34.7)      | 0.02*  |
| CVL                   | 147 (78.1)           | 156 (47.1)      | 0.001* |
| ipH                   | 7.35±0.1             | 7.38±0.11       | 0.1    |
| ipCO <sub>2</sub>     | 35.3±10.7            | 34.52±9.9       | 0.6    |
| iHCO <sub>3</sub>     | 19.76±6.3            | 20.02±5.9       | 0.8    |
| iBE                   | -4.1±12.5            | -3.7±14.5       | 0.6    |
| Lactate (mmol/l)      | 2.8±1.2              | 2.5±1.1         | 0.3    |
| Hb (g/dl)             | 10.22±2.80           | 10.22±4         | 0.9    |
| PLT × 10 <sup>3</sup> | 181.83±16.2          | 151.22±148.2    | 0.2    |
| PT (s)                | 22.19±21.32          | 18.80±8.1       | 0.09   |
| PTT (s)               | 38.70±17.90          | 39.15±12.5      | 0.8    |

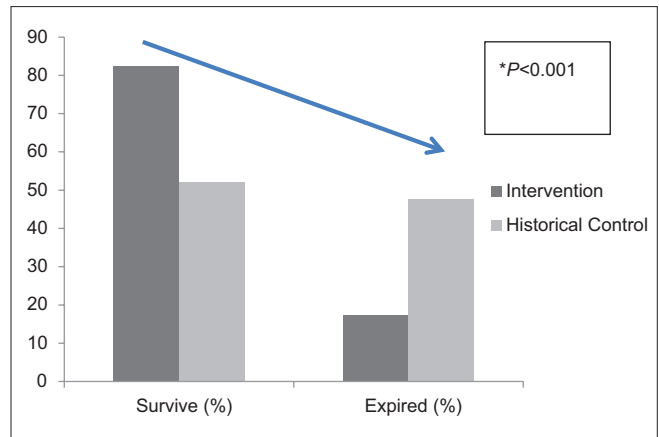
BMI: Body mass index; PRISM: Pediatric Risk of Mortality; PELOD: Pediatric Logistic Organ Dysfunction; BT: Body temperature; RR: Respiratory rate; SBP: Systolic blood pressure; HR: Heart rate; iPIP: Initial positive inspiratory pressure; CVL: Central venous line; Hb: Hemoglobin; PT: Prothrombin time; PTT: Partial thromboplastin time; PLT: Platelet count; MV: Mechanical ventilation, \*P<0.05 statistically significant

**Table 2: Comparison of underlying diseases between the intervention group and the control group**

| Underlying diseases    | Intervention (n=188), n (%) | Control (n=331), n (%) | P      |
|------------------------|-----------------------------|------------------------|--------|
| None                   | 42 (24.00)                  | 116 (35)               | NS     |
| Hematologic malignancy | 78 (44.5)                   | 90 (27.1)              | <0.05* |
| Congenital anomalies   | 16 (8)                      | 30 (9)                 | NS     |
| Liver diseases         | 9 (4.7)                     | 18 (5.4)               | NS     |
| Neurological disorders | 8 (4.2)                     | 16 (4.8)               | NS     |
| Hematological diseases | 6 (3.2)                     | 9 (2.7)                | NS     |
| Chronic lung diseases  | 5 (2.6)                     | 8 (2.4)                | NS     |
| Immunodeficiencies     | 5 (2.6)                     | 8 (2.4)                | NS     |
| Kidney diseases        | 3 (1.5)                     | 5 (1.5)                | NS     |
| Others                 | 16 (8)                      | 31 (3.1)               | NS     |

NS: Not significant, \*P<0.05 statistically significant

from 37% ± 20.7% (preintervention) to 19.4% ± 14.3% (postintervention) [P<0.001; Figure 1]. The duration of PICU admission was also significantly reduced from 12.5 ± 10.2 days to 9.2 ± 11.5 days (P = 0.04). On the multivariate logical



**Figure 1: Comparison of mortality rates between the intervention group and the control group (P < 0.001)**

analysis, the risk of mortality was found to be significantly lower in the interventional group compared to the control group (0.58 [0.46–0.65], P < 0.01).

### The hemodynamic resuscitation bundle

In the present study, the SSC bundles comprised the hemodynamic resuscitation care bundle, which had to be completed in 3 h, and the sepsis treatment bundle, which had to be completed within 24 h. Our overall compliance with the SSC care bundles was approximately 70%. About 0.9% normal saline was selected as the first choice of initial fluid resuscitation in both the intervention group (89%) and the control group (95.4%). There was a significantly higher amount of initial fluid bolus within an hour on hemodynamic resuscitation in the intervention group (38.3 ± 17.2 ml/kg) than in the control group (27.7 ± 10.6 ml/kg) (P = 0.02). Inotropic or vasopressor agents were significantly utilized earlier in the intervention group (1.5 ± 0.7 h) than in the control group (7.4 ± 2.4 h) (P < 0.05). The administration was carried out through a peripheral line after fluid resuscitation to achieve the optimum cardiac output<sup>[15]</sup> before transfer to the PICU. Dopamine was the most common choice of inotrope used as the first line after fluid-refractory shock was suspected. Inotropic agents were administered at a significantly higher rate in the intervention group than in the control group (78% vs. 30.5%, P < 0.01\*) [Table 3]. Central venous lines (CVLs) (internal jugular, subclavian vein, and femoral vein) were also inserted in case of fluid-refractory septic shock to achieve the central venous pressure (CVP) goal of 8–12 mmHg at a significantly higher rate in the intervention group than in the control group (78% vs. 47.1%, P < 0.001\*). The initial CVP upon insertion was measured at 8.2 ± 2.8 mmHg in the intervention group and 7.5 ± 2.8 mmHg in the control group. The SCVO<sub>2</sub> level of at least 70% was achieved during the first 3 h in 85% of the patients in the intervention group who were monitored [Table 4].

### The surviving sepsis campaign treatment bundle

To achieve the optimum oxygen delivery with SCVO<sub>2</sub> ≥ 70%, 90 (47%) patients in the intervention group and 82 (24.7%) in the control group were given blood transfusion. Furthermore,

**Table 3: Comparison of hemodynamic resuscitation (use of fluids and vasopressors) between the intervention group and the control group**

| Parameters                                    | Treatment, n (%)     |                 | P      |
|---|----------------------|-----------------|--------|
|   | Intervention (n=188) | Control (n=331) |        |
| First fluid                                   |                      |                 |        |
| 0.9% NSS                                      | 168 (89.8)           | 314 (95.4)      | NS     |
| Balance salt                                  | 11 (5.8)             | -               |        |
| 5% albumin                                    | 6 (3.2)              | 5 (1.5)         |        |
| FFP   | 1 (0.56)             | 1 (0.3)         |        |
| Total bolus for initial resuscitation (ml/kg) | 38.3±17.2            | 27.7±10.6       | 0.02*  |
| Fluid balance at 24 h (ml/kg)                 | 172.5±45.7           | 180.7±50.7      | 0.1    |
| Fluid balance at 48 h (ml/kg)                 | 240.5±52             | 353.5±42        | 0.03*  |
| First inotrope in 24 h                        |                      |                 |        |
| Dopamine                                      | 147 (78)             | 95 (30.5)       | 0.015* |
| Norepinephrine                                | 22 (11.7)            | 34 (10.9)       | NS     |
| Adrenaline                                    | 12 (6.3)             | 6 (1.9)         | 0.08   |
| Dobutamine                                    | 4 (2.5)              | 18 (5.4)        | NS     |
| Milrinone                                     | 3 (1.5)              | 2 (0.6)         | NS     |

NS: Not significant; NSS: Normal saline; FFP: Fresh frozen plasma, \* $P < 0.05$  statistically significant

55 (29%) in the intervention group and 75 (22.6%) in the control group received fresh frozen plasma and platelets. Within an hour of severe sepsis or septic shock diagnosis, 155 (82.4%) in the intervention group and 145 (43.8%) in the control group were administered antibiotics. SCVO<sub>2</sub> was monitored in 120/188 (63.8%) in the intervention group and only 66/331 (19.9%) in the control group. Moreover, arterial lactate was measured in 150/188 (79%) in interventional group and 70/331 (21.1%) in the control group. The results of blood culture were mostly negative in both group except for S coagulase neg [Table 4]. All the patients in the intervention group and the control group were transferred out of the emergency room or the general ward to the PICU within a few hours after the diagnosis of severe sepsis or septic shock.

### Risk factors associated with mortality rates in the intervention group

From the multivariate logistic regression analysis, the lower initial systolic blood pressure, younger age, higher baseline creatinine, lower bicarbonate, and positive fluid balance at 48 h were associated with higher mortality rates [Table 5].

## DISCUSSION

Septic shock remains one of the most significant causes of death in children worldwide.<sup>[16]</sup> The mortality rates of severe sepsis and septic shock in the PICU in our multicenter trial were quite high, similar to those reports both in industrialized and developing countries.<sup>[2,4,5]</sup> Therefore, it is clear that a sepsis management protocol needs to be implemented in our countries. Based on the present findings, implementing the modified SSC care bundles in our academic referral hospitals was able to significantly reduce the mortality rate from 37% ± 20.7% (preintervention) to 19.14% ± 14.13% (postintervention) ( $P < 0.001$ ). Rivers *et al.* first introduced EGDT management, known as EGDT algorithm, for adult

**Table 4: Blood culture results**

| Hemoculture results                      | Groups       |            | P      |
|--|--------------|------------|--------|
|  | Intervention | Control    |        |
| Hemoculture                              |              |            |        |
| No growth                                | 130 (69.1)   | 256 (77.3) | NS     |
| <i>Escherichia coli</i>                  | 9 (4.79)     | 12 (3.6)   | NS     |
| <i>Pseudomonas aeruginosa</i>            | 6 (3.2)      | 15 (4.5)   | NS     |
| <i>Acinetobacter baumannii</i>           | 5 (2.66)     | 13 (3.85)  | NS     |
| <i>Staphylococcus coagulase negative</i> | 5 (2.66)     | 2 (0.6)    | <0.05* |
| <i>Staphylococcus aureus</i>             | 5 (2.66)     | 11 (3.3)   | NS     |
| <i>Candida spp.</i>                      | 5 (2.66)     | 12 (3.6)   | NS     |
| Other Gram-negatives                     | 8 (4.2)      | 10 (3)     | NS     |

NS: Not significant, \* $P < 0.05$  statistically significant

**Table 5: Risk factors leading to deaths in the intervention group**

| Factor                         | n   | OR (95% CI)       |                   |
|--------------------------------|-----|-------------------|-------------------|
|                                |     | Unadjusted        | Adjusted          |
| Treatment                      |     |                   |                   |
| Intervention                   | 188 | 0.23 (0.15-0.36)  | 0.58 (0.46-0.65)* |
| Control                        | 331 | 1                 | 1                 |
| Gender                         |     |                   |                   |
| Male                           |     | 1.03 (0.72-1.47)  | 1.74 (0.46-5.39)  |
| Female                         |     | 1                 | 1                 |
| Age (month)                    |     | 0.99 (0.99-0.99)* | 0.99 (0.98-1)*    |
| SBP                            |     | 0.97 (0.95-0.98)* | 0.96 (0.92-1.01)  |
| Baseline creatinine            |     | 1.6 (1.12-2.28)*  | 1.39 (0.73-2.6)*  |
| iHCO <sub>3</sub>              |     | 1.17 (1.07-1.29)* | 1.17 (1.05-1.3)*  |
| Positive fluid balance at 48 h |     | 1.7 (1.25-2.5)*   | 2.2 (1.3-2.8)*    |

\*Low Initial bicarbonate level  $P < 0.05$ \*; OR: Odds ratio; CI: Confidence interval; SBP: Systolic blood pressure; iHCO<sub>3</sub>: Initial bicarbonate level

sepsis treated in the emergency department and was later extrapolated to manage children with septic shock.<sup>[17-19]</sup> Han



*et al.* reported that early reversal of pediatric septic shock by community physicians was associated with improved outcomes.<sup>[6]</sup> This indicates that the importance of early and aggressive hemodynamic resuscitation could save life. Our study demonstrated rapid hemodynamic resuscitation within an hour of diagnosis with significant higher amount of initial fluid resuscitation ( $38 \pm 17.2$  ml/kg) in interventional group compared to control ( $27.7 \pm 10.6$  ml/kg,  $P = 0.02^*$ ), more inotrope used, and higher rate of CVL placement in interventional group. In addition, the interventional group had also higher rate of SCVO<sub>2</sub> monitoring and lactate measurement. However, recent studies reported that applying EGDT in the management of adult sepsis did not bring about greater benefits than usual care.<sup>[9,10]</sup> These results may not apply to our study due to different population and environment. Nevertheless, not all of the components in EGDT may not require in managing septic patients successfully. Sankar *et al.* and Oliveira *et al.* previously reported the benefit of using SCVO<sub>2</sub> monitoring EGDT in pediatric septic shock that could reduce the mortality.<sup>[8,13]</sup> We also found that sepsis children in interventional group significantly monitored SCVO<sub>2</sub> and arterial lactate compared to control. This indicates the clinical importance of adequate tissue perfusion monitoring.

Pediatric hemodynamic resuscitation guidelines<sup>[20]</sup> have recently been modified. The updated one emphasizes the use of an appropriate level of fluid resuscitation with closed hemodynamic monitoring to avoid fluid overload. In our study, positive fluid balance at 48 h was associated with a higher mortality rate both in interventional and control group. This finding is consistent with that previous reported demonstrating that overaggressive fluid resuscitation with uncontrol fluid balance may contribute to higher morbidity and mortality.<sup>[21,22]</sup> Furthermore, the early use of inotrope may also contribute to the improvement of our septic shock outcomes. We found significantly used inotropes in children with fluid refractory sepsis in the interventional group compared to control.

Timely and appropriate antimicrobial therapy is another key element in treating septic patients. Every hour of delay in appropriate resuscitation and antibiotic administration was associated with a significant increase in mortality rates.<sup>[23]</sup> Our study demonstrated that 158 (84%) of the participants were administered antibiotics within an hour of enrollment as well as hemodynamic resuscitation immediately after diagnosis. However, there are some limitations to the present study such as different in underlying diseases or adjunctive of sepsis management. There were more children with hematologic malignancies in intervention group that might affect higher mortality. Furthermore, *Staphylococcus epidermidis* sepsis usually carried a better prognosis. Furthermore, noninvasive hemodynamic monitoring may help to guide fluid and vasopressor management, as is the case in 5 (71%) of the centers enrolled in our study. Finally, a challenge remains in improving the early sepsis detection and optimum hemodynamic resuscitation, which are important factors in achieving effective sepsis management and sustainable outcomes.

## CONCLUSION

Based on the findings of this study, the implementation of modified SSC bundles in resource-restrict academic hospitals could significantly reduce sepsis mortality in children presenting with severe sepsis or septic shock. It is also worth noting that each component in the SSC care bundles should be adjusted in line with the capabilities of individual institutions.

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## Conflicts of interest

There was no conflict of interest in this study.

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