EFFECT OF THE 'SURVIVING SEPSIS CAMPAIGN 2012' ON MORTALITY IN THE PEDIATRIC DEPARTMENT OF SIRIRAJ HOSPITAL

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Abstract. In 2012, Siriraj Hospital launched the "Surviving Sepsis Campaign 2012". The aim of this study was to evaluate guideline adherence and patient outcome after implementation and to investigate the factors that significantly associate with risk of morality in this illness. Patients aged 1 month to 15 years who were admitted for severe sepsis and septic shock during the 1 January 2013 to 31 December 2014 study period was enrolled. There were 48 children included. The year 1 and year 2 groups consisted of 23 and 25 patients, respectively. Most patients had comorbidities, and the main underlying disease was hemato-oncology. The most common primary site of infection was blood stream infection (43%) in year 1 and pneumonia (52.5%) in year 2. Most patients were intubated and on mechanical ventilation. After guideline promotion, completion of early goal-directed therapy significantly increased from 17.4% in year 1 to 72% in year 2. When we compared the mortality data from this study to the data collected a few years prior to guideline implementation, the mortality rate significantly decreased from 37.7% to 10.4% (p=0.001). Risk factors that were found to significantly affect mortality outcome were disseminated intravascular coagulation (p=0.04) and acute renal failure (p=0.001). Other risk factors for mortality were low serum albumin, neutropenia, $ScvO_2$ at 6 hours <70%, and higher maximal peak inspiratory pressure (p=0.024, p=0.017, p=0.01, and p=0.003, respectively). From these findings, we conclude that the 'Surviving Sepsis Campaign 2012' guideline has improved the outcome of severe sepsis and septic shock in children.

Keywords: 'Surviving Sepsis Campaign 2012', septic shock in pediatrics, quality improvement, clinical practice guideline, Siriraj Hospital

INTRODUCTION

Severe sepsis and septic shock are common emergency conditions in pediatrics. The overall mortality rate in pediatric severe sepsis and septic shock ranges from 20% to 65% (Proulx *et al,* 1996; Angus *et al,* 2001) Factors that affect outcome include age, site of infection, underlying diseases, pathogens, severity of illness, and the quality of care in the Pediatric Intensive Care Unit (PICU). In the United States, the incidence of this illness is approximately 0.56 cases /1,000 population and the mean mortality rate is 10.3% (Watson *et al,* 2003). Limited data regarding incidence and outcome of sepsis has been reported from Thailand. One study in pediatric severe sepsis and septic shock that was performed at King Chulalongkorn Memorial

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Hospital, a national tertiary care hospital located in Bangkok, Thailand, reported that 30% of this pediatric patient population had positive blood culture, and the mortality was as high as 39% (Samransamruajkit *et al,* 2007). At our center, Siriraj Hospital, there were 122 pediatric severe sepsis and septic shock patients treated during 2009-2011 in our PICUs and the mortality rate was 37.7%. Most mortality during that period associated with multiple organ dysfunction syndromes (Khan *et al,* 2012).

In general, early recognition and diagnosis, administration of proper antibiotics as soon as possible, adequate fluid resuscitation, and hemodynamic support are the factors that most influence patient survival. Most pediatric intensivists around the world have now adopted Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock 2012 guideline as a roadmap for how to manage this life-threatening condition. The objectives of multimodality care bundles in the PICU include adequate cardiac output, optimal organ perfusion, hemodynamic support and other organ-specific support, such as mechanical ventilation and renal replacement therapy (Dellinger *et al,* 2013). Although we now have an established guideline, proper and timely diagnosis and adequate initial resuscitation are still challenge in clinical practice. Common obstacles to initiating treatment according to guideline protocol include a lack of understanding and adherence to the treatment protocol, a lack of experience in managing patients according to the guideline, and difficult IV access for fluid resuscitation in children. In addition, some bundles of early goal-directed therapy can be difficult to practice in real-life situations, such as difficulty or inability to insert a central venous catheter for $ScvO_2$ monitoring and/or to insert an arterial line to monitor continuous blood pressure within the first few hours. These problematic and sometimes prohibitive factors influenced us to investigate the effectiveness of this guideline in reducing mortality in the Pediatric Intensive Care Units at Siriraj Hospital – Thailand's largest national tertiary referral center. Our investigation included an assessment of adherence to each care bundle in the guideline, and we evaluated for clinical factors that significantly affect mortality so that we may more effectively identify patients at high-risk for developing these conditions.

The aim of this study was to evaluate guideline adherence and patient outcome after implementation of the Surviving Sepsis Campaign 2012 guideline for severe sepsis and septic shock in pediatric patients at Siriraj Hospital, and to investigate the factors that significantly associate with risk of morality in this illness.

MATERIALS AND METHODS

Pediatric and adolescent patients aged 1 month to 15 years who were admitted for severe sepsis and septic shock at the Department of Pediatrics, Siriraj Hospital during the 1 January 2013 to 31 December 2014 study period and who met the inclusion criteria were enrolled. Patients were separated into two groups according to two different phases of guideline implementation. Patients admitted during 1 January 2013 to 31 December 2013 were classified as the 1st year group. Accordingly, the patients who were treated during 1 January 2014 to 31 December 2014 were classified as the 2nd year group. Patients with severe cyanotic heart diseases, severe congenital anomalies, severe brain injury, and/or end-stage malignancy were excluded.

Patient medical charts were retrospectively reviewed after implementation of the Surviving Sepsis Campaign 2012 guideline and data relating to both early goal-directed therapy resuscitation and management bundles of post-resuscitation care in the PICU were extracted, recorded, and analyzed. The campaign was continuously promoted, and re-education and small group discussions were organized every 6 months for staff on the wards and PICUs.

Group discussions centered on recent morbidity/mortality cases encountered at our center. Demographic data, respiratory parameters, laboratory parameters, comorbidities, length of hospital stay, length of PICU stay, Pediatric Risk of Mortality III (Prism III) score, and number of ventilator days were recorded and analyzed. The resuscitation bundles evaluated in this study were early lactate level measurement, blood culture before antibiotics, antibiotics started at 1 hour, fluid resuscitation and inotrope, CVP >8 mm Hg, and central venous saturation ($ScVO_2$) >70%. The PICU bundles of care included intravenous steroid for at-risk patients, glycemic control, and limitation of plateau pressure <30 cm of water if patients were on mechanical ventilation. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Data were analyzed using SPSS Statistics version 16 (SPSS, Chicago, IL). Chi-square test was used to investigate significant association between two variables. Unpaired Student's *t*-test and Mann-Whitney *U* test were used to analyze parametric and non-parametric data, respectively. Data are shown as number, number and percentage, mean ± standard deviation, or median and interquartile range. A *p*-value<0.05 was regarded as being statistically significant.

RESULTS

There were 48 severe sepsis and septic shock children who fulfilled the study criteria during the 2013- 2014 study period and all of them were enrolled. The year 1 and year 2 groups consisted of 23 and 25 patients, respectively. Patients in two consecutive years (2013 and 2014) were compared in order to evaluate the effect of efforts to promote the campaign and the effect of organized discussion groups about previous and existing. The average age of patients in the year 1 group was 9.25 years (range: 2 months to 15 years), while the year 2 group had a mean age of 1.1 years (range: 1 month to 14.6 years). Demographic and clinical characteristics of patients are summarized in Table 1. Most patients had comorbidities, and the main underlying disease was hemato-oncology (64.8% in year 1 and 52.6% in year 2). Regarding absolute neutrophil count (ANC), 42.1% of year 1 patients and 26.3% of year 2 patients had an initial absolute neutrophil count of less than 500/mm^3. The median PICU length of stay was 5 days for both year 1 and year 2. The median hospital length of stay was 22 and 19 days for the year 1 and year 2 groups, respectively. The most common primary site of infection in year 1 was blood stream infection (43%), while pneumonia (52.5%) was the most common primary site of infection in the year 2 group.

Approximately half of patients in both groups had positive blood cultures (52% in year 1 and 48% in year 2). The most common organism was methicillin-sensitive *Staphylococcus aureus* (MSSA). Other isolated organisms included methicillin-resistant coagulase-negative *Staphylococcus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumanii*. Most patients were intubated and on mechanical ventilation. The median number of ventilator days was 4 days in both groups. The average time to central venous catheter (CVC) insertion after diagnosis was 4.8 hours in year 1 and 1.8 hours in year 2.

After guideline promotion and small group discussion, completion of early goal-directed therapy (EGDT) significantly increased from 17.4% (4 of 23 patients) in year 1 to 72% (16 of 25 patients) in year 2. The numbers of guideline bundles that were comprehensively adhered to improve in year 2 after the guideline promotion and re-education program. This improvement was demonstrated by an increase in the rate of rapid fluid resuscitation in the first 24 hours, and the completeness of the resuscitation bundles

Table 1
Demographic and clinical characteristics of patients.

Characteristic	1st year after SSC	2nd year after SSC	*p*-value
Number of patients, *n*	23	25	-
Boys, *n* (%)	15 (65.2)	16 (64)	NS
Age (years), median [IQR]	9.25 [0.17-15]	1.1 [0.08-14.6]	0.012
Comorbidities, *n* (%)	19 (82.6)	19 (76.0)	NS
Hemato-oncology	13 (68.4)	10 (52.6)	-
Neuromuscular disease	3 (15.8)	2 (10.5)	-
Chronic lung disease	1 (5.3)	2 (10.5)	-
Cardiovascular disease	0 (0.0)	1 (5.3)	-
VUR	1 (5.3)	2 (10.5)	-
Primary immune defierency	1 (5.3)	1 (5.3)	-
GI	0 (0.0)	2 (10.5)	-
ANC <500, *n* (%)	8 (42.1)	5 (26.3)	NS
PRISM III score, mean±SD	9.9±7.2	6.04±4.1	NS
ICU LOS (days), median [IQR]	5 [1-31]	5 [1-64]	NS
Hospital LOS (days), median [IQR]	22 [2-126]	19 [2-105]	NS
Ventilator days, median [IQR]	4 [1-24]	4 [2-35]	NS

SCC, Surviving Sepsis Campaign 2012; GI, gastrointestinal disease; IQR, interquartile range; VUR, vesicoureteral reflux; ANC, absolute neutrophil count; LOS, length of stay; PRISM, pediatric risk of mortality score; NS, non-significant; SD, standard deviation.

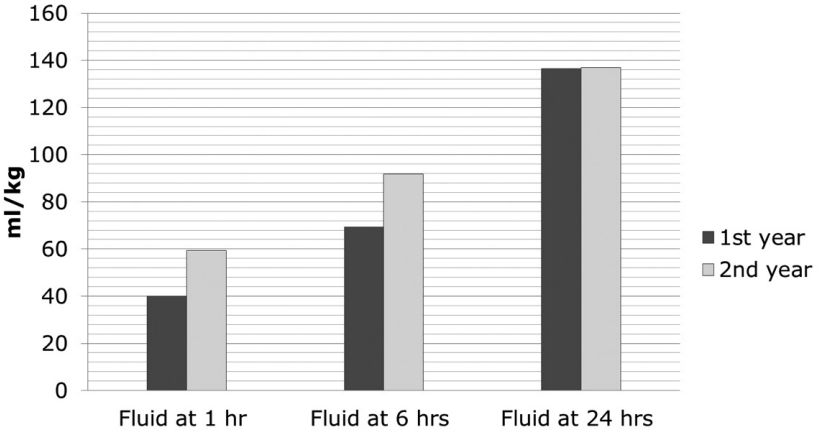

Fig 1- Total fluid resuscitation by time point in the first 24 hours.

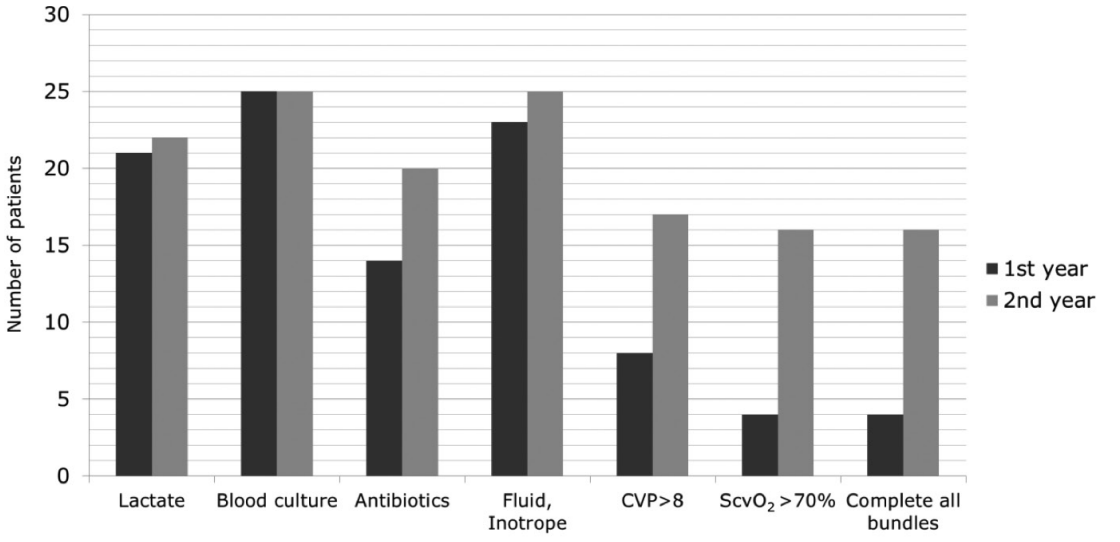

Fig 2- Number of patients that completed each resuscitation bundle component in years 1 and 2 after implementation of SSC 2012.

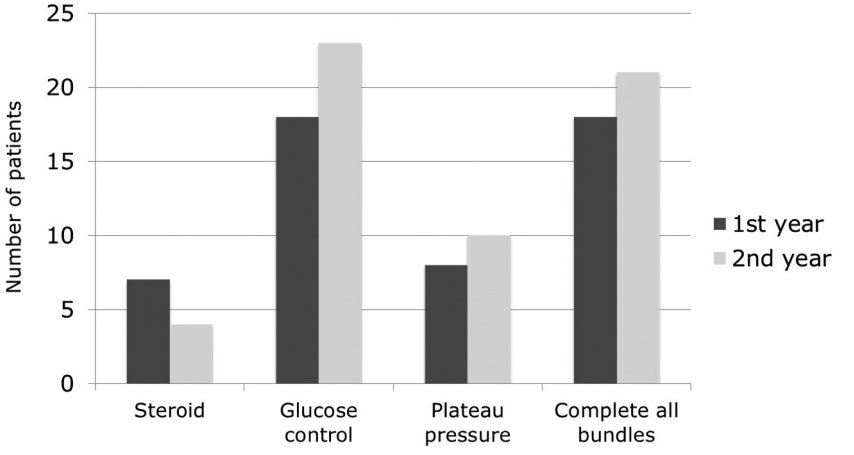

Fig 3- Number of patients that completed each post-resuscitation care component in the ICU in years 1 and 2 after implementation of SSC 2012.

and the post-resuscitation care (Figs 1, 2, and 3). A new ultrasonic cardiac output monitoring (USCOM) system was procured in 2011, and this real-time monitoring made it easier to achieve adequate cardiac output. Eighteen of 23 (78.3%) septic shock patients in year 1 and 18 of 25 (72%) in year 2 were monitored by the USCOM machine, and the cardiac index (CI) was maintained from 3.3 to 6.0 liters/min/m^2 according to early goal-directed therapy (EGDT) protocol. In this study, the average Cardiac index (CI) was 5.6±1.4 and 5.03±1.1 liters/min/m^2 in

the year 1 and year 2 group, respectively.

After guideline implementation for 2 years, 48 severe sepsis and septic shock patients were managed in PICU at Siriraj Hospital. Seventeen of them (35.4%) were complicated with disseminated intravascular coagulation (DIC) and 7 of them (14.5%) had acute renal failure (ARF). Two patients with ARF required either continuous veno-venous hemofiltration (CVVH) or acute peritoneal dialysis (PD) as an acute renal replacement therapy (CRRT). Although we have a protocol management in ICU, 5 of them were not survived (Table 2). However, when we compared the mortality data from this study to the data collected a few years prior to guideline implementation, the mortality rate significantly decreased from 37.7% to 10.4% (p=0.001). The mortality rate was found higher in patients with DIC (5 of 17: 29.4%), and patients with ARF (5 of 7: 71.4%). Risk factors that were found to significantly affect mortality outcome were DIC [odds ratio (OR)=1.417, 95% CI: 1.042-1.925; p=0.04) and acute renal failure (ARF) (OR: 3.5, 95% CI:1.085-11.292; p=0.001). Other risk factors for mortality were low serum albumin, neutropenia, $ScvO_2$ at 6 hours <70%, and higher maximal peak inspiratory pressure (p=0.024, p=0.017, p=0.01, and p=0.003, respectively).

DISCUSSION

In this study, we found that the Surviving Sepsis Campaign 2012 guideline that was instituted at Siriraj Hospital improved the outcome of pediatric severe sepsis and septic

Table 2
Factors that affected morality in severe sepsis and septic shock patients.

Parameter	Dead (n=5)	Survived (n=43)	p-value
Respiratory parameters			
PaO_2/FiO_2, mean±SD	181.25±97.63	285.46±107.2	0.126
Maximal PIP, mean±SD	28.2±1.8	22.9±3.2	0.003
Initial oxygen index, mean±SD	7.5±2.2	5.0±2.5	0.705
Laboratory parameters			
$ScvO_2$ at 6 hrs, mean±SD	64.5±4.0	75.5±16.2	0.001
ANC, median [IQR]	0 [0-7,440]	6,500 [0-50,280]	0.017
Serum albumin, mean±SD	2.7±0.4	3.3±0.5	0.024
Initial creatinine, median [IQR]	1.9 [0.4-2.3]	0.41 [0.1-2.26]	0.008
Serum ionized calcium, mean±SD	3.82±0.76	4.3±0.78	0.104
Associated comorbidities			
DIC, cases [OR, 95%CI]	5	12	0.04 [1.41,1.04-1.92]
ARF, cases [OR, 95%CI]	5	2	0.001 [3.5, 1.08-11.29]

PaO_2, pulmonary arterial oxygen tension; FiO_2, fraction of inspired oxygen; $ScvO_2$, O_2 saturation in central vein; PIP, maximum peak inspiratory pressure; ANC, absolute neutrophil count; DIC, disseminated intravascular coagulation; ARF, acute renal failure; SD, standard deviation; IQR, interquartile range; OR, odds ratio; 95%CI, 95% confidence of interval.

shock patients. Using this guideline, most of our patients achieved the following goals of treatment: CVP > 8 mm Hg, $ScvO_2$ at 6 hours >70%, and CI between 3.3-6.0 liters/min/m^2 by USCOM. Moreover, patients that required additional specific organ support, such as mechanical ventilation and continuous renal replacement therapy, received faster support. These improvements in quality of care reduced the mortality rate in this patient population at Siriraj Hospital by half from 2013 to 2014.

Although we previously attempted to improve the outcome of severe sepsis and septic shock patients at Siriraj Hospital by using early versions of clinical practice guidelines, we did not achieve good results. Prior to the implementation of the new guideline, the mortality rate was as high as 37.7% at our center. After the new international severe sepsis and septic shock campaign was launched in 2012, the Thai Pediatric Pulmonary and Critical Care Forum set up a dedicated organizing committee that set forth to improve the morbidity and mortality of children with this condition in Thailand. By the time the guideline was fully implemented in Thailand, results were being reported from around the world that attested to the efficacy of the 2012 guideline. These reports influenced and motivated our team to implement this program and to realize these same levels of improvement in patient. Moreover, this is an indicator to compare the quality of care and level of standard to the others as a bench mark. After implementation of the Surviving Sepsis Campaign 2012 guideline, we set forth to improve our care network, to improve adherence to the treatment protocols, and to promote, remind, and discuss the program with all members of the care team. The result of this campaign has been a decrease in mortality at Siriraj Hospital from 37.7% to 10.4% in 2014. A similar decrease was observed at other centers in Thailand, including King Chulalongkorn Memorial Hospital (Faculty of Medicine, Chulalongkorn University) where mortality in this population decreased from 42% to 19.1% (Samransamruajkit *et al,* 2014). This significant decrease in mortality may be attributable to a focus on several components of care, including early recognition and diagnosis, appropriate antibiotics as soon as possible, early adequate fluid resuscitation, inotrope and vasopressor infusion, and goal-directed therapy to stabilize patients in the PICU (Belletti *et al,* 2016; Lane *et al,* 2016).

In order to realize optimal benefit from the guideline, care teams must be trained how to perform each component of care according to the guideline, and performance and outcomes should be monitored to identify problems and to ensure continuous compliance and improvement. In this study, we found that continued promotion of the campaign, along with group discussions to discuss and learn from prior and existing cases, helped to improve adherence to the guideline. Improvements included fluid given more rapidly, but not in excess; more patients received central venous catheters; and patients were transferred earlier to the PICU. Two recently published large reviews reported that attempting to resuscitate patients according to the EGDT protocol may not be necessary, and that trying to achieve that goal sometimes resulted in patients receiving too much fluid, which led to a need for more ventilator support (Angus *et al,* 2015; Coccolini *et al,* 2016). Similar to the finding by Lane *et al* (2016) we found that close monitoring, frequent assessment and reevaluation, and adjustment of the management plan according to clinical findings are more important and more applicable than specifically achieving the set point of EGDT.

Most of the patients in this study had underlying diseases. Half of patients were hemato-oncology patients, which are prone to difficulties in IV access, more severe infections, and more serious complications than patients with other disorders. This high proportion of hemato-oncology patients in our study is similar to the finding of other studies, in which referral

hospitals are customarily tasked with caring for complex cases (Samransamruajkit *et al,* 2014; Breuling *et al,* 2015; Scheer *et al,* 2016). Moreover, we could demonstrate the risks of mortality which were DIC, acute renal failure (ARF), low serum albumin, neutropenia, $ScvO_2$ at 6 hours <70% and high maximal peak inspiratory pressure on ventilator (Breuling *et al,* 2015). These results indicate that we might have to put more effort on specific organ support such as early initiation of renal replacement therapy for the septic patients who had acute renal insufficiency as comorbidity to get better outcome in future.

In conclusion, from these findings we conclude that the 'Surviving Sepsis Campaign 2012' guideline has improved the outcome of severe sepsis and septic shock in children at our center. Guideline adherence and patient outcomes improved with ongoing promotion of the 'Surviving Sepsis Campaign 2012' initiative and small group case-study discussions. Children with hemato-oncology disorders were the least likely to survive their disease. Risk factors that were found to significantly affect mortality outcome were disseminated intravascular coagulation and acute renal failure. Other risk factors for mortality were low serum albumin, neutropenia, $ScvO_2$ at 6 hours <70%, and higher maximal peak inspiratory pressure. Maintenance of CVP >8 cm of Hg, $ScvO_2$ >70%, and CI between 3.3-6.0 liters/min/m^2 is helpful for managing septic shock children in a critical setting.

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CONFLICTS OF INTEREST

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

REFERENCES

Angus DC, Barnato AE, Bell D, *et al.* A systematic review and meta-analysis of early goal-directed therapy for septic shock: the arise, process and promise investigators. *Intensive Care Med* 2015;41:1549-60.

Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-10.

Belletti A, Benedetto U, Biondi-Zoccai G, *et al*. The effect of vasoactive drugs on mortality in patients with severe sepsis and septic shock. A network meta-analysis of randomized trials. *J Crit Care* 2016;37:91-8.

Breuling T, Tschiedel E, Grosse-Lordemann A, *et al*. Septic shock in children in an urban area in Western Germany--outcome, risk factors for mortality and infection epidemiology. *Klin Padiatr* 2015;227:61-5.

Coccolini F, Sartelli M, Catena F, Ceresoli M, Montori G, Ansaloni L. Early goal-directed treatment versus standard care in management of early septic shock: meta-analysis of randomized trials. *J Trauma Acute Care Surg* 2016;81:971-8.

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.

Khan MR, Maheshwari PK, Masood K, Qamar FN, Haque AU. Epidemiology and outcome of sepsis in a tertiary care PICU of Pakistan. *Indian J Pediatr* 2012;79:1454-8.

Lane RD, Funai T, Reeder R, Larsen GY. High reliability pediatric septic shock quality improvement initiative and decreasing mortality. *Pediatrics* 2016;138.pii:e20154153.

Proulx F, Fayon M, Farrell CA, Lacroix J, Gauthier M. Epidemiology of sepsis and multiple organ dysfunction syndrome in children. *Chest* 1996;109:1033-7.

Samransamruajkit R, Hiranrat T, Prapphal N, Sritippayawan S, Deerojanawong J, Poovorawan Y. Levels of protein C activity and clinical factors in early phase of pediatric septic shock may be associated with the risk of death. *Shock* 2007;28:518-23.

Samransamruajkit R, Uppala R, Pongsanon K, Deelodejanawong J, Sritippayawan S, Prapphal N. Clinical outcomes after utilizing surviving sepsis campaign in children with septic shock and prognostic value of initial plasma NT-proBNP. *Indian J Crit Care Med* 2014;18:70-6.

Scheer CS, Fuchs C, Kuhn SO*, et al.* Quality improvement initiative for severe sepsis and septic shock reduces 90-day mortality: a 7.5-year observational study. *Crit Care Med* 2016;45:241-52.

Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med* 2003;167:695-701.