นิพนธ์ต้นฉบับ ▪ Original Article

อัตราการเสียชีวิตและปัจจัยที่เกี่ยวข้องหลังใช้แนวทางการรักษาภาวะติดเชื้อรุนแรงในกระแสโลหิต และภาวะช็อกจากการติดเชื้อในเด็กในโรงพยาบาลศรีนครินทร์

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Mortality and Predictive Factors in Pediatric Severe Sepsis and Septic Shock after Implementation of Surviving Sepsis Campaign Guideline in Srinagarind Hospital

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หลักการและวัตถุประสงค์: การรักษาภาวะติดเชื้อรุนแรงในกระแสโลหิตและภาวะช็อกจากการติดเชื้อในเด็ก อย่างทันท่วงทีทำให้ผู้ป่วยมีโอกาสรอดชีวิตมากขึ้น ปัจจุบันมีการใช้แนวทางการรักษาภาวะดังกล่าวในหลายสถาบัน แต่พบว่ายังไม่แพร่หลายนักในประเทศกำลังพัฒนาเนื่องจากความขาดแคลนทรัพยากรการศึกษานี้มีวัตถุประสงค์เพื่อศึกษาอัตราการเสียชีวิตและปัจจัยที่มีผลเกี่ยวข้องกับอัตราการเสียชีวิตในเด็ก ที่ได้รับการวินิจฉัยภาวะติดเชื้อรุนแรงในกระแสโลหิต และภาวะช็อกจากการติดเชื้อหลังใช้แนวทางการดูแลรักษาภาวะติดเชื้อรุนแรงในกระแสโลหิตและภาวะช็อกจากการติดเชื้อ

วิธีการศึกษา: เป็นการศึกษาแบบ Retrospective descriptive study ในผู้ป่วยเด็กทุกรายที่มีอายุตั้งแต่ 1 เดือนถึง 15 ปี ที่เข้ารับการรักษาในแผนกผู้ป่วยระยะวิกฤตเด็ก โรงพยาบาลศรีนครินทร์ โดยค้นทะเบียนข้อมูลผู้ป่วยเด็กที่ได้รับการวินิจฉัยภาวะติดเชื้อรุนแรงในกระแสโลหิตและภาวะช็อกจากการติดเชื้อในเด็ก ตั้งแต่วันที่ 1 มกราคม ถึง 31 ธันวาคม 2556 (หลังได้นำแนวทางการดูแลรักษาภาวะติดเชื้อรุนแรงในกระแสโลหิตและภาวะช็อกจากการติดเชื้อในเด็กมาใช้) เปรียบเทียบกับข้อมูลผู้ป่วย 1 ปี ย้อนหลัง

ผลการศึกษา: มีประชากรที่ได้รับการวินิจฉัยภาวะติดเชื้อรุนแรงในกระแสโลหิตและภาวะช็อกจากการติดเชื้อทั้งหมดจำนวน 30 ราย ค่ากลางอายุประชากรศึกษาอยู่ที่ 8.5 ปี โรคประจำตัวที่พบมากสุดสองอันดับ คือ โรคมะเร็งเม็ดเลือดขาว (ร้อยละ 37.9) และกลุ่มโรคทางระบบเนื้อเยื่อเกี่ยวพัน (ร้อยละ 13) หลังจากใช้แนวทางการรักษาภาวะติดเชื้อรุนแรงในกระแสโลหิตและ

Background and objective: Prompt treatment of sepsis and septic shock in pediatric patients could lead to an improved outcome. The Surviving Sepsis Campaign have been launched to guide treatments and has been followed by most contemporary centers. However, it has not been widely utilized in developing countries due to inadequate resources in multiple levels. This study aimed to investigate mortality rates and associated factors in children with severe sepsis and septic shock treated in the Pediatric Intensive Care Unit (PICU) of Srinagarind hospital, Khon Kaen university (KKU) after the implementation of the survival sepsis campaign guideline.

Method: A retrospective chart review was conducted on patients aged 1 month – 15 years treated in the PICU of Srinagarind hospital for sepsis and septic shock in 2013 after the distribution of the sepsis bundle guideline to pediatric residents. The mortality rate was compared with a historical control (Patients treated with sepsis and septic shock in 2012).

Results: Thirty patients, median aged 8.5 years (2 months – 14.5 years) were included. The two most common co-morbidities were hematologic malignancies (37.9%) and connective tissue disease (13%). After the implementation of the sepsis bundle guide-

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ภาวะช็อกจากการติดเชื้อในเด็ก พบว่าอัตราการเสียชีวิตลดลงเมื่อเปรียบเทียบกับข้อมูล 1 ปีย้อนหลัง อย่างมีนัยสำคัญทางสถิติ (23.3% vs 65.2% p = 0.002) และพบว่าปัจจัยที่มีความสัมพันธ์กับอัตราการเสียชีวิตอย่างมีนัยสำคัญทางสถิติคือ ภาวะ DIC (OR 10.5, 95%CI 1.06 – 103.5, p = 0.02), $ScvO_2$ น้อยกว่า 70% (OR 16.5, 95% CI 1.0 - 250.1, p = 0.02) และระดับ lactate ที่มากกว่า 4 mmol/L (OR 28.3, 95% CI 2.3 - 336.0, p <0.01) อัตราการเสียชีวิตที่ลดลงอาจเป็นผลจากการให้สารน้ำที่เหมาะสมให้ยาปฏิชีวนะที่รวดเร็วรวมทั้งให้ยาเพิ่มแรงบีบตัวของกล้ามเนื้อหัวใจ (inotropic agents) ที่รวดเร็วและเหมาะสม

สรุป: การใช้แนวทางการรักษาภาวะติดเชื้อรุนแรงในกระแสโลหิตและภาวะช็อกจากการติดเชื้อในเด็ก สามารถลดอัตราการเสียชีวิตในผู้ป่วยได้อย่างมีนัยสำคัญทางสถิติ ในโรงพยาบาลระดับตติยภูมิ ในประเทศกำลังพัฒนา

คำสำคัญ: ภาวะติดเชื้อรุนแรงในกระแสโลหิต, ภาวะช็อกจากการติดเชื้อ, แนวทางการรักษาภาวะติดเชื้อรุนแรงในกระแสโลหิตและภาวะช็อกจากการติดเชื้อ

line, the mortality rate has significantly decreased from 65.2% to 23.3% (p=0.002). Factors associated with increased mortality included the DIC (OR 10.5, 95%CI 1.06 – 103.5), central venous oxygen saturation ($ScvO_2$) <70% (OR 16.5, 95% CI 1.0 - 250.1), and lactate level > 4 mmol/L (OR 28.3, 95% CI 2.3 - 336.0). Improved outcomes could potentially be explained by adequate initial fluid resuscitation, appropriate use of antibiotics, and earlier initiation of inotropic agents.

Conclusions: Implementation of the sepsis bundle guideline in a tertiary care center in developing country lead to outcome improvement. A multicenter prospective study in a larger population could better clarify its role in developing countries.

Keywords: Guideline implementation, septic shock, severe sepsis, severe sepsis resuscitation bundle, Surviving Sepsis Campaign

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Introduction

Despite advancement in intensive critical care settings, sepsis and septic shock are still major causes of death in children.[1-3] Early recognition of the condition and prompt initiation of initial resuscitation are critical for favorable outcomes.[4-8] Most common causes of septic shock are pneumonia, intra-abdominal infection, urinary tract infection, and skin and soft tissue infection.[9-11] Septicemia could lead to septic shock and related to multi-organ failure, affecting cardiovascular, renal, pulmonary, neurological, hematological, and hepatobiliary systems.[9,11]

Survival Sepsis Campaign initiatives were launched to guide management and hopefully lead to outcome improvement.5 The Surviving Sepsis Campaign Bundles summarized the core concepts of the guidelines, and included recommendations on fluid therapy, obtaining blood cultures, timing of antibiotics therapy, timing of inotropic drugs therapy, central venous pressure (CVP) monitoring, documentation of superior vena cava oxygen saturation ($SCVO_2$), and documentation of lactate levels. The areas with highest compliance were documentation of lactate levels at one-hour after the diagnosis, obtaining blood cultures before starting antibiotics, and following recommendations on IV fluid resuscitation and inotropic drugs management, while keeping $SCVO_2$ above 70% and CVP above 8 mmHg were less successful.[9,11]

Several studies have evaluated the efficacy of the guidelines, however, most of them were performed in adults. For example, Shiramizo, et al., compared treatment outcomes before and after using survival sepsis campaign guidelines in adult medicine and surgery ICU during July 2005 to April 2006, found the success rate according to 6-hour and 24-hour goals improve from 6% to 13.7% and 15.1% to 44.4% respectively.[9] The mortality rate was also reduced from 54% to 16.2%. In addition, Wang et al, reported a reduction in mortality rate from 44.4 to 31.6% in adult patients,12 found that mortality rate in adults from June 2008 to December 2009 decreased from 44.4% to 31.6%.12 Samransamruajkit et al evaluated the mortality rates in pediatric patients treated at King Chulalongkorn Memorial hospital from 2008 – 2012 and found the improvement from 42% to 19% after implementing Survival Sepsis Campaign.[13] However, the feasibility of implementing the Survival Sepsis Campaign Guidelines in a tertiary care center far away from Bangkok, where results are inadequate in multiple levels have not been evaluated.

Here, we evaluated the mortality rate and associated factors in pediatric patients with severe sepsis and septic shock treated in the Pediatric

Intensive Care Unit (PICU), Department of Pediatrics, Srinagarind hospital, Khon Kaen university, Thailand after the Survival Sepsis Campaign guidelines were utilized. The objective of this study was to study the mortality rate and associated factors of those patients after the implementation of the guidelines. We conducted a retrospective chart review on patients treated in our PICU for severe sepsis and septic shock in 2013 which we established the treatment protocol and implement guideline to all residents, and compared the mortality rate with patients treated a year prior to the implementation of the guidelines.

Materials and Methods

A retrospective medical record review was performed on pediatric patients aged 1 month – 15 years with diagnosis of severe sepsis and septic shock by SIRS criteria treated in the PICU, Department of Pediatrics, Srinagarind hospital, KKU from January 1st, 2013 – December 31st 2013. Exclusion criteria were dengue shock syndrome, congenital heart disease, and end stage disease or receiving palliative.

The sepsis bundle guideline for treating sepsis and septic shock was distributed to pediatric residents in the PICU in the beginning of 2013. Thirty patients met the inclusion criteria. The mortality rate was compared with historical control (patients treated with sepsis and septic shock in 2012).

Data are presented as mean ± 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

Thirty patients (13 females, 17 males) were diagnosed with severe sepsis and septic shock during the study period. Table 1 shows demographic characteristics of the patients. The median age was 8.5 years (2 months – 14.5 years). According to age group, under 1-year-old was 13.3% (N=4) and over 1-year-old was 86.7% (N=26). Average duration admitted in the hospital and PICU was 18.9 days and 6.3 days, respectively.

Twenty six of the patients had no underlying disease. Previously diagnosis with hematological malignancy was the most common medical history (36.7%). Secondly, connective tissue disease was found 13.3%, majorly were SLE with renal involvement receiving immunosuppressive drugs and one case with juvenile idiopathic arthritis. Other underlying diseases included chronic lung disease, and neuromuscular disease as was shown in Table 1.

The sources of infection were respiratory tract infection (25%), infective diarrhea (25%), bacteremia (17.8%), skin and soft tissue infection, infective endocarditis and suppurative parotitis. Positive blood cultures were documented in 42.8% of patients. The most common organisms included Burkholderia pseudomallei (3 patients, 10.7%), MRSE (3 patients, 10.7%) and Pseudomonas aeruginosa (2 patients, 7.1%). Drug resistance organisms were found in 7 patients (25%) , such as MRSE (3 patients, 10.7%), Pseudomonas aeruginosa MDR (2 patients, 7.1%), Acinetobacter baumannii MDR (1 patient, 3.5.%) and Klebseilla pneumoniae ESBL (1 patient, 3.5%) (Table 1).
After the implementation of the sepsis bundle guideline, the mortality rate had significantly decreased from 65.2% to 23.3% (p=0.002) compared to the previous year record (Figure 1).

Resuscitation compliance

93.1% of the patients received antibiotics within one hour after diagnosis. 88% of initial fluid resuscitation was 0.9% NaCl with an average of 17.0 ± 5.5 mL/kg in the first 15 min and 40.0 ± 12.7 mL/kg in the first 1 hour. Most common first inotropic agents was dopamine (96%) (Table 2).

68.9% patients were undergone central venous catheter including femoral vein (70%), internal

Clinical factors

In severe sepsis and septic shock, we found DIC was most common complication (20%) follow by renal failure (13.3%) and liver failure (6.7%). Clinical manifestation associated with increasing significant mortality rates were DIC (OR 10.5, 95%CI 1.0 – 103.6, p = 0.02) (Table 3).

Laboratory parameters and severity scores were

Table 1 Demographic data

	N (%)
Age (years), median (±SD)	8.5 ± 5
Gender	
Male	17 (56.7)
Female	13 (43.3)
ICU length of stay (days), mean (±SD)	6.3 ± 7.2
Hospital length of stay (days), mean (±SD)	18.9 ± 18.3
Co-morbidities	
Absent	8 (26.7)
Present	22 (73.3)
Hematologic malignancy	11 (36.7)
Connective tissue disease	4 (13.3)
Chronic lung disease	2 (6.7)
Neuromuscular disease	1 (3.3)
Others	4 (13.3)
Source of infection	
Pneumonia/ other respiratory tract infection	7 (25)
Infective diarrhea	7 (25)
Bacteremia	5 (17.8)
Skin and soft tissue infection	3 (10.7)
Others	6 (21.4)
Clinical picture of sepsis – source not identified	4 (14.3)
Bacterial endocarditis	1 (3.5)
Suppurative parotitis	1 (3.5)
Positive blood culture	12 (42.8)
Burkholderia pseudomallei	3 (10.7)
MRSE	3 (10.7)
Pseudomonas aeruginosa	2 (7.1)
Acinetobacter baumannii	1 (3.5)
Candida spp.	2 (7.1)
Other	1 (3.5)

MRSE – Methicillin-resistant *Staphylococcus epidermidis*, SD – standard deviation

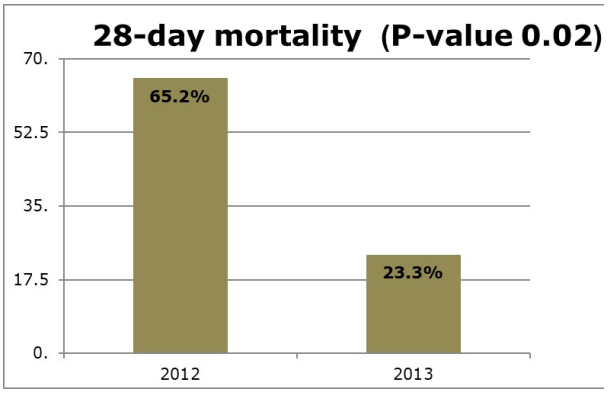

Figure 1 Demonstrates the difference of sepsis mortality compared between after the implementation of the sepsis bundle guideline and the previous year record

Table 2 Performance of bundle compliance

	N (%)
Total	30 (100)
ATB 1st hour	28 (93.1)
Initial fluid resuscitation	
0.9%NaCl	27 (88)
5% human albumin	3 (12)
Fluid in first 15 min (ml/kg)	17 ± 5.5
Fluid in first hour (ml/kg)	40 ± 12.7
1st Inotropic drug	
Dopamine	29 (96)
Norepinephrine	1 (4)
Central venous catheter site	20 (68.9)
Femoral vein	14 (70)
Internal jugular vein	5 (5)
Subclavian vein	1 (5)
Mean initial CVP (cmH_2O)	10.1 ± 4.4

differences between survival and mortality group as shown in Table3 and Table 4 such as initial $SCVO_2$<70% (OR 16.5, 95% CI 1.0 - 250.1, p =0.02) mean 86.9 ± 8.15 vs 73.8 ± 13.1 p = 0.02 (95% CI 2.0- 24.2) and initial lactate level > 4 mmol/L (OR 28.3, 95% CI 2.3 - 336.0, p <0.01) mean 1.7 ± 1.8 vs 8.3 ± 6.2 p<0.01 [95% CI (-9.7)-(-3.4)].

Discussion

Since application of the "Early goal-directed bundled care guideline", Our study show mortality rate has significantly decreased. The improvement in

Table 3 Risk factors associated with death in severe sepsis and septic shock patients

Factors	N (%)	odds ratio (95%CI)	p-value
Clinical factors			
DIC	6 (20)	10.5 (1.0-103.6)	0.02
Renal failure	4 (13.3)	3.5 (0.6-20.8)	0.14
Liver failure	2 (6.7)	1.8 (0.2-12.8)	0.55
Lab parameters			
Initial Lactate > 4 (mmol/l)	5 (16.7)	28.3 (2.3-336.0)	< 0.01
HCO3 < 16 (mmol/l)	2 (6.7)	1.2 (0.1-8.7)	0.8
Calcium < 8 (mg/dl)	3 (10)	1.2 (0.2-7.4)	0.78
Initial $SCVO_2$ < 70 (%)	3 (10)	16.5 (1.0-250.1)	0.02

DIC; disseminated intravascular coagulopathy, SCVO2; superior vena cava oxygen saturation

Table 4 Risk factors associated with death in severe sepsis and septic shock patients compare in two groups, survival and mortality groups

Laboratory parameters	Survival group	Mortality group	p-value (95%CI)
Total (N)	23	7	
PRISMIII, (mean±SD)	8.8 ± 6.2	4.9 ± 13.0	0.09 [(-13.2)-1.2]
Initial $SCVO_2$ (%)	86.9 ± 8.15	73.8 ± 13.1	0.02 (2.0- 24.2)
CVP initial (mmHg)	11.5 ± 3.2	7.5 ± 5.5	0.07 [(-0.4)-8.5]
HCO3 (mmol/l)	17.8 ± 6.3	16.2 ± 6.5	0.58 [(-4.2)-7.2]
Calcium (mg/dl)	8 ± 0.6	7.9 ± 1.3	0.83 [(-0.7)-0.9]
Initial lactate (mmol/l)	1.7 ± 1.8	8.3 ± 6.2	<0.01 [(-9.7)-(-3.4)]
Initial pH (mean±SD)	7.33 ± 0.1	7.26 ± 0.15	0.18 [(-0.03)-0.18]

DIC; disseminated intravascular coagulopathy, SCVO2; superior vena cava oxygen saturation

mortality rates could be explained by rapid initial fluid resuscitation, appropriate use of antibiotics and earlier initiation of inotropic agents.

Previous studies indicated that $SCVO_2$ was an important tool to evaluate for adequate treatment in severe sepsis and septic shock and $SCVO_2$ reflect tissue perfusion.[14,15] This study had similar results with adults that $SCVO_2$ less than 70% associated with increasing mortality rates (OR 16.5, 95% CI 1.0 - 250.1, p = 0.02).[16,17] Although $ScvO_2$ in this study mostly was monitored by using femoral line, it was still associated with more mortality. Therefore, if we cannot monitor $SCVO_2$ from internal jugular vein or subclavian vein, it might be possible to use from femoral vein which might reflect $SCVO_2$. The PRISMIII score was observe higher in the survival group but no statistical significant. However, this study had limitation and needed more sample size.

In literature, patients with severe sepsis and elevated lactate were increased risk for mortality[16-18], which this study also found that lactate level > 4 mmol/L (OR 28.3, 95% CI 2.3 - 336.0, p <0.01) associated with that. Serially measure lactate levels and keep lactate level within acceptable range (less than 4 mmol/L) in order to achieve one of the targets for severe sepsis and septic shock treatment may improve its outcomes. Our result had demonstrated that initial lactate and $SCVO_2$ monitoring had clinical benefits.

In conclusion the implementation of the sepsis bundle guideline leads to an improvement of treatment outcomes in a tertiary care center in developing country.

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