Septic Death in Adults at Surin Hospital: An Investigation of Real-Life Clinical Practice vs. Empirical Guidelines

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Objective: To explore the cause of death from sepsis and to evaluate the hospital practice in septic patients. **Material and Method:** A cross-sectional, retrospective study was conducted between October 2004 and September 2005, at Surin Hospital. The present study included 119 adults (≥ 15 year of age) who were admitted with community-acquired sepsis.

Results: According to the ACCP/SCCM definition, 85.7% of the patients had severe sepsis and up to 71.4% had septic shock. The overall hospital mortality was 73.9% for septic patients and 88.2% for patients in septic shock. The factors that were significantly associated with death from sepsis were age ≥ 60 years, presence of co-morbidity, septic shock, organ dysfunctions ≥ 3 , and acidosis (HCO₃ < 20 mEq/L). During hospitalization, 5.9% of patients received ICU care, 29.4% adequate fluid resuscitation, but none had been monitored for Svo₂ or Scvo₂, and 36.4% had more than a 1-hr delay in the administration of antibiotics. The main cause of death was refractory hypotension (77.3%), in which the amount of fluid therapy during initial resuscitation was significantly associated with the survival of septic shock.

Conclusion: Septic shock is the most common cause of death in septic patients. Delayed and inadequate hemodynamic management, including a delay in the administration of antibiotics are the main problems in real-life clinical management of septic patients.

Keywords: Death, Patient care management, Sepsis, Septic shock, Thailand

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Sepsis is defined as the systemic inflammatory response to infection⁽¹⁾, a major cause of morbidity and mortality, and its incidence is increasing. Martin et $al^{(2)}$ analyzed the occurrence of sepsis in the United States from 1979 through 2000 and found the incidence of sepsis increased from 82.7 cases per 100,000 population to 240.4 cases per 100,000. Recently, Sundararajan et $al^{(3)}$ studied the epidemiology of sepsis in Victoria, Australia, and found an increasing population-incidence from 166 cases per 100,000 in 1999 to 194 per 100,000 in 2002. Thus, despite recent advances in antimicrobial agents, supportive care and new adjunctive therapies, sepsis remains associated with a high mortality rate (about 30% in severe sepsis and up to 60% when associated with shock)⁽⁴⁻⁶⁾.

The mortality rate of sepsis, especially severe sepsis and septic shock, is a major public health con-

cern. Presently, the epidemiological data of sepsis in Thailand are limited. Infectious diseases, however, are the third leading cause of death in Thailand⁽⁷⁾, while septicemia (ICD-10 code A41.9) is the leading cause of death at Surin Hospital (population incidence, 9.2 per 100,000)⁽⁸⁾. In order to implement better, rational treatment of septic patients, it is important to analyze the details of death from sepsis. The present study was conducted at Surin Hospital in Northeast Thailand: 1) to explore the causes of death from sepsis, and 2) to evaluate the real-life hospital management of septic patients.

Material and Method

Study design and population

A cross-sectional retrospective study was conducted between October 1, 2004, and September 30, 2005, at the Department of Medicine, Surin Hospitala 697-bed, regional hospital in Northeast Thailand. In-patients 15 years and older with community-acquired

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sepsis, who were diagnosed upon initial arrival at the hospital were included.

To identify cases of sepsis, the author used the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) code A41.9. Sepsis and sepsis-related conditions were defined according to the criteria reported by 1992 ACCP/SCCM consensus conference⁽¹⁾, and the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference⁽⁹⁾.

Data collection

Patients' charts were identified using the Surin Hospital computerized database. From all of the studied patients, the authors recorded: (1) demographic characteristics, (2) any underlying co-morbidity, (3) type of admission (external refer or emergency department), (4) initial clinical symptoms and signs, (5) laboratory finding, (6) infectious etiology, (7) presence of organ dysfunctions, (8) antibiotic usage, (9) hemodynamic monitoring and management, (10) site of care (intensive care unit (ICU) or ward), (11) causes of death, (12) length of hospital stay, and (13) total hospital cost.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 13.0. The results for the categorical variables were expressed as number of patients and percentages, while for continuous variables the author used means and standard deviations (for normally distributed data) and median and Inter-quartile range (IQR) (for non-normally distributed data). Differences between the survivor group and the non-survivor were tested with the use of Chi-square test, Fisher's exact test for categorical variables, or Mann-Whitney U test for continuous variables. A two-tailed p-value < 0.05 represented statistically significant difference.

Results

During the study period, 144 patients had a discharge diagnosis of sepsis. The author excluded 25 patients (17.4%) because they were incorrectly coded. The present study population, therefore, comprised 119 patients, 53.8% of whom were female and 46.2% male. Age averaged 57.2 ± 16.9 years (range, 17-96). Approximately 62% of the patients had an underlying disease, most commonly diabetes mellitus (26%), liver cirrhosis (13.4%), or hypertension (8.4%). All of the patients had two or more criteria for systemic inflammatory response syndrome (SIRS); of whom 31.9% met two criteria, 39.5% three criteria, and 28.6% all of the

SIRS criteria. According to the ACCP/SCCM definition, 85.7% of patients were defined as severe sepsis and 71.4% septic shock. Nearly two-thirds (61.3%) of the patients were referred from a community hospital. The median length of hospital stay (LOS) was 32 h (IQR: 3-160) (Table 1).

Organ dysfunctions and infection characteristics are presented in Table 2. Nearly half (49.6%) of the patients had dysfunction of three or more organs. The most common organ dysfunctions included circulatory (79%) and respiratory (67.2%). The most frequent site of infection was pulmonary (27.7%) and abdominal (27.7%), followed by urinary tract (16.8%) and skin (15.1%). According to the causative organisms, Klebsiella pneumoniae was the major isolated (25%) from respiratory tract infection, followed by Streptococcus pneumoniae (12.5%), Burkholderia pseudomallei (6.25%), and unknown (56.25%). Escherichia coli were the most frequently isolated from abdominal and urinary tract infection. Hemoculture was done on nearly half (47.9%) of the patients, of whom only 21.3% had hemoculture positivity (i.e., 83.3% gram-negative vs. 16.7% gram-positive). The most prevalent causative

 Table 1. Demographics and characteristics of patients with sepsis

1	
Characteristic	n = 119
Mean age in years (SD)	57.2 (16.9)
Male sex, %	46.2
Median length of stay, h (IQR)	32 (3-160)
Underlying diseases*, %	62.2
Diabetes mellitus	26.0
Cirrhosis	13.4
Hypertension	8.4
Previous pulmonary tuberculosis	5.9
Chronic renal failure	3.4
Coronary artery disease	3.4
HIV infection	3.4
No. of SIRS criteria, %	
2	31.9
3	39.5
4	28.6
Type of presentation, %	
Transferred from other hospital	61.3
Emergency department visit	34.5
Shock on admission, %	65.9
ICU admission, %	5.9

* Some patients had more than one underlying disease,

HIV: human immunodeficiency virus, ICU: intensive care unit, IQR: inter-quartile range, SD: standard deviation, SIRS: systemic inflammatory response syndrome

	%
No. of organ dysfunctions	
1	10.9
2	25.2
\geq 3	49.6
Type of organ dysfunctions	
Cardiovascular	79.0
Respiratory	67.2
Renal	35.3
Neurologic	33.6
Hematologic	18.5
Hepatic	6.7
Site of infection	
Pulmonary	27.7
Abdominal	27.7
Urinary tract	16.8
Skin	15.1
Central nervous system	3.4
Other	5.9
Unknown	3.4

 Table 2. Organ dysfunctions and infection characteristics in 119 patients with sepsis

organisms were *Burkholderia pseudomallei* (41.7%), followed by *Escherichia coli* (25%), *Klebsiella pneumoniae* (16.7%), and *Staphylococcus aureus* (16.7%).

Shock during hospitalization developed in 71.4% of the patients, of whom 65.9% had thus presented at admission. Only 5.9% of the patients were admitted to ICU. Of the patients not in ICU, vital signs were obtained every 1 h in 9.2% of cases, every 2 h in 23.5%, every 4 h in 57.1%, and every 8 h in 10.1%.

Volume status assessment with central venous pressure (CVP) was performed in only 29.4% of patients with septic shock, the average CVP was 10.5 ± 4.2 mmHg. Of those not monitored for CVP, the median volume of

fluid resuscitation before receiving vasopressors was 0.2 L (Inter-quartile range: 0-1.8). The two most commonly used vasopressors were dopamine (94.1%) and epinephrine (52.9%). Neither mixed venous oxygen saturation (Svo_2) nor central venous oxygen saturation (Scvo_2) were monitored in the patients included in this present study.

Most (99.1%) of the patients received antibiotics for treatment of infection, of which 3rd generation cephalosporin was the most common. The median time before receiving the first dose of antibiotics after admission was 1 h (Inter-quartile range: 0-12); however, 36.4% waited more than 1 h.

The overall hospital mortality of the septic patients was 73.9%, and up to 88.2% when associated with shock. The factors that significant associated with death from sepsis were: 1) age \geq 60 years; 2) present of co-morbidity; 3) septic shock; 4) organ dysfunctions \geq 3; and, 5) acidosis (HCO₃ < 20 mEq/L) (Table 3). In the subgroup of patients with septic shock, there were no significant differences between the survivor group and non-survivor in CVP monitoring, frequency of vital signs observation, and time to receive antibiotics. However, the amount of fluid therapy during initial resuscitation was significantly associated with the survival of septic shock (Table 4).

Refractory hypotension was the most common cause of death in the studied population (77.3%), followed by arrhythmia (11.8%), acute respiratory distress syndrome (ARDS) (8.4%) and sudden arrest (4.2%). The median total hospital cost was THB 7,002 (Inter-quartile range: 3,018-28,213).

Discussion

Mortality from sepsis continues to be unacceptably high, especially vis- -vis severe sepsis

	Survivor $(n = 31)$	Non-survivor ($n = 88$)	p-value
Age \geq 60 years, %	19.4	56.8	0.001**
Male sex, %	48.4	45.5	0.942**
Present of co-morbidity, %	35.5	71.6	0.001**
Septic shock, %	32.3	85.2	< 0.001**
Organ dysfunctions $\geq 3, \%$	3.2	65.9	< 0.001**
Acidosis (HCO ₃ < 20 mEq/L), %	19.4	79.8	< 0.001**
Median time to received antibiotics, h (IQR*)	0.75 (0-2.9)	1 (0-14.2)	0.118***

Table 3. Factors associated with death from sepsis in 119 patients

* IQR, inter-quartile range

** Test of significance was obtained with the Chi-square test, or the Fisher's exact test

*** Test of significance was obtained with the Mann-Whitney U test

	Survivor ($n = 10$)	Non-survivor ($n = 75$)	p-value
Median amount of initial fluid therapy, L (IQR*)	1 (0.6-1.8)	0.2 (0-1.8)	< 0.001***
CVP monitoring, %	20.0	30.7	0.716**
Vital signs observation every 1 h, %	10.0	10.7	1.000**
Median time to received antibiotics, h (IQR*)	0.5 (0-3)	1 (0-13)	0.100***

Table 4. Subgroup analysis of patients with septic shock (n = 85)

* IQR, inter-quartile range

** Test of significance was obtained with the Fisher's exact test

*** Test of significance was obtained with the Mann-Whitney U test

and septic shock. As in previous studies^(4,6,10-12); the present study confirms that older age, presence of comorbidity, septic shock, multiorgan dysfunction, or metabolic acidosis are the factors that affect the survival of septic patients. According to the ACCP/SCCM Consensus Conference on the definition of sepsis⁽¹⁾, approximately 90% of the study population in the present study had severe sepsis and most (71.4%) had septic shock. These subgroups of sepsis had the most severe inflammatory response to infection⁽¹³⁾.

In the present study, the author found refractory hypotension was the most common cause of death in septic patients, in which septic shock was associated with a very high mortality rate (88.2%). Compared with previous studies^(4,6,14), the mortality rate associated septic shock was 50-60%. The explanation for this may be the patients had received management falling far short of the evidence-based clinical guidelines for severe sepsis and septic shock, the Surviving Sepsis Campaign (SSC) guidelines⁽¹⁵⁾. Therefore, this present study evaluated the real-life clinical practice at Surin Hospital, Northeast Thailand, of the management of septic patients.

Adequate fluid resuscitation is one of the keystones in the management of septic shock. According to the SSC guidelines⁽¹⁵⁾, during the first 6 h of resuscitation, a CVP of 8-12 mm Hg was set as one the goals of initial resuscitation. Notwithstanding, only 29.4% of patients in the present study with septic shock were monitored for intravascular filling pressure via CVP.

Of those on whom CVP was not performed, the median volume of fluid resuscitation before initiating vasopressors was only 0.2 L, which is insufficient for achieving adequate filling pressure. In previous studies^(16,17), large volume repletion (*i.e.*, of up to 6 L of crystalloid solutions or 2 L of colloid solutions) may be required during initial resuscitation. Thus, most of the patients in the present study received inadequate hemodynamic management for optimization of filling pressure before and during the use of vasopressors, which may have worsened the already inadequate tissue perfusion. Furthermore, the author also found that the amount of initial fluid therapy was significant associated with the survival of septic shock. The surviving patients received more fluids, the median amount of 1 L in the survivor group compared with 0.2 L in non-survivors. In this respect, River et al⁽¹⁷⁾ reported the early goal-directed therapy (EGDT) provides significant benefits with respect to outcome in patients with severe sepsis and septic shock, which the patients in EGDT group received more fluids, transfusions, and dobutamine in the first 6 h. The explanation for a very low fluid resuscitation in non-survivors in this present study may be the physicians do not understand the important of aggressive initial fluid resuscitation in septic shock.

Instead of using arterial cannulation for continuous measurement of arterial pressure in all patients with septic shock requiring vasopressors, as recommended in the current guidelines^(18,19), a cuff was routinely used in the study patients for intermittent measurement of arterial pressure (mainly, every 4 h). This resulted in inaccurate, arterial pressure-monitoring and delayed hemodynamic management. The main limitation was the lack of ICU beds, so that only 5.9% of patients in the present study were treated in the ICU. Similarly, Lundberg et al(20) found a trend toward increased mortality for patients whose shock developed in a general ward vs. ICU. The explanation, suggested by these authors⁽²⁰⁾, was that before being diagnosed the patients on the ward deteriorated for several hours (as vital signs were routinely obtained only every 8 h).

Svo₂ is a useful index of tissue oxygenation, reflecting the balance between oxygen supply and demand⁽²¹⁾. However, Scvo₂ is becoming increasingly popular as an alternative because the measurement provides a clinically useful approximation to Svo₂ and can be obtained from a central venous catheter, which is less risky, less costly, and more routinely used than the pulmonary artery catheter^(19,22-24). The present study showed that these parameters were not routinely monitored in real-life clinical practice.

The ultimate goals of hemodynamic therapy in septic shock are: (1) to restore effective tissue perfusion and (2) to normalize cellular metabolism⁽¹⁵⁾. Rady et al⁽²⁵⁾ found that normalization of hemodynamic variables (*viz.*, heart rate, mean arterial pressure, and CVP) does not adequately reflect the optimal endpoint (*i.e.*, adequate tissue oxygenation) of initial therapy in shock. Thus, Scvo₂ should be monitored and optimized in these patients. Interestingly, the mortality of severe sepsis and septic shock were significantly decreased in the study by Rivers et al who used Scvo₂ as a parameter of the resuscitation endpoint⁽¹⁷⁾.

Use of antibiotics is another cornerstone in the management of septic patients. Early, appropriate, antibiotic therapy was associated with reduced mortality among these patients^(26,27). Conversely, inadequate initial antibiotic therapy was associated with up to 4.1-8.1 times greater hospital mortality⁽²⁸⁻³⁰⁾. According to the SSC guidelines⁽¹⁵⁾, empiric intravenous antibiotic therapy should be started within the first hour of recognition of severe sepsis. On the same subject, up to 36.4% of patients in the present study had more than a 1 h delay in the administration of antibiotics, and some had only received their first dose of antibiotics 24 h after admission. In this respect, Kumar et al⁽³¹⁾ showed that delayed initiation of antibiotic therapy, after the first hour following onset of septic shock, was associated with a significantly increased risk of death. In this present study, however, survivor and non-survivor were not significantly different in timing of first dose of antibiotic therapy, because most of them received antibiotics within the first hour.

Blood cultures were obtained for only 47.9% of patients in the present study, *contra* the SSC guide-lines⁽¹⁵⁾, which recommends that all patients with severe sepsis undergo culture before antibiotic therapy is initiated. In general, bacteremia was detected in 30-50% of patients presenting with a clinical syndrome of severe sepsis or shock^(30,32). By contrast, blood cultures positivity in the present study was detected in only 21.3% of cases, possibly because up to two-thirds were transferred from community hospitals, where they may have received antibiotics. This may have affected the mortality of septic patients if they received inappropriate initial antibiotic therapy.

The present study has some limitations. First, in order to identify the occurrence of sepsis, the author

used the ICD-10 code rather than clinical or microbiological criteria. In order to get the most accurate diagnosis, the author carefully reviewed the medical records to exclude incorrectly coded patients. The author found 82.6% of cases were correctly coded; they all met the definition of sepsis according to the widely international accepted definition used in clinical practice and used for the inclusion criteria in numerous clinical trials. Second, this was a single centre study at a governmentrun, regional hospital in Northeast Thailand; therefore, it may not be representative of management of septic patients throughout Thailand. However, this is probably true in most of the province hospitals. This data suggests urgent revolution of sepsis treatment in both community and referral hospitals.

As in the present study, failure to implement the SSC guidelines in the treatment of septic patients in real-life clinical practice has been observed elsewhere⁽³³⁾. Hence, the sepsis bundle has been developed in order (1) to eliminate a piecemeal application of the SSC guidelines, and (2) to make it easier for clinicians to bring the guidelines into practice⁽³⁴⁾. Shapiro et al⁽³⁵⁾ and Trzeciak et al⁽³⁶⁾ demonstrated that the comprehensive sepsis treatment protocol is practicable in routine practice and Kortgen et al⁽³⁷⁾ the effectiveness of its implementation resulting in a significant (26%)reduction in mortality of septic shock. Notwithstanding, Gao et al(38) found the rate of non-compliance with this sepsis bundle ~50-70%, which must have a significant impact on patient mortality over against the compliance group.

In summary, the present study shows that delayed and inadequate hemodynamic management, including a delay in the initiation of antibiotics, are the main problems in real-life, clinical management of septic patients. Were clinicians to adopt routinely the evidence-based, comprehensive sepsis treatment guidelines (*i.e.*, the *sepsis bundle*), the quality of care and patient outcome would improve. Future studies should be conducted to determine outcome improvement with guidelines implementation.

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การเสียชีวิตจากภาวะ sepsis ในผู้ใหญ่ ณ โรงพยาบาลสุรินทร์

กิตติศักดิ์ เชื้อสกุลวนิช

วัตถุประสงค์: เพื่อศึกษาสาเหตุการเสียชีวิตและประเมินเวชปฏิบัติการดูแลรักษาผู้ป่วย sepsis **วัสดุและวิธีการ**: เป็นการศึกษาข้อมูลย้อนหลังในช่วงเดือนตุลาคม พ.ศ. 2547 ถึงเดือนกันยายน พ.ศ. 2548 ในผู้ป่วย ผู้ใหญ่ 119 ราย (อายุ ≥ 15 ปี) ที่เข้ารับการรักษาตัวในโรงพยาบาลสุรินทร์ด้วย community-acquired sepsis **ผลการศึกษา**: 85.7% ของผู้ป่วยมีภาวะ severe sepsis และ 71.4% มีภาวะ septic shock อัตราการเสียชีวิตโดยรวม 73.9% โดยสูงถึง 88.2% ในภาวะ septic shock พบว่าปัจจัยที่สัมพันธ์กับการเสียชีวิตของผู้ป่วย sepsis ได้แก่ 1) อายุ มากกว่า 60 ปี, 2) มีโรคประจำตัว, 3) septic shock, 4) มีอวัยวะล้มเหลวตั้งแต่ 3 อวัยวะขึ้นไป, และ 5) acidosis (HCO₃ < 20 mEq/L) ในระหว่างที่ได้รับการรักษาตัวในโรงพยาบาลพบว่า มีเพียง 5.9% ได้เข้ารับการรักษาใน หออภิบาลผู้ป่วยวิกฤต, 29.4% ได้รับสารน้ำที่เพียงพอ, ไม่มีผู้ป่วยรายใดที่ได้รับการตรวจติดตามค่า Svo₂ หรือ Scvo₂, และ 36.4% ได้รับยาต้านจุลซีพที่ล่าช้ากว่า 1 ชั่วโมง สาเหตุการเสียชีวิตที่สำคัญคือ ภาวะความดันโลหิตต่ำที่ไม่ ตอบสนองต่อการรักษา (77.3%) ซึ่งพบว่าปริมาณสารน้ำที่ผู้ป่วยได้รับในช่วงแรกของการรักษามีความสัมพันธ์กับ การรอดชีวิตของผู้ป่วย septic shock

สรุป: ภาวะ septic shock ถือว่าเป็นสาเหตุการเสียชีวิตที่สำคัญของผู้ป่วย sepsis โดยการให้การรักษาทาง hemodynamic ที่ล่าช้าและไม่เพียงพอ รวมทั้งความล่าช้าในการให้ยาต้านจุลชีพถือเป็นปัญหาสำคัญในชีวิตจริงของ เวชปฏิบัติในการดูแลรักษาผู้ป่วย sepsis