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Effect of sepsis protocol in inpatient departments triggered by Ramathibodi Early Warning Score (REWS) on treatment processes

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ABSTRACT:

Background: Sepsis needs to be more focused on the effect of patient management at the ward level. We aimed to evaluate the effect of implementing the sepsis protocol triggered by the Ramathibodi Early Warning Score (REWS) on treatment processes in inpatients with new-onset sepsis.

Methods: We conducted a prospective observational study among adult medical patients admitted to the general wards. A 25-month pre-protocol period was assigned as a control, and a 14-month protocol period was allocated to a protocol group. An inpatient sepsis protocol comprised a nurse-initiated sepsis protocol with REWS ≥2 plus suspected infection, prompt antibiotic, lactate measurement, and fluid resuscitation. Primary outcomes were the achievement of sepsis treatment processes, including the resuscitation and management bundle, namely: 1) the percentage of patients who were taken for the initial laboratory workup for sepsis, especially lactate and blood culture taking before antibiotics; 2) the percentage of patients who received appropriate antibiotics; 3) the percentage of patients who received optimal fluid resuscitation and management; 4) the percentage of patients who performed inferior vena cava ultrasound; 5) the percentage of patients who received steroid and vasopressor drugs; 6) "time-to-antibiotic," the duration from diagnosis of sepsis to receiving antibiotic treatment; 7) "time-to-optimal intravenous fluid management;" 8) "time-to-transfer to ICU.

Results: 282 patients were evaluated (141 pre-implementation, 141 post-implementation); 94.7% of patients with sepsis had REWS ≥2. More patients in the protocol period had a lactate measurement and fluid management (89 [63.1%] vs. 44 patients [31.2%], p<0.001 and (50 [35.4%] vs. 22 patients [15.6%], p<0.001, respectively). More patients in the protocol period received antibiotics within 1 hour than in the pre-protocol period (80 [56.7%] vs. 53 patients [37.6%], p=0.001). The time to antibiotic treatment (mean, SD) in the protocol period was shorter than that in the pre-protocol period (81.7 [77.86] vs. 138.22 [145.17], p=0.007). The length of the intensive care unit (ICU) stay was shorter in the protocol period (8 d [3, 16.5] vs. 10 d [5, 20.5], p=0.011). The two groups did not differ in in-hospital mortality, length of hospital stay, or time-to-transfer to the ICU.

Conclusions: Implementing an in-hospital sepsis protocol was associated with significant improvement in sepsis treatment processes, namely lactate measurement, starting antibiotic treatment within 1 hour, fluid management, and a shorter length of ICU stay.

Keywords: Sepsis; Sepsis protocol; Implementation protocol; Antibiotics; Lactate measurement; Fluid management

INTRODUCTION

In Thailand, the prevalence of sepsis has increased annually, and it is the most important cause of death in hospitals. The Ministry of Public Health and the National Health Security Office of Thailand reported that in 2018, approximately 175,000 people had sepsis, and 45,000 people died from sepsis. Recently, several investigators have developed protocols for the early identification and prompt management of patients with sepsis to improve patient outcomes in the emergency department and intensive care unit (ICU). However, few studies have focused on managing new-onset sepsis in inpatient departments, especially in general medical wards [1,2]. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) suggested using the quick Sepsis-related Organ Failure Assessment criteria for early sepsis identification. The latest surviving sepsis campaign bundle recommends the completion of the sepsis bundle. The recommendations include 1) lactate level measurement, 2) obtaining blood cultures before administering antibiotics, 3) administering broad-spectrum antibiotics within three hours, 4) administration of 30 mL/kg crystalloid for hypotension or lactate > 4 mmol/L, and 5) applying vasopressors if hypotensive to maintain mean arterial blood pressure ≥65 mmHg [3,4].

We aimed to compare the effect of implementing the sepsis protocol triggered by the Ramathibodi Early Warning Score (REWS) on achieving sepsis treatment processes, including the resuscitation and management bundle in in-patients with a new onset of sepsis, with pre-protocol implementation.

We hypothesized that implementing this protocol would result in better sepsis treatment processes and patient outcomes.

KEY MESSAGE:

- This study aimed to evaluate the effect of implementing sepsis protocol triggered by the Ramathibodi Early Warning Score on treatment processes in inpatients with new-onset sepsis. We found that more patients in the protocol period underwent lactate measurement, fluid management, inferior vena cava ultrasound examination, and vasopressor drug administration, as well as received antibiotic treatment within one hour of presentation than in the pre-protocol period. The protocol implementation did not reduce hospital mortality but did decrease ICU length of stay.

MATERIALS AND METHODS

We conducted a prospective observational study with historical controls among medical patients aged over 15 years admitted to a general ward in a university hospital. A 25-month pre-protocol period (August 2016 to August 2018) was assigned as a control, and a 14-month protocol period (September 2018 to October 2019) was allocated for the prospective protocol group. The Ramathibodi sepsis committee developed the Ramathibodi inpatient sepsis protocol based on the latest Surviving Sepsis Campaign bundle and literature review. This sepsis protocol was triggered using the REWS system, which was implemented for several years in our hospital. The protocol was planned for implementation in September 2018, as shown in the flow chart (Figure 1).

The Institutional Review Boards at Mahidol University reviewed and approved this study protocol in accordance with the International Guidelines for Human Research Protection, namely TheDeclaration of Helsinki, the Belmont Report, the CIOMS Guidelines, and the International Conference on Harmonization in Good Clinical Practice. However, the need for informed consent was waived because the study was observational and conducted under a quality improvement project (COA. MURA2018/442).

The abstract for this paper was presented at the 40th International Symposium on Intensive Care and Emergency Medicine Brussels, Belgium. 24-27 March 2020: an electronic poster presentation with interim findings (https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-2772-3).

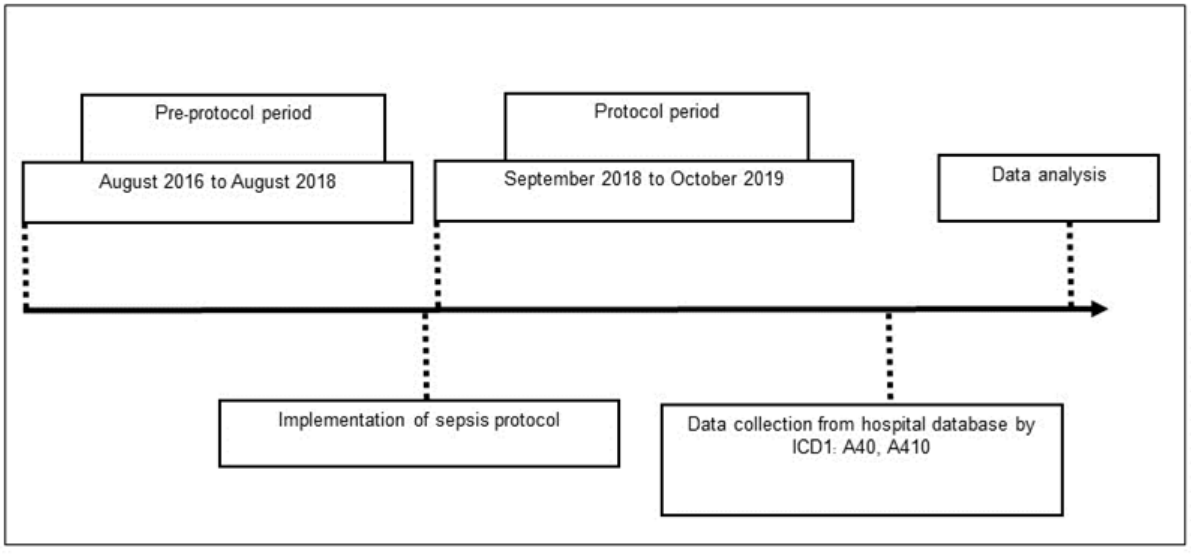

Figure 1. Study flow chart.

Patients

We included all patients over 15 years of age who were admitted to the general medical ward with new-onset sepsis. We excluded patients who were receiving palliative care from this study. In addition, patients diagnosed with sepsis in the emergency department were excluded, and only those who developed new-onset sepsis during hospitalization were included.

Diagnosis of sepsis

In the pre-protocol period, the time to start diagnosis of sepsis was defined by when the patients met ≥2 SIRS criteria, namely a heart rate >90 beats/min, a respiratory rate >20 breaths/min, a temperature >38 or <36°C, a white blood cell count >12,000 or <4,000 /mm^3; and the presence of infection. Septic shock was defined as sepsis with hypotension [5,6]. During the protocol period, patients with sepsis were defined as having a REWS ≥2 with infection and having at least one simplified organ dysfunction criteria (Figure 2; Time Zero). Septic shock was defined as sepsis with hypotension where fluid resuscitation could not maintain a mean arterial pressure >65 mmHg or that required use of a vasopressor or lactate clearance <20% in 2 hours.

Pre-protocol period

Patients admitted to the general medical ward received standard management from the patient care team, comprising medical residents, medical fellows, attending staff, and nurses. Since 2015, the Ramathibodi Rapid Response System has been implemented in general wards to manage patients' deterioration early. The REWS detects an event and triggers a systematic response. The REWS includes respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate, and level of consciousness (Table 1), all routinely recorded every 4 hours. The low-, moderate-and high-risk patients were defined using a summation of those scores. When the REWS reflected moderate or high risk, nurses would more closely monitor patients and notify clinicians for triage and stabilization using individual bundles such as initial lab investigation, fluid management, antibiotics, and ICU transfer. During the pre-protocol period, no sepsis protocol was implemented in the general medical wards [7].

Protocol implementation

Figure 2 shows the Ramathibodi Sepsis Protocol approved by the hospital sepsis committee and implemented in general medical wards in September 2018. This protocol was followed by nurse staff, medical residents, medical fellows, and attending staff participating in the ward. In addition, the hospital sepsis committee provided a course about the sepsis protocol, including sepsis definition, evaluation, and management, to the staff before implementing the protocol.

The inpatient sepsis protocol comprised the following; First, nurses were triggered to action by REWS ≥2 plus a suspected infection. They notified clinicians to evaluate patients to diagnose sepsis and provide prompt, appropriate antibiotic treatment if there were ≥2 systemic inflammatory response syndrome (SIRS) criteria. Initial laboratory investigations, such as blood cultures from two sites and lactate level measurements, were performed. The lactate measurement could be venous or arterial. The arterial lactate was obtained for confirmation if the venous lactate was more than 4 mmol/L. The complete blood count, blood urea nitrogen, electrolyte, creatinine, liver function test, point of care glucose, chest x-ray, urinalysis, and urine culture were performed after excluding those laboratory investigations that had been completed within the previous 12 hours.

The diagnosis of sepsis was made based on the criteria for suspected sepsis, as previously described, and the presence of at least one simplified organ dysfunction criteria.

Since the patients in the study were individuals diagnosed with sepsis while admitted to the hospital, most were already undergoing treatment involving fluids.

When evaluating fluid resuscitation, the process began with 10-15 ml/kg fluid loading while awaiting an ultrasound machine (modified fluid loading) (Figure 1). With an ultrasound examination, the inferior vena cava (IVC) diameter was found to be less than 1.5 or collapsed more significantly than 50% , which was considered fluid responsiveness. If the ultrasound machine was unavailable, the attending physician performed the clinical judgment for fluid loading based on physical examinations. Intravenous fluid was administered as a 250 ml crystalloid solution infusion over 15 minutes and evaluated using ultrasound or clinical evaluation. If fluid responsiveness persisted, this loading process was repeated up to four times within one hour. If the patient could still not maintain a mean arterial blood pressure (MAP) of 65 mmHg or higher, initiation of a norepinephrine infusion

Table 1. Adult Ramathibodi Early Warning Score (REWS).

Score	RR(/min)	SpO_2 (%)	Temp (°c)	SBP (mmHg)	HR or PR (/min)	AVPU
3	≤ 10	≤ 84	≤ 33.9	≤ 89	≤ 39	**U**nresponsive
2		85-89	34-34.9			Response to **P**ain
1		90-92	35-35.9	90-99	40-49	Response to **V**oice
0	11-20	≥ 93	36-37.9	100-199	50-99	**A**lert
1	21-30		38-38.9		100-109	
2	31-35		≥ 39	≥ 200	110-129	
3	≥ 36				≥ 130	

Abbreviations: RR: Respiratory rate; Min: per minute; SpO_2: Oxygen saturation; Temp: Temperature; SBP: Systolic blood pressure; HR: Heart rate; PR: Pulse rate; A: Alert; V: Verbal; P: Pain; U: Unresponsiveness.

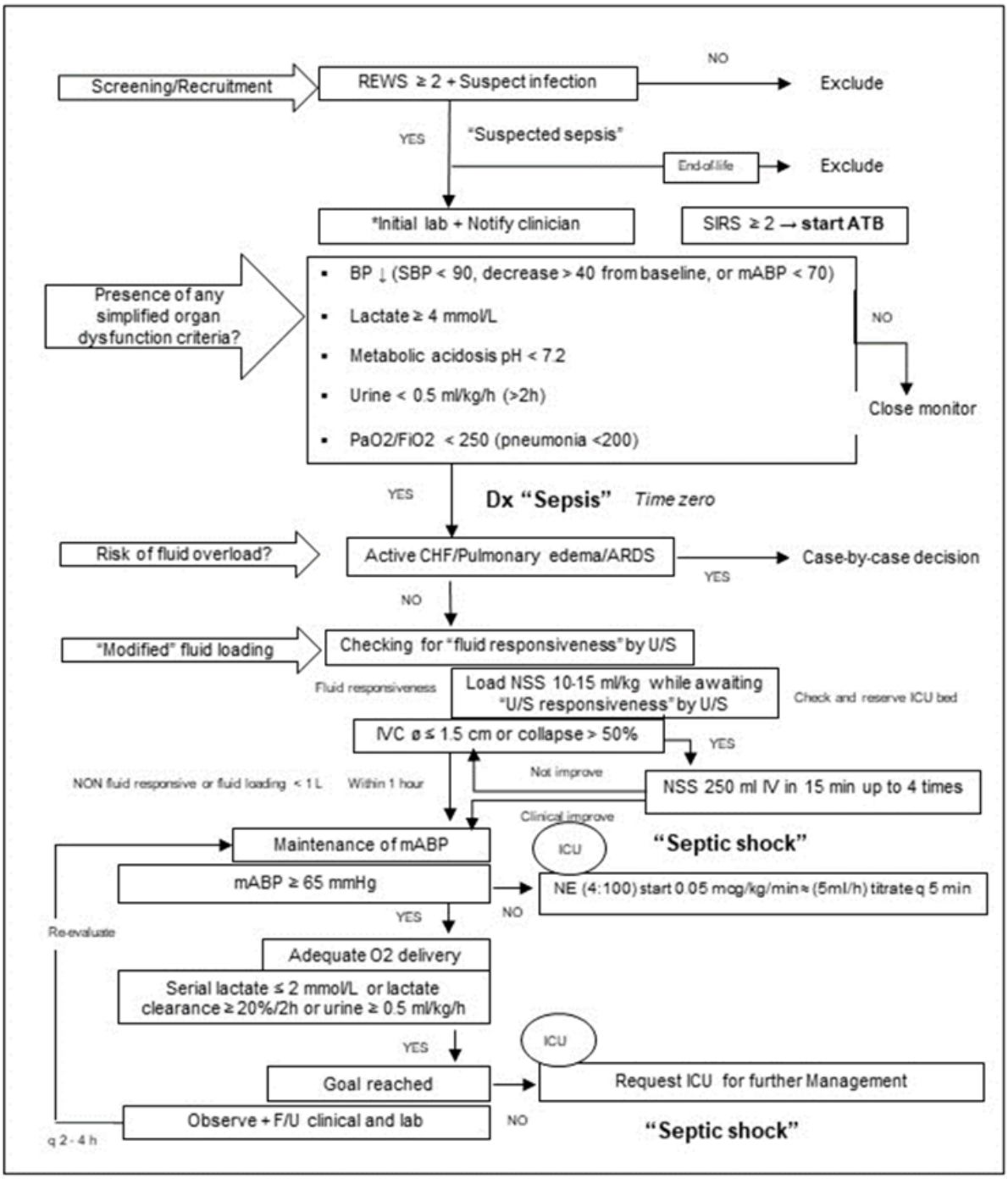

Figure 2. Ramathibodi inpatient sepsis protocol

*The initial laboratory workup for sepsis includes a complete blood count, blood urea nitrogen, creatinine, electrolyte, serum lactate, liver function test, point-of-care glucose testing, chest X-ray, urine analysis, and urine culture. In selected cases, further investigations, such as electrocardiography, arterial blood gas, coagulogram, and fibrinogen, may be evaluated depending on the physician's decision.

REWS: Ramathibodi Early Warning score; SIRS: systemic inflammatory response syndrome; ATB: antibiotic; BP: blood pressure; SBP: systolic blood pressure; mABP: mean arterial blood pressure; Dx: diagnosis; CHF: congestive heart failure; ARDS: acute respiratory distress syndrome; U/S: ultrasound; NSS: normal saline solution; IV: intravenous; IVC: inferior vena cava; L: liter; ICU: intensive care unit; NE: norepinephrine; mcg: microgram; q: every; min: minute; O_2: oxygen; F/U: follow up; h: hour; kg: kilogram; mmHg: millimeter mercury; cm: centimeter; ml: milliliter.

at a rate of 0.05 mcg/kg/min, approximately 5 ml/hr, was warranted. The patients would be diagnosed with septic shock, necessitating consideration for transfer to the ICU. After resuscitation, the patients were closely monitored. The MAP was maintained at more than 65 mmHg, urine output at more than 0.5 mL/kg/h, lactate clearance >20% in 2 hours, and no worsening organ function.

DATA COLLECTION AND OUTCOME MEASUREMENTS

Patient data were collected from the hospital database by searching for the appropriate ICD10 codes (A40, A41). Investigators who were not involved in patient management reviewed and obtained the information from electronic medical records.

Patient characteristics, including age, sex, ward admission, co-morbidities, admission diagnosis, infection source, microbiology, the presence of any organ dysfunction (defined by a sequential organ failure assessment score), and antibiotics used, were recorded. SIRS criteria and REWS were collected.

OUTCOME MEASUREMENTS

Primary outcomes were the achievement of sepsis treatment processes, including the resuscitation and management bundle, namely: 1) the percentage of patients who were taken for the initial laboratory workup for sepsis, especially lactate and blood culture taking before antibiotics; 2) the percentage of patients who received appropriate antibiotics; 3) the percentage of patients who received optimal fluid resuscitation and management; 4) the percentage of patients who performed IVC ultrasound; 5) the percentage of patients who received steroid and vasopressor drugs; 6) "time-to-antibiotic," the duration from diagnosis of sepsis to receiving antibiotic treatment; 7) "time-to-optimal intravenous fluid management;" 8) "time-to-transfer to ICU.

The secondary outcomes were organ dysfunction, ICU length of stay, hospital length of stay, and in-hospital mortality.

Statistical analysis

We calculated the sample size needed to assess the effect of implementing the sepsis protocol on increasing the percentage of optimal fluid resuscitation from 15% to 30%. We will use the following formula [8]:

$$n = (A + B)^2 / C$$

Where $A = Z_\alpha \sqrt{\mathrm{P}(1 - \mathrm{P})(1/q_1 + 1/q_0)}$

$$B = Z_\beta \sqrt{P_1(1 - P_1)(1/q_1) + P_0(1 - P_0)(1/q_0)}$$

$$C = (P_1 - P_0)^2$$

We aim for 20% power (β = 0.2, Zβ = 0.84), with a 95% confidence interval (α = 0.05, Zα = 1.96). The parameters q0 and q1 represent the proportions of pre-protocol and post-protocol patients, respectively (q0 = 0.5, q1 = 0.5). P0 and P1 denote the prevalence of optimal fluid resuscitation in the two groups (0.15 and 0.30, respectively), with P being the pooled proportion (P = 0.23). For continuity correction [9], we require an additional 13 cases in each group. Based on these calculations, the sample size required for our study is 268 cases.

The data were analyzed using IBM SPSS Version 26 (IBM Corporation, Armonk, NY, USA). Continuous variables are reported as mean ± standard deviation (SD) and were tested using a two-tailed t-test for independent samples. For variables that are not normally distributed, the median with an interquartile range (IQR) is reported. A nonparametric test was used to compare non-normally distributed variables. For independent samples, we used a two-tailed t-test for analysis. The categorical variables were compared using the chi-squared test and Fisher's exact test. A P-value < 0.05 was considered statistically significant. The probability of ICU admission in the pre-protocol and protocol periods was also analyzed using Cox proportional hazards regression. The results are presented as Kaplan–Meier curves with a log-rank test for survival equality. The logistic regression analysis was performed to show the relationship between sepsis resuscitation and management bundles and in-hospital mortality.

RESULTS

During the study period, 2,754 patients were diagnosed with sepsis. Of these, 149 patients in the pre-protocol period and 159 patients in the protocol period with a new onset of sepsis in the inpatient department were included. Eight patients in the pre-protocol period and eighteen patients in the protocol period were excluded from analysis because they were receiving palliative care. Finally, 282 patients were included in the analysis, with 141 patients in the pre-protocol period and 141 patients in the protocol period (Figure 3)

Table 2 demonstrates the clinical and demographic characteristics of the patients in our study. The mean patient ages were 60 ± 19.54 years in the pre-protocol group and 60 ± 19.74 years in the protocol group. Regarding admission criteria, chemotherapy, and renal disease were more common in the protocol group. In addition, the percentage of patients with hematologic disease was higher in the protocol period.

The total REWS, which was used as the screening tool for sepsis diagnosis, in the protocol period was not different between the two groups (4.42 ± 2.22 points in the pre-protocol period vs. 4.72 ± 2.44 points in the protocol period [p=0.274]). The percentage of patients with REWS ≥2 did not differ between the two groups (93.6% in the pre-protocol period vs. 95.7% in the protocol period, p=0.43).

Table 3 summarizes the site of infection and microbiology. There were no statistically significant differences in the source of sepsis, and the lungs were the most common source of infection. A higher likelihood of isolating gram-negative bacteria as the causative agent of

infection was also observed. Nevertheless, there was no significant difference between the pre-protocol and protocol groups.

Table 4 shows the presence of organ dysfunction between the pre- and post-protocol periods. A higher percentage of patients in the protocol period had cardiovascular dysfunction and neurological impairment than in the pre-protocol period.

Outcome

More patients in the protocol period received antibiotics within 1 h of presentation than in the pre-protocol period (80 [56.7%] vs. 53 patients [37.6%], p=0.001). The time-to-antibiotic treatment was shorter in the protocol period than in the pre-protocol period (81.97 ± 77.86 min vs. 138.22 ± 145.17 min, p=0.007). Time to optimal fluid management and time to ICU transfer were not statistically significantly different between the two groups (Figure 4).

The compliance with the sepsis protocol implementation was evaluated in two bundles, namely the resuscitation and management bundles. In the resuscitation bundle, more patients in the protocol period underwent lactate measurement (89 [63.1%] vs. 44 [31.2%] patients, p<0.001]. Initial laboratory and blood culture testing before antibiotic treatment and the prescription of antibiotics were no different between the two groups (Table 5). Regarding the management bundles, fluid management differed between the two groups (50 [35.4%] vs. 22 [15.6%] patients, p<0.001). The frequency of ultrasound measurement of the inferior vena cava (IVC) and vasopressor drug use was higher in the protocol group than in the pre-protocol group (Table 5).

The length of ICU stay was shorter in the protocol period than the pre-protocol period (8 d [3, 16.5] vs. 10 d [5, 20.5], p=0.011). There was no difference in in-hospital mortality or length of hospital stay between the pre-protocol group and protocol group (51[36.2%] vs.44[31.2%], p=0.387 and 31.0 d [18.5,55.5] vs. 30.0 d [14,52.5], p=0.362, respectively) (Table 5).

After implementing the sepsis protocol, we found that patients in the protocol group tended to be less likely to be admitted to the ICU than those in the pre-protocol group; however, the difference was not statistically significant (Supplementary Figure).

In our investigation into the relationship between sepsis resuscitation and management bundles and in-hospital mortality, the logistic regression analysis, which adjusted for variables namely, age, gender, and the numbers of organ dysfunction, revealed that the time-to-antibiotic, time-to-optimal intravenous fluid management, time-to-transfer to the ICU, and the numbers of patients who underwent lactate measurement and received optimal fluid resuscitation and management were not associated with in-hospital mortality (Supplementary Table 1).

DISCUSSION

The main findings of our study can be summarized as follows; first, more patients in the protocol period received antibiotic treatment within 1 hour of presentation than in the pre-protocol period. Nevertheless, the time to optimal fluid management and time to ICU transfer were not statistically significantly different between the two groups. Second, regarding compliance with the sepsis protocol implementation, more patients in the protocol period underwent lactate measurement, fluid management, IVC ultrasound examination, and vasopressor drug administration. Third, the protocol implementation did not reduce hospital mortality but did decrease ICU length of stay.

Sepsis is now identified early and managed following triage in the emergency department. Previous studies have found that better compliance with the Surviving Sepsis Campaign guidelines is related to better outcomes [1,10]. Furthermore, appropriate early management, i.e., appropriate early antibiotic treatment, early goal-directed therapy, and proper hemodynamic monitoring, is associated with improved clinical outcomes[10]. One of the critical challenges facing healthcare providers is identifying and recognizing patients with sepsis and impending organ dysfunction who deteriorate in the hospital. Since 2016, a rapid response system and hospital protocol in response to patient deterioration in general wards, stratified using an early warning score, have been implemented [7]. Nevertheless, in our inpatient general medical ward, the care of patients with new-onset sepsis and septic shock was followed inconsistently, possibly due to a lack of adequate education or an inpatient sepsis protocol that fit the workflow in the general medical ward. Therefore, we have implemented the Ramathibodi inpatient sepsis protocol and aimed to demonstrate the effects of this protocol, which is triggered by an early warning score, on patient outcomes and compliance in the general medicine department. In our study, the REWS was used as the screening tool for early identification of sepsis and promptly managing with the resuscitation bundle and management bundle, followed by protocol. The main reason to explain why we use the REWS as the screening tool is that REWS includes respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate, and level of consciousness, which resembles the quick Sepsis-related Organ Failure Assessment (qSOFA) score [11]. Churpek et al. reported that the early warning score provided higher sensitivity than the qSOFA score for predicting adverse outcomes and mortality in the emergency department and on the wards [12]. Furthermore, data suggest that general early warning scores add useful predictive information to clinical judgment. In the emergency department, the time to ICU admission for adult patients with sepsis improved after the implementation of the REWs [13]. Thus, the REWS could be used to detect patients with sepsis early [14,15]. In our study, we found that 94.7% of sepsis patients had REWS ≥2.

We found that more patients in the protocol period received antibiotics within 1 hour of presentation than in the pre-protocol period. Moreover, the time from sepsis diagnosed by clinicians to the initiation of antibiotic treatment was faster in the protocol period than in the pre-protocol period. Time is vital in the management of

Table 2. Clinical and demographic characteristics.

	Pre-Protocol (n=141)	Post-Protocol (n=141)	p-value
Age, years, mean (SD)	60.35(±19.54)	60.01(±19.74)	0.891
Gender, female, n, (%)	78(55.3)	71(50.4)	0.387
Co-morbidities, n, (%)			
- Diabetes mellitus	36(25.5)	38(27)	0.783
- Hypertension	52(36.9)	51(36.2)	0.900
- Thyroid diseases	4(2.8)	8(5.7)	0.250
- Renal diseases	32(22.7)	27(19.1)	0.468
- Cardiovascular diseases	33(23.4)	25(17.7)	0.229
- Autoimmune diseases	14(9.9)	6(4.3)	0.032
- Liver diseases	14(9.9)	19(13.5)	0.338
- Neurological diseases	18(12.8)	19(13.5)	0.870
- Pulmonary diseases	23(16.3)	18(12.8)	0.425
- Hematologic diseases	5(3.5)	16(11.3)	0.013
- HIV Infection	4(2.8)	2(1.4)	0.416
- Solid Malignancy	21(14.9)	29(20.6)	0.218
- Hematologic Malignancy	47(33.3)	52(36.9)	0.555
Admission Diagnosis, n, (%)			
- Cardiac diseases	9(6.4)	14(9.9)	0.253
- Pulmonary diseases	3(2.1)	4(2.8)	0.707
- Gastrointestinal diseases	5(3.5)	3(2.1)	0.481
- Renal diseases	1(0.7)	8(5.7)	0.019
- Neurological diseases	12(8.5)	8(5.7)	0.373
- Infectious diseases	49(34.8)	31(22)	0.134
- Endocrine	4(2.8)	2(1.4)	0.416
- Oncology	4(2.8)	5(3.5)	0.707
- Autoimmune diseases	6(4.3)	3(2.1)	0.319
- Hematologic diseases	16(11.3)	9(6.4)	0.202
- Received Chemotherapy	29(20.6)	43(30.5)	0.038
- For medical procedure	2(1.4)	4(2.8)	0.416
- Others	1(0.7)	7(5)	0.033

Table 3. Source of infection and microbiology.

	Pre-Protocol (n=141)	Post-Protocol (n=141)	p-value
Infection source, n, (%)			
- Lung	40(28.4)	45(31.9)	0.601
- Abdomen	13(9.2)	12(8.5)	0.836
- Urinary tract	27(19.1)	22(15.6)	0.670
- Blood stream infection	28(19.9)	26(18.4)	0.049
- Joint and musculoskeletal	2(1.4)	3(2.1)	0.656
- Skin and soft tissue	7(5.0)	12(8.5)	0.088
- Eyes, Ears, Nose and Throat	1(0.7)	2(1.4)	0.319
- Unknown	23(16.3)	19(13.5)	0.467
Microbiology, n, (%)			
- Gram-negative aerobe	44(31.2)	52(36.9)	0.315
- Gram-positive aerobe	18(12.8)	28(19.9)	0.107

Table 3. **(Continued)** Source of infection and microbiology.

	Pre-Protocol (n=141)	Post-Protocol (n=141)	p-value
- Polymicrobial	12(8.5)	15(10.6)	0.544
- Anaerobe	5(3.5)	0(0)	0.024
- Virus	9(6.4)	2(1.4)	0.031
- Protozoa	1(0.7)	0(0)	0.316
- Fungus	1(0.7)	2(1.4)	0.562
- Mycobacterium	0(0)	1(0.7)	0.316
- No growth	51(36.2)	41(29.1)	0.204

Table 4. The presence of organ dysfunction by sequential organ failure assessment score of patients between pre and post protocol period.

Definition of each organ dysfunction	Pre-Protocol (N=141)	Protocol (N=141)	p-value
Cardiovascular (MAP <70 or requiring vasopressor drug)	27(19.15)	51(36.2)	0.002
Renal (Creatinine ≥ 1.2 mg/dL or urine < 0.5 ml/kg/hr)	65(46.10)	64(45.39)	1.000
CNS (GCS <15)	5(3.55)	23(16.3)	<0.001
Respiratory (PaO_2/FiO_2 < 400)	32(22.70)	58(41.13)	0.145
Hematology (Platelet < 150000/mcL)	76(53.90)	81(57.45)	0.632
Liver (Bilirubin ≥ 1.2 mg/dL)	57(40.43)	53(37.59)	0.714

Table 5. The achievement of sepsis management bundle and clinical outcomes between pre and post-protocol period.

Sepsis management bundle and clinical outcomes	Pre-protocol (N = 141)	Post-protocol (N = 141)	p-value
Primary outcome			
Resuscitation bundle, n, (%)			
1. Initial Laboratory work up for sepsis	138(97.9)	140(99.3)	0.319
2. Lactate measurement	44(31.2)	91(64.5)	<0.001
3. Blood cultures taking be-fore antibiotics	137(97.2)	140(99.3)	0.181
4. Appropriate antibiotics	138(97.9)	135(95.7)	0.258
Management bundle, n, (%)			
1. Fluid resuscitation and management	22(15.6)	51(36.2)	<0.001
2. Inferior vena cava ultra-sound	12(8.5)	31(22)	0.002
3. Steroid use	10(7.1)	18(12.8)	0.131
4. Vasopressor drugs	16(11.3)	34(24.1)	0.005
Secondary outcome			
ICU LOS (days)	10.0 (5.0, 20.5)	8.0 (3.0, 16.5)	0.011
Hospital LOS (days)	31.0 (18.5 ,55.5)	30.0 (14 ,52.5)	0.362
Hospital Mortality	51(36.2)	44(31.2)	0.387

ICU: Intensive care unit; LOS: length of stay.

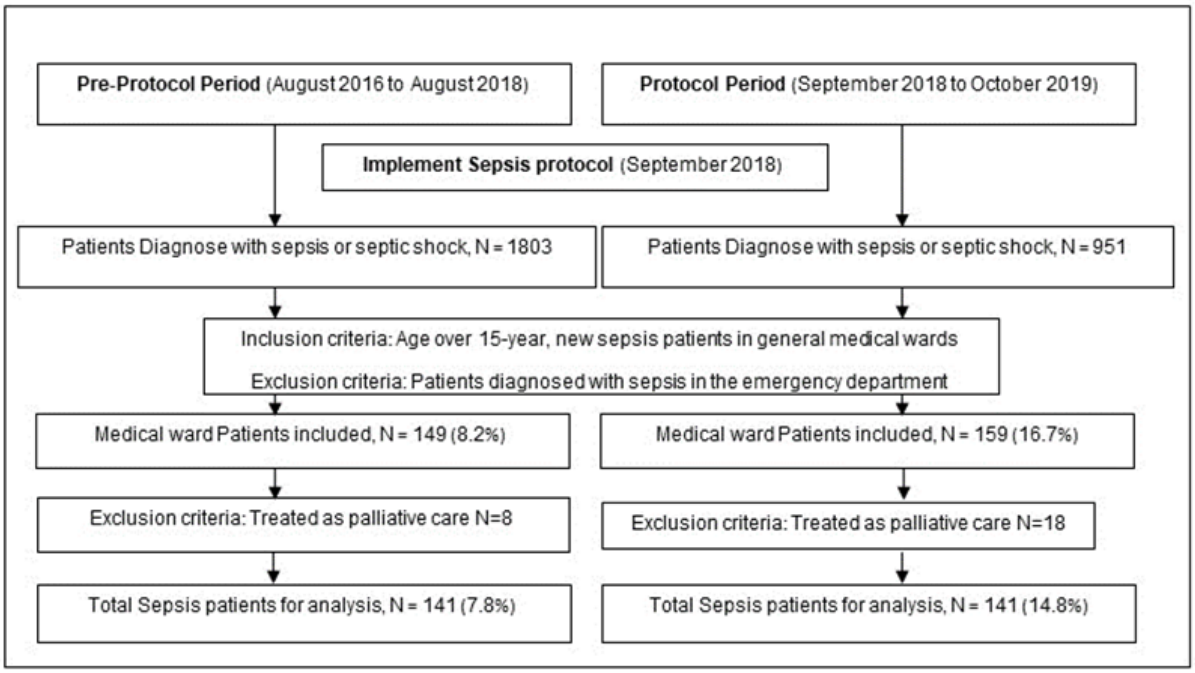

Figure 3. Study population.

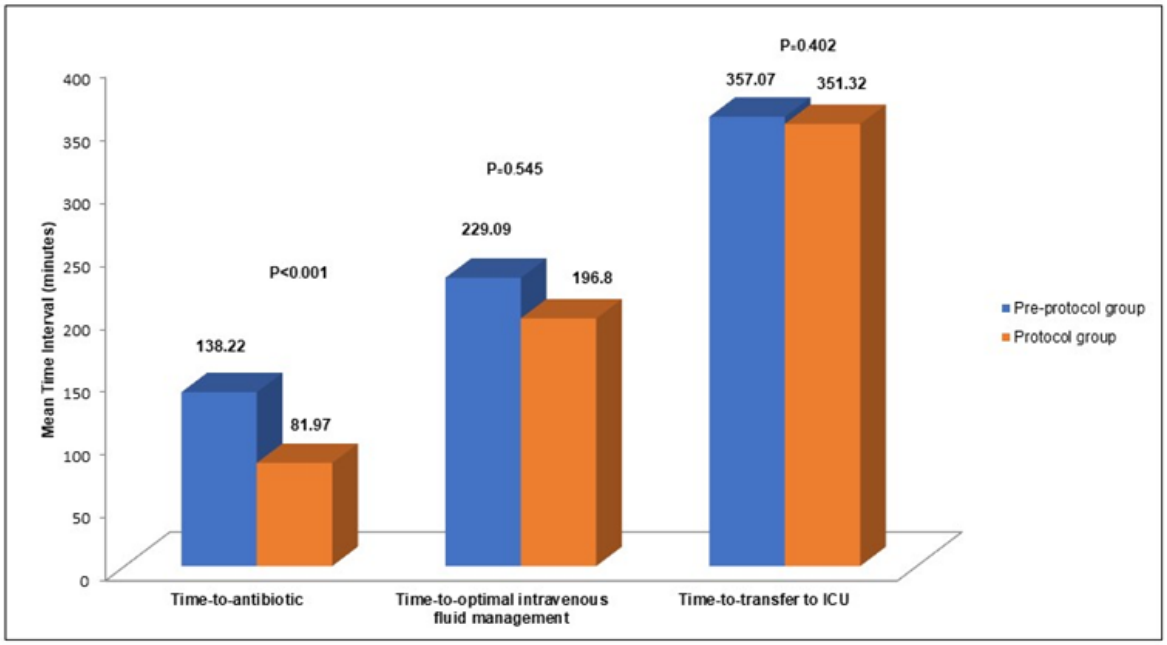

Figure 4. Primary outcome of sepsis protocol regarding the achievement of sepsis resuscitation and management bundle.

patients with sepsis. Recent studies found that the time to antibiotic initiation after protocol implementation was faster than in the pre-protocol group [16], similar to our finding. We have to focus not only on time for antibiotic treatment but also on time for optimal fluid management and resuscitation and time for ICU, which may improve patient outcomes [17-19]. However, in our study, time to optimal fluid management and time to ICU transfer were not statistically significantly different between the two groups. The main reason to explain this finding is that patients who were admitted to the ward often received maintenance fluid therapy; thus, they sometimes had a positive fluid balance. Consequently, not many patients received more fluid, even if they had sepsis. Therefore, the time to optimal fluid management and resuscitation was not different between the two groups. Moreover, our hospital encountered a problem regarding a shortage of ICU beds; thus, patients who may have fulfilled the criteria for ICU admission might have experienced delayed ICU transfer.

A recent study by Levy et al. [20] demonstrated that an increase in compliance with sepsis bundles was associated with a reduction in the mortality rate. Compliance was defined as evidence that all bundle elements were

achieved within the specified time frame. Regarding compliance with the sepsis protocol implementation, more patients in the protocol period underwent lactate measurement, fluid management, IVC ultrasound examination, and vasopressor drug administration. Nevertheless, not all bundle elements were achieved within a specific time, which may explain why there was no difference in in-hospital mortality between the two groups. Nevertheless, the strength of our study is that we used a 1-hour bundle from the Surviving Sepsis Campaign 2018 to compare pre-protocol and protocol periods and compared our results with other studies that used a 6-h resuscitation bundle or 24-h management bundle [20].

In patients who were transferred to the ICU after protocol implementation, the protocol implementation reduced the length of the ICU stay. The protocol implementation [18] promoted education regarding identifying sepsis early as well as earlier management, such as administering appropriate antibiotics, monitoring, and fluid therapy, resulting in a decreased length of ICU stay. This may also reduce the probability of ICU transfer; however, this difference was not statistically significant.

The rapid response system has been increasingly adopted worldwide, including Thailand. Combinations of early warning scores and rapid response systems for sepsis detection and treatment are likely to be used more frequently. Choi et al. reported that the rapid response system had improved compliance with sepsis bundles, which was associated with reduced mortality in patients with septic shock in hospital wards [21]. The multicenter studies of combinations of early warning scores and rapid response systems for sepsis detection and treatment warrant validation.

Limitations

There are some limitations to our study. First, this is a prospective trial, but the effect of implementing the inpatient sepsis protocol was assessed relative to a historical cohort; thus, the potential for selection bias exists. The baseline characteristics and severity of the patient condition were not comparable. The disease severity in the protocol period was higher than in the pre-protocol period; therefore, the effect of the protocol on clinical outcomes, i.e., in-hospital mortality, might not be apparent. Furthermore,inpatient sepsis was underdiagnosed and underreported during the pre-protocol period. Second, there was no rigorous compliance checking in our study; thus, not all the bundle elements were achieved within a specific time frame.

CONCLUSION

Implementing an in-hospital sepsis protocol was associated with improvements in sepsis treatment processes, namely lactate measurement, starting antibiotic treatment within 1 hour, fluid management, and a shorter length of ICU stay.

CONFIDENTIALITY

None

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AUTHORS' CONTRIBUTIONS

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SUPPLEMENTARY MATERIALS

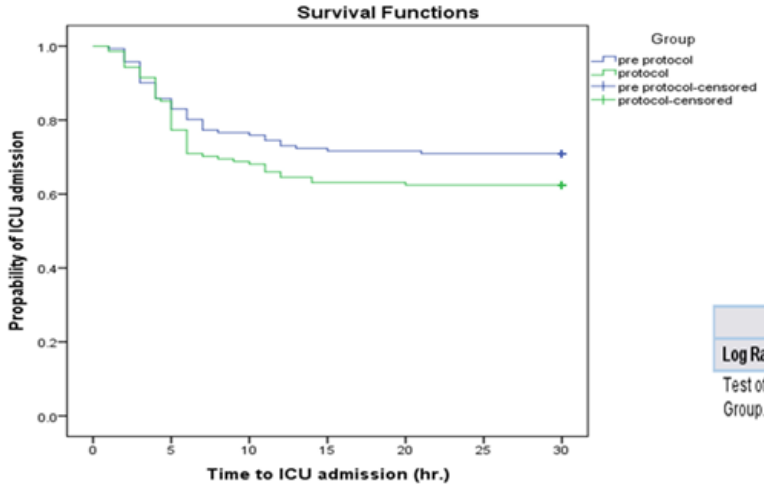
Supplementary Table 1. The associations of the achievement of sepsis resuscitation and management bundle with in-hospital mortality.

	Unadjusted			Adjusted*		
Sepsis management bundle variables	**OR**	**95%CI**	**p-value**	**OR**	**95%CI**	**p-value**
Time-to-antibiotic	0.99	0.99-1.00	0.526			
Time-to-optimal intravenous fluid management	0.99	0.99-1.00	0.145			
Lactate measurement	0.40	0.24-0.66	<0.001	1.25	0.66-2.36	0.489
Fluid resuscitation and management	0.46	0.26-0.79	<0.01	0.70	0.34-1.42	0.319
Time-to-transfer to ICU	0.99	0.99-1.00	0.335			

ICU: Intensive care unit.

*Adjusted by age, gender, and numbers of organ dysfunction

Supplementary Figure. Probability of ICU admission between two groups.



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	2.164	1	.141

Test of equality of survival distributions for the different levels of Group.