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Influence of full-time intensivist and the nurse-to-patient ratio on the implementation of severe sepsis bundles in Korean intensive care units

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Abstract

Purpose: The reported actual compliance for severe sepsis bundles was very low, suggesting the presence of barriers to their implementation. The purpose of this study was to assess the influence of full-time intensivist and nurse-to-patient ratio in Korean intensive care units (ICUs) on the implementation of the severe sepsis bundles and clinical outcome.

Materials and Methods: A total of 251 patients with severe sepsis were enrolled from 28 adult ICUs during the July, 2009. We recorded the organizational characteristics of ICUs, patients' characteristics and clinical outcomes, and the compliance for severe sepsis bundles.

Results: Complete compliance with the resuscitation bundle and totally complete compliance with all element targets for resuscitation and management bundles were significantly higher in the ICU with full-time intensivist and a nurse-to-patient ratio of 1:2 ($P < .05$). The hazard ratio (HR) for hospital mortality was independently reduced by the presence of full-time intensivist (HR, 0.456; 95% confidence interval, 0.223-0.932), and a nurse-to-patient ratio of 1:2 was independently associated with a lower 28-day mortality (HR, 0.459; 95% confidence interval, 0.211-0.998).

Conclusions: The full-time intensivist and the nurse-to-patient ratio had a substantial influence on the implementation of severe sepsis bundles and the mortalities of patients with severe sepsis.

1. Introduction

Severe sepsis is a major health care problem with an increasing incidence. Although mortality resulting from sepsis has been decreasing, sepsis-induced death rates remain unacceptably high, having been reported at 25% to 30%. Progression to septic shock, co-occurring with multiple-organ dysfunction syndrome, is the leading cause of morbidity and mortality for patients admitted to intensive care units (ICUs), developing in about 15% of all ICU admissions with an associated mortality risk between 40% and 70%. Regarding the management of sepsis syndrome, a disease continuum that includes severe sepsis and septic shock, as well as early recognition and rapid administration of best practice therapy, is the key for reducing mortality [1].

The Surviving Sepsis Campaign (SSC) guidelines for the management of severe sepsis and septic shock were initially published in 2004 [2] and updated in 2008 [3]. The aim of the guidelines was to reduce severe sepsis mortality through the rapid administration and appropriate therapy during the initial hours of the syndrome progression. In the guidelines, 2 bundles are outlined as articulated therapeutic frameworks, the 6-hour resuscitation and the 24-hour management bundles [4]. Every element of the bundles has individually been shown to be effective in a clinical setting [3]. When implemented together as "a care of bundle," the improvement of compliance of bundles has been reported in several studies to be an effective method of reducing hospital mortality [5,6]. However, the reported actual baseline compliance rates for completing all elements of the resuscitation and management bundles were very low [5-7], suggesting that there are barriers to their implementation, even in Westernized and developed countries.

The possible barriers to implementing evidence-based clinical practice guidelines are knowledge, attitude, and behavioral (external) barriers [8]. Among these barriers, environmental-related factors such as insufficient staff have been suggested to be an important component of external barrier. Although there are controversies in the association between critical care physician management and patient mortality in the ICU [9,10], a critical shortage of nursing staff has been reported to be a primary barrier to implementing early goal-directed therapy in emergency departments (EDs) [11]. However, there are no studies regarding the impact of the presence of adequate critical care personnel on the practice of SSC guidelines. The critical care resources and facilities of university hospitals in South Korea are very limited compared with those of other developed countries of North America and Europe. Especially, there is a shortage of critical care personnel including full-time intensivist and a low nurse-to-patient ratio, which is a serious issue for clinical practice. These limitations act as huge barriers to implementing evidence-based clinical care to critically ill patients and may be the cause of dissimilarities in the degree of bundle compliance and the clinical impact of sepsis treatment, compared with the countries where the guidelines were developed.

This study is a domestic subanalysis of the Management Of Severe sepsis in Asia's Intensive Care units (MOSAICS) study, which was a multinational, prospective observational study assessing the compliance of Asia's ICUs with the recommendations of the SSC's resuscitation and management bundles [7]. The purposes of the analysis were to assess the influence of the presence of full-time intensivist and the nurse-to-patient ratio on the rate of compliance with elements of the severe sepsis resuscitation and management bundles and evaluate the association between the degree of compliance and patients' clinical outcome in university hospital ICUs in South Korea.

2. Materials and methods

2.1. Patients and data collection

This multicenter, prospective, and observational study was performed as a local survey for the MOSAICS study [7]. Twenty-eight adult ICUs including 22 medical ICUs (MICUs) and 6 surgical ICUs (SICUs) from 25 university hospitals were included. Predominantly, pediatric, neurosurgical, or coronary ICUs were not included. The institutional review boards of every participating center approved the study. Patients' consents were not needed because this study was an observational study without any intervention.

From 1 to 31 of July 2009, we enrolled all the patients admitted to the aforementioned ICUs for severe sepsis, from ED or other wards, and those who developed severe sepsis in the ICU. *Severe sepsis* was defined as sepsis with one of the following organ dysfunctions: hypotension (a systolic blood pressure <90 mm Hg or a decrease >40 mm Hg or mean arterial pressure <65 mm Hg), hyperlactatemia (≥2 mmol/L), renal dysfunction (an acute increase in serum creatinine to >176.8 mmol/L or a urine output <0.5 mL kg^{-1} h^{-1} for >2 hours), lung dysfunction (acute lung injury [ALI], with the ratio of the partial pressure of arterial oxygen to the fractional inspired oxygen being ≤300 mm Hg), liver dysfunction (an acute increase in bilirubin to >34.2 μmol/L), thrombocytopenia (an acute decrease to <100 000/μL), and/or coagulopathy (an international normalized ratio >1.5 or a partial thromboplastin time >60 seconds). *Septic shock* was defined as sepsis-induced hypotension (a systolic blood pressure <90 mm Hg or decrease >40 mm Hg or mean arterial pressure <65 mm Hg) despite adequate fluid resuscitation, and the definition of acute respiratory distress syndrome was a severe form of ALI, with the ratio of the partial pressure of arterial oxygen to the fractional inspired oxygen being ≤200 mm Hg.

To minimize any changes in behavior resulting from knowledge of the ongoing study, only the physicians representing each ICU were recognized with the study design. Data were collected prospectively through a Web-based electronic case report form. Before patient enrollment, we collected the characteristic data of the participating ICUs, such as the ICU specialty (medical or surgical), number of beds, the presence of full-time intensivist, and the nurse-to-patient ratio. The definition of intensivist was a board-certified physician who is certified in critical care medicine. The *ICU with full-time intensivist* was defined as the ICU covered by intensivists by turns of duty for 24 hours. The clinical and demographic characteristics of all patients, including age, sex, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, primary source of severe sepsis, and organ dysfunction at sepsis presentation were recorded. The onset of severe sepsis (time zero) was determined according to the patient's location within the hospital when severe sepsis was diagnosed [5]. In patients diagnosed as having severe sepsis in the ED, *time zero* was defined as the time of triage. For patients who developed severe sepsis in the medical and surgical wards or any other non-EDs, time zero was determined by searching the clinical documentation for the time of diagnosis of severe sepsis. In patients who developed severe sepsis in the ICU, time zero was determined by searching the clinical documentation for the time of diagnosis of severe sepsis. If no time and date could be found by these methods, the default time of presentation was the time of admission to the ICU.

2.2. Bundle targets and outcome measurements

The 6-hour resuscitation bundle was adopted from the original SSC standard severe sepsis resuscitation bundle. However, the elements of 24-hour resuscitation bundle were modified from the original SSC standard severe sepsis management bundle as follows: for the maintenance of adequate glycemic control, an upper limit for glucose of 10.0 mmol/L was decided based on the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study [12]; the lower limit was set at 4.5 mmol/L according to Leuven study [13] for avoiding of the adverse effects of hypoglycemia. The glucose target was considered unmet if any measurements fell outside this range. To prevent excessive inspiratory plateau pressures, the SSC guidelines recommend the monitoring of plateau pressure and its maintenance at less than 30 cm H_2O for mechanically ventilated patients; this was modified to the most frequently delivered tidal volume of utmost 6 mL/kg of predicted body weight in the first 24 hours [14] because of concerns regarding the feasibility of the measurement of accurate plateau pressure in multiple ICUs. Administration of low-dose steroids for septic shock according to a predetermined therapeutic method was not included because of ongoing controversy [3] and differences in policy between ICUs. Administration of recombinant human-activated protein C was excluded because of its unavailability in South Korea.

Certain targets only needed to be met under specific clinical scenarios (Table 1); both a failure to attempt and a

Table 1 Definition of the elements of the sepsis resuscitation and management bundles

Elements	Clinical scenarios	Targets to be achieved
6-h resuscitation bundle		
Lactate	Severe sepsis	Measure serum lactate
Blood culture		Obtain blood cultures before antibiotics
Antibiotics		Administer broad-spectrum antibiotics within 3 h of ED admission and within 1 h of non-ED admission
Fluids	Hypotension and/or serum lactate ≥4 mmol/L	Deliver an initial minimum of 20 mL/kg of crystalloid or equivalent
Vasopressors	Hypotension not responding to initial fluid resuscitation to maintain MAP ≥65 mm Hg	Apply vasopressors
CVP	Hypotension and/or serum lactate ≥4 mmol/L	Achieve CVP ≥8 mm Hg
Venous oxygen saturation		Achieve $ScvO_2$ ≥70% or SvO_2 ≥65%
24-h management bundle		
Glucose	Severe sepsis	Lowest glucose value ≥4.5 mmol/L and highest value ≤10.0 mmol/L
Low tidal volume	Severe sepsis with invasive mechanical ventilation and ALI/ARDS	Delivered tidal volumes ≤6 mL/kg of predicted body weight

ARDS, acute respiratory distress syndrome; MAP, mean arterial pressure; $ScvO_2$, central venous oxygen saturation; SvO_2, mixed venous oxygen saturation.

failed attempt may have resulted in targets not being met. In assessing the achievement of each target, only those patients in relevant clinical scenarios were included. Complete compliance with the targets of the entire resuscitation (complete resuscitation bundle, or CRB) or management bundles (complete management bundle, or CMB), and totally complete compliance for both bundles (totally complete, or TC) were decided when the targets of every individual element were met; compliance was assumed for any target that was not required in a given clinical scenario.

The primary outcome measure was overall hospital mortality. Patients who were still in hospital on the 23rd October 2009 were deemed survivors. Patients who were discharged to another hospital were also deemed survivors, unless we received specific information regarding their death from the receiving hospital. Secondary outcome measures were 28-day mortality, ICU mortality, ICU and hospital length of stay, and the duration of invasive mechanical ventilation (defined as the time from initiating ventilation to successful extubation or breathing through a tracheostomy tube for ≥48 hours).

2.3. Statistical analysis

Descriptive statistics included frequencies and percentages for categorical variables and means, SDs, confidence intervals (CIs), medians, and interquartile ranges for continuous variables. To compare continuous variables, a *t* test or Mann-Whitney test was used when appropriate. To analyze categorical variables, a χ^2 analysis or Fisher exact test was performed. When normality and homogeneity assumptions were satisfied, differences in quantitative variables were assessed using parametric tests; otherwise, the equivalent nonparametric tests were used. The Bonferroni correction was used for pairwise comparisons. Multivariate Cox regression was performed, with hospital mortality as the dependent variable and age, male sex, APACHE II score, presence of full-time intensivist, nurse-to-patient ratio, CRB, and CMB as independent variables. All tests were 2 tailed, and a $P < .05$ defined statistical significance. All analyses were conducted using SAS (version 9.1.3; SAS Institute Inc Cary, North Carolina).

3. Results

3.1. Patient characteristics

Of the 2442 patients admitted to the 28 ICUs during the study period, 251 (10.28%) were diagnosed as having severe sepsis. The mean (SD) age of the patients with severe sepsis was 65.52 (13.2) years, 61.35% (n = 154) of them were male, and the mean (SD) APACHE II score was 22.09 (8.84). The overall hospital mortality rate was 34.26% (n = 86), and the ICU mortality and 28-day mortality were 29.08% (n = 73) and 30.28% (n = 76), respectively. Pneumonia/Lung (60.16%; n = 151) was the most prevalent primary source of severe sepsis, and hemodynamic dysfunction was observed in 72.91% (n = 183) of patients. One hundred forty five (57.77%) patients with severe sepsis were diagnosed in an ED, and 83.67% (n = 210) were treated in a MICU. Most patients (91.6%) were medical/nonoperative patients. In a comparison between survivors and nonsurvivors, nonsurvivors had a significantly higher mean APACHE II score, serum lactate concentration, pneumonia/lung as primary source, thrombocytopenia, and number of organ dysfunction than did the survivors ($P < .05$). Patients diagnosed as having severe sepsis at an ED had a significantly higher survival rate than did patients diagnosed at a WARD (the hospital ward or other area of the hospital ward) or ICU ($P = .005$). There were no differences in survival rate according to the type of ICU or patient type ($P > .05$) (Table 2).

Table 2 Baseline characteristics of total patients, survivors, and nonsurvivors

Characteristic	Frequency (%), mean ± SD			P [a]
	Total	Survivors	Nonsurvivors	
No. of patients	251	165 (65.74%)	86 (34.26%)	
Age (y)	65.52 ± 13.2	64.69 ± 13.1	67.12 ± 13.3	.1674
Male	154/251 (61.35)	95 (57.58)	59 (68.60)	.0886
APACHE II score	22.09 ± 8.84	19.85 ± 8.61	26.39 ± 7.64	<.0001
Lactate (mmol/L)	4.84 ± 6.8	3.98 ± 5.5	6.47 ± 8.6	.0465
Primary source of severe sepsis				
Pneumonia/Lung	151/251 (60.16)	91 (55.15)	60 (69.77)	.0248
Abdomen other than urinary tract	55/251 (21.91)	42 (25.45)	13 (15.12)	.0602
Urinary tract	34/251 (13.55)	26 (15.76)	8 (9.30)	.1561
Meningoencephalitis/Nervous system	1/251 (0.40)	1 (0.61)	0 (0.00)	1.0000
Soft tissue/skin	6/251 (2.39)	4 (2.42)	2 (2.33)	1.0000
Bones and joints	0/251 (0.00)	0 (0.00)	0 (0.00)	–
Intravascular catheter	4/251 (1.59)	2 (1.21)	2 (2.33)	.6084
Infective endocarditis	2/251 (0.80)	1 (0.61)	1 (1.16)	1.0000
Primary bacteremia	7/251 (2.79)	4 (2.42)	3 (3.49)	.6939
Unknown	14/251 (5.58)	10 (6.06)	4 (4.65)	.7769
Other	4/251 (1.59)	2 (1.21)	2 (2.33)	.6084
Organ dysfunction				
Hemodynamic	183/251 (72.91)	120 (72.73)	63 (73.26)	.9287
Hyperlactemia	101/251 (40.24)	60 (36.36)	41 (47.67)	.0829
Renal	72/251 (28.69)	41 (24.85)	31 (36.05)	.0627
Lung	131/251 (52.19)	80 (48.48)	51 (59.30)	.1035
Liver	54/251 (21.51)	34 (20.61)	20 (23.26)	.6278
Thrombocytopenia	75/251 (29.88)	39 (23.64)	36 (41.86)	.0028
Coagulopathy	64/251 (25.50)	39 (23.64)	25 (29.07)	.3486
Other	1/251 (0.40)	1 (0.61)	0 (0.00)	1.0000
No. of organ dysfunction	2.71±1.35	2.51±1.27	3.10±1.41	.0008
Site at time zero				
ED	145/251 (57.77)	107 (73.79)	38 (26.21)	.0050
Ward	79/251 (31.47)	45 (56.96)	34 (43.04)	
ICU	27/251 (10.76)	13 (48.15)	14 (51.85)	
ICU type				
MICU	210/251 (83.67)	137 (65.24)	73 (34.76)	.7062
SICU	41/251 (16.33)	28 (68.29)	13 (31.71)	
Type of patients				
Medical/Nonoperative patient	230/251 (91.63)	151 (65.65)	79 (34.35)	.9444
Scheduled/elective postoperative patient	7/251 (2.79)	5 (71.43)	2 (28.57)	
Unscheduled/emergent postoperative patient	14/251 (5.58)	9 (64.29)	5 (35.71)	

[a] Survivors vs nonsurvivors.

3.2. Compliance with the sepsis resuscitation and management bundles

Among the target elements of the sepsis resuscitation bundle, only 3 had compliance rates higher than 50%: blood culture (68.13%), fluids (87%), and vasopressors (91.93%). Lactate and antibiotics were implemented in 49% and 40.64% of severe sepsis cases, respectively. For the septic shock cases, central venous pressure (CVP) was adequately achieved in 42.5%, but venous oxygen saturation only had a 16% compliance rate. Regarding the sepsis management bundle, glucose and low tidal volume were adequately achieved in only 21.91% and 21% of cases, respectively. The rates of complete compliance with all the targets of each bundle were very low: 12.35% for the sepsis resuscitation bundle (CRB) and 15.54% for the sepsis management bundle (CMB). Only 5.58% of patients were totally and completely compliant for sepsis resuscitation and management bundles (TC) (Table 3). In the analysis according to the site at time zero, the patients diagnosed as having severe sepsis in an ED were significantly more likely to be compliant with the lactate, blood culture, antibiotics, CRB, and TC targets than those patients diagnosed at a WARD or ICU ($P < .05$) (Table 4). The patients treated in a SICU exhibited significantly higher compliance rates for the lactate, CVP, venous oxygen saturation, CRB, and TC targets than those treated in a MICU ($P < .05$) (Table 4).

Table 3 Compliance rates for the elements and bundles

	Total N/n of cases (%)	Survivors, n (%)	Nonsurvivors, n (%)	P [a]
No. of patients	251	165 (65.74)	86 (34.26)	
Sepsis resuscitation bundle				
Lactate	123/251 (49.00)	87 (52.73)	36 (41.86)	.1022
Blood culture	171/251 (68.13)	124 (75.15)	47 (54.65)	.0009
Antibiotics	102/251 (40.64)	74 (44.85)	28 (32.56)	.1525
Fluids	174/200 (87.00)	111 (85.38)	63 (90.00)	.3546
Vasopressors	148/161 (91.93)	92 (89.32)	56 (96.55)	.1373
CVP	85/200 (42.50)	55 (42.31)	30 (42.86)	.9402
Venous oxygen saturation	32/200 (16.00)	24 (18.46)	8 (11.43)	.1957
Sepsis management bundle				
Glucose	55/251 (21.91)	34 (20.61)	21 (24.42)	.4883
Low tidal volume	21/100 (21.00)	12 (26.09)	9 (16.67)	.2490
CRB	31/251 (12.35)	24 (14.55)	7 (8.14)	.1432
CMB	39/251 (15.54)	32 (19.39)	7 (8.14)	.0195
TC	14/251 (5.58)	13 (7.88)	1 (1.16)	.0087

[a] Survivors vs nonsurvivors.

3.3. Effects of compliance on clinical outcome

The compliance rates for the blood culture, CMB, and TC targets were significantly higher in survivors than nonsurvivors ($P < .05$) (Table 3). We analyzed clinical outcomes according to the degree of compliance with the CRB, CMB, and TC targets (Table 5). Among the survivors whose treatment was compliant with the CRB target, the length of stay in the ICU was significantly shorter than those whose treatment was noncompliant ($P = .0355$). Compliance with the CMB significantly decreased hospital, ICU, and 28-day mortalities and mechanical ventilator duration for all patients and survivors ($P < .05$). Those patients who were compliant with the TC had a significantly lower hospital mortality rate and shorter ICU lengths of stay and mechanical ventilator durations ($P < .05$).

In the subgroup analysis of patients with septic shock, those patients compliant with the CRB and CMB targets had shorter lengths of stay in the ICU and mechanical ventilator durations, respectively ($P < .05$; data were not shown). The TC target compliance significantly reduced all mortality parameters, ICU length of stay, and mechanical ventilator duration ($P < .05$; data were not shown).

3.4. Influence of full-time intensivist and nurse-to-patient ratio on mortality and compliance

Only 3 ICUs (10.71%) were covered by full-time intensivist, and the number of ICUs with a nurse-to-patient ratio of 1:2 was 5 (17.86%). Among the 3 ICUs with full-time intensivist, the nurse-to-patient ratio of 2 ICUs was 1:2, and that of 1 ICU was 1:3. Of 5 ICUs with a nurse-to-patient

Table 4 Compliance rates according to site at time zero and the type of ICU

	ED, n (%)	WARD, n (%)	ICU, n (%)	P [a]	MICU, n (%)	SICU, n (%)	P [b]
No. of patients	145 (57.77)	79 (31.47)	27 (10.76)		210 (83.67)	41 (16.33)	
Sepsis resuscitation bundle							
Lactate	85 (58.62)	32 (40.51)	6 (22.22)	.0005	91 (43.33)	32 (78.05)	<.0001
Blood culture	120 (82.76)	38 (48.10)	13 (48.15)	<.0001	144 (68.57)	27 (65.85)	.7327
Antibiotics	94 (64.83)	8 (10.13)	0 (0.00)	<.0001	86 (40.95)	16 (39.02)	.8182
Fluids	108 (86.40)	48 (85.71)	18 (94.74)	.5692	146 (85.88)	28 (93.33)	.3811
Vasopressors	92 (95.83)	41 (82.00)	15 (100.00)	.0130	126 (92.65)	22 (88.00)	.4278
CVP	55 (44.00)	21 (37.50)	9 (47.37)	.6465	62 (36.47)	23 (76.67)	<.0001
Venous oxygen saturation	20 (16.00)	9 (16.07)	3 (15.79)	.9996	20 (11.76)	12 (40.00)	.0005
Sepsis management bundle							
Glucose	33 (22.76)	18 (22.78)	4 (14.81)	.6406	42 (20.00)	13 (31.71)	.0974
Low tidal volume	14 (26.92)	5 (14.71)	2 (14.29)	.3179	19 (21.35)	2 (18.18)	1.0000
CRB	30 (20.69)	1 (1.27)	0 (0.00)	<.0001	19 (9.05)	12 (29.27)	.0003
CMB	26 (17.93)	10 (12.66)	3 (11.11)	.4641	31 (15.24)	8 (29.27)	.4425
TC	13 (8.96)	1 (1.27)	0 (0.00)	.0279	4 (1.90)	10 (24.39)	.0028

[a] Among ED, WARD, and ICU.
[b] MICU vs SICU.

Table 5 Clinical outcomes according to the rate of compliance with the targets of the complete resuscitation and management bundles and TC

	CRB			CMB			TC		
	n (%), median (range)		*P*	n (%), median (range)		*P*	n (%), median (range)		*P*
	Compliant	Noncompliant		Compliant	Noncompliant		Compliant	Noncompliant	
No. of patients	31 (12.35)	220 (87.65)		39 (15.54)	212 (84.46)		14 (5.58)	237 (94.42)	
Hospital mortality	7 (22.58)	79 (35.91)	.1432	7 (17.95)	79 (37.26)	.0195	1 (7.14)	85 (35.86)	.0387
ICU mortality	5 (16.13)	68 (30.91)	.0898	6 (15.38)	67 (31.60)	.0404	1 (7.14)	72 (30.38)	.0729
28-d mortality	7 (22.58)	69 (31.36)	.3190	5 (12.82)	71 (33.49)	.0098	1 (7.14)	75 (31.65)	.0705
ICU length of stay									
All patients	5 (24)	7 (85)	.1986	5 (84)	7 (85)	.4012	3 (18)	7 (85)	.0135
Survivors only	5 (17)	8 (85)	.0355	5.5 (84)	7 (85)	.4606	3 (15)	8 (85)	.0013
Hospital length of stay									
All patients	20 (83)	21 (155)	.5170	16 (90)	22 (155)	.5183	21 (75)	21 (155)	.9051
Survivors only	19.5 (79)	24 (154)	.2319	16.5 (102)	25 (154)	.1729	22 (75)	23.5 (154)	.5703
Mechanical ventilator duration									
All patients	4 (24)	3 (91)	.7727	0 (91)	4 (52)	<.0001	0 (19)	3 (91)	.0202
Survivors only	2 (16)	1 (91)	.8426	0 (91)	3 (52)	.0014	0 (16)	2 (91)	.0391

ratio of 1:2, 3 ICUs were without full-time intensivist. From the 3 ICUs with full-time intensivist, 78 (31.08%) patients were enrolled. Despite APACHE II scores being similar between patients enrolled from ICUs with or without full-time intensivist ($P = .5125$), the hospital, ICU, and 28-day mortality rates of patients enrolled in ICUs with full-time intensivist were 17.95%, 14.1%, and 15.38%, respectively, which were significantly lower than in the ICUs without full-time intensivist ($P < .05$) (Table 6). In the ICUs with full-time intensivist, compared with those without, among the elements of the sepsis resuscitation bundle, compliance rates with lactate, blood culture, CVP, and venous oxygen saturation targets were significantly higher ($P < .05$). Compliance with the CRB and TC targets were also higher in ICUs with full-time intensivist ($P < .05$). The nurse-to-patient ratios of the participating ICUs were 1:2 in 5 ICUs, 1:3 in 10 ICUs, and 1:4 or more in 13 ICUs. In the ICUs with a nurse-to-patient ratio of 1:2, hospital, ICU, and 28-day

Table 6 Mortality and compliance rates according to the presence of full-time intensivist and the nurse-to-patient ratio in an ICU

Variables	Full-time intensivists			Nurse-to-patients ratio			
	n (%), mean ± SD		*P*	n (%), mean ± SD			*P*
	Presence	Absence		1:2	1:3	≥1:4	
No. of patients	78 (31.08)	173 (68.92)		75 (29.88)	80 (31.87)	96 (38.25)	
APACHE II score	22.359 ± 8.448	21.965 ± 9.030	.5125	22.187 ± 8.534	20.8 ± 8.949	23.083 ± 8.836	.2323
Mortality							
Hospital	14 (17.95)	72 (41.62)	.0002	15 (20)	31 (38.75)	40 (41.67)	.0034
ICU	11 (14.10)	62 (35.84)	.0004	11 (14.67)	28 (35)	34 (35.42)	.0029
28-d	12 (15.38)	64 (39.99)	.0005	11 (14.67)	26 (32.5)	39 (40.63)	.0005
Sepsis resuscitation bundle							
Lactate	65 (83.33)	58 (33.53)	<.0001	52 (69.33)	29 (36.25)	42 (43.75)	<.0001
Blood culture	60 (76.92)	111 (64.16)	.0446	56 (74.67)	50 (62.5)	65 (67.71)	.2656
Antibiotics	30 (38.46)	72 (41.62)	.6374	31 (41.33)	21 (26.25)	50 (52.08)	.0024
Fluids	58 (93.55)	116 (84.06)	.0649	63 (96.92)	45 (77.59)	66 (85.71)	.0058
Vasopressors	44 (84.62)	104 (95.41)	.0284	44 (89.80)	45 (90.00)	59 (95.16)	.4823
CVP	39 (62.9)	46 (33.33)	<.0001	35 (53.85)	20 (34.48)	30 (38.96)	.0691
Venous oxygen saturation	22 (35.48)	10 (7.25)	<.0001	21 (32.31)	4 (6.90)	7 (9.09)	<.0001
Sepsis management bundle							
Glucose	16 (20.51)	39 (22.54)	.7189	14 (18.67)	19 (23.75)	22 (22.92)	.7131
Low tidal volume	3 (18.75)	18 (21.43)	1.0000	7 (31.82)	3 (9.68)	11 (23.4)	.128
CRB	17 (21.79)	14 (8.09)	.0023	16 (21.33)	4 (5.00)	11 (11.46)	.008
CMB	13 (16.67)	26 (15.03)	.7403	12 (16)	13 (16.25)	14 (14.58)	.9466
TC	12 (15.38)	2 (1.16)	<.0001	13 (17.33)	0 (0)	1 (1.04)	<.0001

Table 7 Multivariate analysis of factors associated with hospital and 28-day mortalities

Factors	Hospital mortality			28-d mortality		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	0.996	0.977-1.015	.6719	0.997	0.977-1.017	.786
Male sex	0.713	0.450-1.130	.1500	0.762	0.469-1.239	.2726
APACHE II score	1.066	1.039-1.093	<.0001	1.07	1.043-1.097	<.0001
Full-time intensivist (+)	0.456	0.223-0.932	.0313	0.568	0.264-1.22	.1468
Nurse-to-patient ratio 1:2	0.654	0.331-1.291	.2208	0.459	0.211-0.998	.0496
CRB	1.080	0.487-2.395	.8495	1.066	0.481-2.363	.8757
CMB	1.648	0.756-3.593	.2088	2.085	0.836-5.199	.1151

mortality rates were significantly lower than those in ICUs with nurse-to-patient ratios of 1:3 and 1:4 or more ($P < .05$), despite similar APACHE II scores ($P = .2323$) (Table 6). The ICUs with a nurse-to-patient ratio of 1:2 exhibited a significantly higher compliance rate for bundle element targets including lactate, fluids and venous oxygen saturation elements of the resuscitation bundle, CRB, and TC ($P < .05$). In the multivariate COX regression analysis for factors associated with mortality, the hazard ratio (HR) for hospital mortality was independently reduced by the presence of full-time intensivist (HR, 0.456; 95% CI, 0.223-0.932), and a nurse-to-patient ratio of 1:2 was independently associated with a lower 28-day mortality (HR, 0.459; 95% CI, 0.211-0.998) (Table 7).

4. Discussion

In the present study, compliance rates for the elements of the sepsis resuscitation and management bundles were highly variable. Complete compliance with the resuscitation and management bundles were very low, and achievement of the TC compliance with both bundles was unacceptably low. Compliance with the resuscitation and management bundles did have beneficial effects on the clinical outcomes of patients with severe sepsis. Regarding the implementation of the elements and bundles of sepsis resuscitation and management guideline, the presence of full-time intensivist and a higher nurse-to-patient ratio were both associated with a higher rate of compliance, as well as with improved mortality rates.

The successful implementation of clinical practice guidelines should improve quality of care by reducing inappropriate variation in therapy and expediting the application of effective advances to everyday practice [15,16]. Despite the widespread of evidence-based clinical practice guidelines, there are limitations to changing actual clinical practices [17,18]. In critical care medicine, the incomplete implementations of clinically proven practices have been observed in early goal-directed therapy [19], ventilator-associated pneumonia prophylaxis [20-22], hand washing [23,24], and lung-protective ventilation for ALI [25]. An understanding of the barriers stopping the implementation of critical care guidelines is essential for developing effective interventions to improve practice [26]. Although little is known about the factors responsible for the poor implementation of clinical guidelines, there has been reported to be 3 major groups of barrier that disrupt the application of guidelines: knowledge barriers (lack of awareness or of familiarity), attitude barriers (lack of agreement, self-efficacy, outcome expectancy, or the inertia of previous practice), and behavioral barriers (external barriers) [8]. Among the external barriers, which include guideline-, patient-, and environment-related barriers, insufficient staff is a major factor beyond physician control of environment-related barriers [8]. It has recently been reported that a critical shortage of nursing staff is one of the most important barriers to the implementation of protocol-based sepsis resuscitation in the ED [11]. The clinically beneficial effects of sepsis bundles has been confirmed in many studies performed in the ICUs of developed countries, which have relatively homogeneous conditions regarding critical care staff [5,6,27-30]; however, to date, there have been no studies evaluating the insufficient critical care personnel to the implementation of SSC guidelines in ICUs.

In the present study, the targets of more elements of the resuscitation bundle were accomplished in those ICUs with full-time intensivist and/or a nurse-to-patient ratio of 1:2. Also, the rates of implementation of CRB and TC were also significantly higher in those ICU. Although CRB was not an independent risk factor for the mortalities in multivariate analysis, the presence of full-time intensivist and a nurse-to-patient ratio of 1:2 were independently correlated with lower hospital and 28-day mortalities, respectively. These findings suggest that sufficient critical care personnel may reduce the mortality rate of patients with severe sepsis through the improved of implementation of severe sepsis bundles. The result of the significantly higher compliance of CRB with lower mortality in those ICUs with full-time intensivist and/or a high nurse-to-patient ratio was contrary to the results of the MOSAICS study. In the MOSAICS study, there were no differences in compliance with the entire resuscitation bundle and hospital mortality according to the presence of full-time intensivist and nurse-to-patient ratio [7]. The most plausible reason of this discrepancy might have been the differences in organizational characteristics between the

participating centers of the MOSAICS study and those in South Korea. In the MOSAICS study, the percentage of ICUs with full-time intensivist and a nurse-to-patient ratio of 1:2 were 66.0% and 83.3%, respectively. It was enormously higher than for South Korea (10.71% and 17.86%), suggesting that there is severe heterogeneity and a shortage of critical care personnel in South Korea compared with other Asian countries participated in the MOSAICS study. This heterogeneity in critical care personnel in the participating ICUs in South Korea made it possible to identify the role of full-time intensivist and the nurse-to-patient ratio in the implementation of sepsis care bundles. Despite the fact that all participating ICUs were part of university hospitals, there were many other differences in critical care facilities other than critical care personnel. Although the presurvey about ICU facilities and equipment showed that all participating ICUs had essential and basic measures for performing care based on severe sepsis bundles, there were possibilities that the ICUs with full-time intensivist and/or a nurse-to-patient ratio of 1:2 had a higher degree of complexity than did the other ones. These differences in complexity might influence the mortality ratio. However, quantitative and/or qualitative comparisons of such a complexity were not performed. The lack of adequate statistical comparisons of these factors is a major limitation of this study. The presence of full-time intensivist independently reduced hospital mortality but not 28-day mortality; the nurse-to-patient ratio of 1:2 was independently associated with lower 28-day mortality but not hospital mortality. The most plausible reason of such a discrepancy is the relatively small sample size of the study to demonstrate an association between compliance rates with the severe sepsis bundles and patient clinical outcomes.

The implementation of severe sepsis bundles of this study is similar to other studies that reported low compliance. Although compliance rates for the sepsis management bundle of this study cannot be compared with those of other studies (because of the differences in the number of elements and element definitions), the 12.35% compliance rate of the CRB in this study is comparable with those of the MOSAICS study (7.6%) [7] and of the preeducational program of Edusepsis study (5.3%) [5] and SSC study (10.9%) [6]. In comparison with MOSAICS study in which the compliances rate with elements and bundles (excepting fluid ± vasopressors, venous oxygen saturation, and low tidal volume) were significantly higher in survivors than nonsurvivors, the present study provided significant results only for blood culture and CMB. This dilution in clinical impact might have been due to the decreased sample size (from n = 1285 in the MOSAICS study to n = 251 in this study). However, compliance with the CRB reduced ICU length of stay among survivors, and compliance with the CMB reduced mechanical ventilation duration, in addition to significantly lowering hospital, ICU, and 28-day mortalities, ratifying previous studies that have shown positive clinical effects of severe sepsis bundles application. In the analysis of the site at time zero for severe sepsis diagnosis and type of ICU, the compliance rates of the ED and SICU were significantly higher in more elements of the targets of resuscitation bundle, CRB, and TC. The patients who were in an ED at time zero had higher survival rates and compliance rates of lactate, blood culture, antibiotics, CRB and TC than those in a WARD or ICU. These results are compatible with those of previous studies [5-7] and could be resulted from immediate implementation of therapies of bundle in EDs. Therefore, analysis between the average time to full resuscitative bundle compliance and mortality is important; however, such an analysis could not be performed in this study. According to the results of Edusepsis [5] and SSC [6] studies, education program about severe sepsis bundle significantly increased compliances of elements and bundles, along with clinical outcomes. Before and during the patient enrollment period of this study, July 2009, the organized education programs for SSC guideline were not common in the Korean ICUs. The primary objective this study was to assess the compliance of Korean ICUs to the severe sepsis bundle under the specific education program-naive condition. Although some differences of education program in each ICU were present, all ICUs did not have education programs that specialized in severe sepsis bundle.

The present study had some limitations. First, the nature of observational study may have led to some unknown bias that may actually be the cause of both the differences in compliance with interventions and the differences in mortality and other clinical outcomes observed. Second, despite only the physicians representing each ICU were recognized with the study design to minimize behavioral changes resulting from knowledge of the ongoing study; inevitably, the participating investigators were simultaneously clinical practitioners and observers of the study, resulting in changes in clinical practice. In fact, the compliance rates of the lactate, fluids, and CVP elements were significantly greater in the last 10 days of the study period compared with the first 10 days, corroborating the potential effects of educational program reported in other studies [5,6]. Third, the exact and full clinical impact of the severe sepsis bundles may not have been measured effectively because other risk factors for death, such as the severity of late-stage severe sepsis (ie, the Sequential Organ Failure Assessment score) or patients' comorbidity, may have had an impact any decisions regarding inotropes or mechanical ventilation. Fourth, the relatively small sample size of the study has reduced our ability to demonstrate an association between compliance rates with the severe sepsis bundles and patient clinical outcomes. Finally, 31.08% and 29.88% of the patients were enrolled from the ICUs with full-time intensivist and a nurse-to-patient ration of 1:2, respectively. Therefore, there was a possibility of selection bias in the enrollment of patients, and it could influence severe sepsis bundle compliance and clinical outcomes.

5. Conclusion

The higher compliance with severe sepsis bundles through sufficient critical care personnel was closely associated with better clinical outcomes of patients with severe sepsis. For improvement of the clinical outcomes of patients with severe sepsis through the efficient application of evidence-based clinical practice guidelines, efforts should focus on increasing compliance with the targets of these interventions in appropriate patients. Further studies identifying barriers to the implementation of sepsis bundles in various intensive care environments are required to effectively achieve this goal.

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