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A MODIFIED GOAL-DIRECTED PROTOCOL IMPROVES CLINICAL OUTCOMES IN INTENSIVE CARE UNIT PATIENTS WITH SEPTIC SHOCK: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT—We evaluated whether a goal-directed protocol, without measurement of central venous oxygen saturation, would improve survival in medical intensive care unit (ICU) patients with septic shock. This is a prospective, controlled study in a 24-bed medical ICU at a tertiary care hospital. From a total of 241 consecutive patients with septic shock, 224 were randomly assigned to receive therapy with or without a written protocol using central venous pressure, mean arterial pressure, and urine output as therapeutic goals. Baseline characteristics were similar between groups. Implementation of goal-directed therapy caused a more rapid reversal of persistent shock (47 ± 22.8 vs. 65.4 ± 32.1 h, $P = 0.006$) and decreases of ICU (50% vs. 67.2%, $P = 0.009$) and in-hospital (53.7% vs. 71.6%, $P = 0.006$) mortality rates compared with non–goal-directed therapy. Patients receiving goal-directed therapy also had less risk for developing central nervous system or renal failure than patients without. Patients with goal-directed therapy received more fluid during the period of persistent shock (136.2 ± 119 vs. 88.6 ± 57.7 mL h^{-1}, $P = 0.034$) and less delay in vasopressor administration (78 ± 22.2 vs. 104.4 ± 29 min, $P = 0.001$) than patients with non-goal therapy. Implementation of a goal-directed protocol improves survival and clinical outcomes in ICU patients with septic shock. These benefits may arise from adequate fluid resuscitation, earlier vasopressor administration, rapid shock reversal, and protection of major organ function. With central venous oxygen saturation measurement to detect tissue perfusion, the clinical outcomes may be further improved.

KEYWORDS—Goal-directed, protocol, sepsis, shock, survival

INTRODUCTION

The invasion of microorganisms into the human body causes a systemic inflammatory response syndrome, which may progress to severe sepsis and septic shock (1, 2). During septic shock, global tissue hypoxia caused by an imbalance between systemic oxygen delivery and oxygen demand results in multiple organ failure and increased mortality rate (3). Experimental and clinical studies of septic shock support the concept that persistent shock has an adverse impact on survival in a time-dependent manner (4–6). Therapeutic strategies which target early recognition and rapid reversal of shock benefit survival and clinical outcomes (7).

Protocol-directed therapy has been shown to substantially improve patient outcome in critical illness (8–11). Protocol-directed therapy uses a protocol to guide therapy to achieve a predetermined target. The potential benefits of protocol usage arise from reducing variability of medical practice and decreasing errors, thereby improving clinical outcomes and reducing medical costs. A pivotal issue in the success of a protocol-directed therapy is the selection of specific goals (12). The end points used to achieve the desired therapeutic targets should be safe and attainable and associated with improved outcomes.

Recent progress in hemodynamic optimization has proven beneficial to survival outcome among patients with severe sepsis and septic shock. Rivers et al. (9) showed that when early goal-directed therapies (EGDT) were implemented in the emergency department, survival outcomes in patients with severe sepsis and septic shock significantly improved. In this study, aggressive resuscitation conformed to specific therapeutic targets of central venous pressure (CVP) between 8 and 12 mmHg, mean arterial pressure (MAP) between 65 and 90 mmHg, urine output 0.5 mL kg^{-1} h^{-1} or more, and continuous monitoring to keep central venous oxygen saturation ($ScVO_2$) at 70% or above. The benefits of EGDT in survival of patients with severe sepsis and septic shock appear to arise from early recognition, protocol-directed resuscitation, and restoration of a balance between oxygen delivery and oxygen demand by means of $ScVO_2$ monitoring.

The aim of this study is to investigate whether such a goal-directed therapy provides similar beneficial effects on those patients with septic shock in medical intensive care unit (ICU). According to the protocol used by EGDT, most of the therapeutic goals have been achieved before the patients were admitted to the ICU (9), whereas medical ICU patients were not all transferred from the emergency department but also from medical wards. The patients transferred from medical wards may have experienced deterioration of their medical condition or nosocomial infection before admission to the ICU. The illness severity and incidence of nosocomial infection, multidrug-resistant microorganisms, and multiple organ dysfunction of patients transferred from the medical wards may be much higher than those of patients directly recruited from the emergency department. For those patients with septic shock in medical ICU, an organized approach with evident goals of therapy, such as EGDT, may lead to an early adoption of adequate antibiotics to

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control infection and prevent rapid deterioration of multiple organ failure directly or indirectly induced by septic shock.

We, therefore, hypothesize that implementation of a goal-directed protocol would be also beneficial in improving survival in medical ICU patients with septic shock. Herein, we established a goal-directed protocol in our ICU for management of patients with septic shock using CVP, MAP, and urine output as the therapeutic goals. Continuous monitoring of $ScVO_2$ percentage required special facility and equipment which was not everyday available in our ICU. Thus, the goal of continuous $ScVO_2$ percentage monitoring was not included in the protocol. Because of new evidence of beneficial effects of low doses of corticosteroid supplement on survival of patients with septic shock and relative adrenal insufficiency (13), we also included screening for adrenal insufficiency in the protocol.

MATERIALS AND METHODS

Patients

The study population was recruited from adult ICU patients admitted to a 24-bed university-affiliated medical center medical ICU. The institutional review board approved this study, and informed consent was obtained from the patients or surrogates. The study was conducted from June 2003 to January 2004. The population of patients was recruited from the emergency department and medical wards. They were transferred to the medical ICU once sepsis with organ failure was found and included in the study when shock developed during their stay in the ICU. In addition, patients with septic shock in the emergency department or medical wards were included in this study if they were transferred to the medical ICU within 4 h. Septic shock was defined as that by the consensus committee of the American College of Chest Physicians and Society of Critical Care Medicine (14). Briefly, patients must have a known origin of infection, at least two of the criteria for systemic inflammatory response syndrome, and a blood pressure no higher than 90 mmHg (after a crystalloid-fluid challenge of 20 – 30 mL kg^{-1} within 30 min). Exclusion criteria included ages less than 18 years, pregnancy, or the presence of an acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, cardiac dysrhythmias (as a primary diagnosis), active gastrointestinal (GI) hemorrhage, seizure, drug overdose, burn injury, trauma, a requirement for immediate surgery, uncured cancer, immunosuppression, do-not-resuscitate status, or patient or family refusal to participate. After written informed consents were obtained, patients were randomized either to goal-directed therapy or to non–goal-directed therapy in computer-generated blocks of two to eight. The study group assignments were placed in sealed, opaque, randomly assorted envelopes, which were opened by a hospital staff member who was not one of the study investigators.

Baseline assessment

Each patient and their family members were interviewed, and the medical records were also reviewed to obtain baseline information. Acute Physiology and Chronic Health Evaluation (APACHE) III score was rated by chart review of data obtained within 24 h of ICU admission, and the worst values were compared between groups. The number of organ failures was recorded within 24 h of ICU admission. The definition of organ failure was according to the consensus committee of the American College of Chest Physicians and Society of Critical Care Medicine (14): respiratory failure, requiring mechanical ventilation; cardiovascular failure, systolic BP equal to or less than 90 mmHg or MAP equal to or less than 60 mmHg for 1 h despite fluid bolus; renal failure, low urine output (e.g., <0.5 mL kg^{-1} h^{-1}), increased creatinine level (≥50% increase from baseline), or requiring acute dialysis; hematologic failure, low platelet count (<100,000 mm^{-3}), or prothrombin time/activated partial thromboplastin time greater than the upper limit of normal; metabolic failure, low pH with high lactate (e.g., pH <7.30 and plasma lactate greater than the upper limit of normal); hepatic failure, liver enzymes greater than two times the upper limit of normal; central nervous system (CNS) failure, altered consciousness or a reduced Glasgow Coma Scale score. The sequential development of CNS, renal, and hepatic failure after the onset of septic shock was defined as sepsis-associated organ failure. The baseline vital signs, Glasgow Coma Scale score, CVP, laboratory values, and underlying medical history were also collected.

Treatment

All patients underwent arterial and central venous catheterization when septic shock was detected. Blood, urine and other relevant specimens for culture were obtained before administration of antibiotics. Antibiotics were given according to clinicians' decisions related to the local prevalence of bacteria in the annual report of the Infection Control Committee of the institute. Adequate antimicrobial therapy was defined as the *in vitro* sensitivities of the identified microorganisms concordant with the administered antibiotics in the ICU (15). The patients in the goal-directed protocol group were treated according to a step-by-step algorithm in written form (Fig. 1). Patients assigned to goal-directed therapy received step-by-step goal assessments and the three goals were continuously monitored through the course of treatment. If any one of the three goals no longer fulfilled their targets, therapeutic strategies were administered according to the step-by-step algorithm to assure that all of three goals were maintained above target levels. In contrast, the patients in the non–goal-directed therapy group were treated according to clinician judgment according to guidelines for hemodynamic support without any fixed algorithm (16). The clinicians of the ICU in our hospital consist of senior residents (the third- or fourth-year residents) and attending physicians. The attending physicians were in the hospital 24 h per day to make the decisions. The levels of clinicians involved in the protocol-directed and control groups were similar. The details of the protocol for goal-directed therapy were as follows: a 500-mL bolus of crystalloid (L-lactate Ringer's or 0.9% saline) was given every 30 min to achieve the first goal of CVP of 8 to 12 mmHg. If the MAP was still less than 65 mmHg after reaching the first goal, vasopressors were given to maintain a MAP of at least 65 mmHg. In addition, 50 mg of hydrocortisone was administrated i.v. every 6 h for 7 days, if relative adrenal insufficiency was diagnosed. Relative adrenal insufficiency was defined as serum level of cortisol less than 15 μg dL^{-1} or failure of an increase in cortisol level of 9 μg dL^{-1} or above within 60 min in response to corticotropin (i.m. or i.v. administration of 250 μg of corticotropin, with plasma cortisol levels measured at 30 and 60 min) (13, 17). Because the cortisol levels usually need 24 h to obtain the result, 50 mg of hydrocortisone was administered to the patients who were suggestive of relative adrenal insufficiency (patients chronically received exogenous glucocorticoids or had refractory septic shock) after collecting the blood sample. If the cortisol levels were reported to be normal, hydrocortisone was stopped immediately. The percentage of patients who received corticotrophin stimulation test was similar between protocol-directed therapy and nonprotocol-directed groups (54/80 [67.5%] vs. 46/81 [56.8%]), respectively, $P = 0.256$). The achievement of treatment goals was defined as CVP between 8 and 12 mmHg, MAP 65 mmHg or above, and urine output greater than 0.5 mL kg^{-1} h^{-1}. If patients had persistent low urine output despite normal CVP and MAP, a Swan-Ganz (Baxter Healthcare Corp., Irvine, CA) catheter was introduced to determine the cardiac index after repeated confirmation of CVP and MAP values. If the cardiac index was decreased, dobutamine was

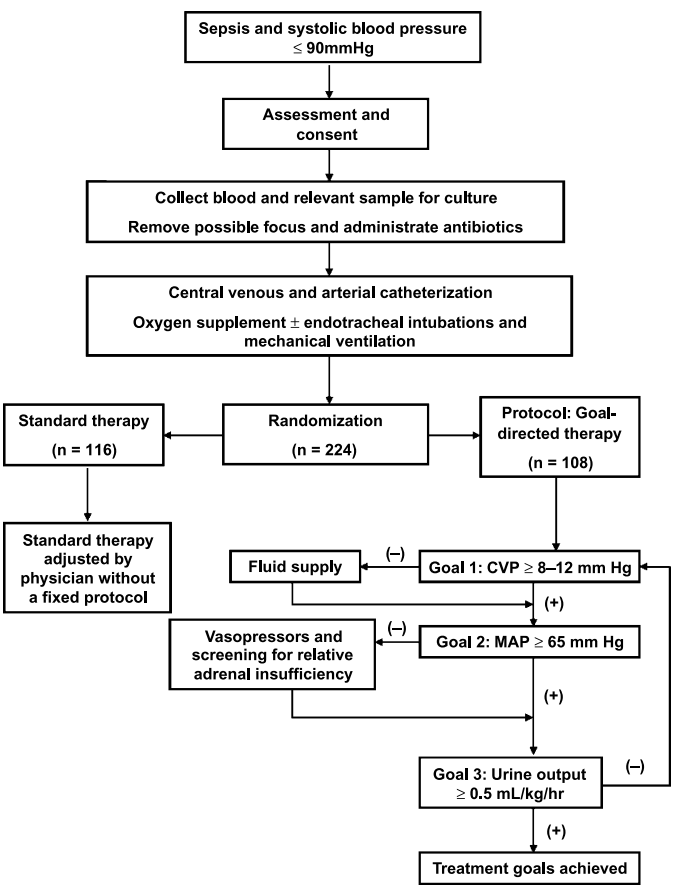

FIG. 1. **Protocol for management of patients with septic shock.**

TABLE 1. **Baseline characteristics of patients**

Characteristic	Protocol (n = 108)	No protocol (n = 116)
Age (y)	67.2 ± 15.0	68.7 ± 13.9
Female sex	44 (40.7)	50 (43.1)
Body weight (kg)	53.8 ± 9.1	51.5 ± 9.0
APACHE III score	66.5 ± 16.9	64.9 ± 14.4
No. organ failures	3.2 ± 0.9	3.4 ± 1.2
Glasgow Coma Scale score	9.2 ± 3.9	8.9 ± 3.9
CVP (mmHg)	5.6 ± 4.7	6.5 ± 4.5
Chronic coexisting conditions		
Diabetes mellitus	30 (27.8)	38 (32.8)
Hypertension	38 (35.2)	40 (34.5)
Congestive heart failure	28 (25.8)	24 (20.7)
Coronary arterial disease	7 (6.5)	4 (3.4)
Arrhythmia	16 (14.8)	22 (19)
Renal insufficiency	14 (13)	18 (15.5)
Neurological disease	13 (12)	17 (14.7)
Chronic obstructive pulmonary disease	16 (14.8)	12 (10.3)
History of malignancy	14 (13)	12 (10.3)
Primary origin of sepsis		
Pneumonia	65 (60.2)	69 (58.5)
Urosepsis	11 (10.2)	14 (12.1)
Peritonitis	13 (12.0)	16 (13.8)
Other	19 (14.8)	17 (14.2)
Transferred from		
Emergency department	40 (37.0)	46 (39.7)
Medical wards	68 (63.0)	70 (60.3)

Values are expressed as mean ± SD or no. (%).

administrated. There were only 2 patients (1.9%) in this study with persistent low urine output and requiring Swan-Ganz catheterization.

Outcome assessment

The outcome variables included ICU and in-hospital mortality rates, length of ICU stay, length of hospital stay, duration of mechanical ventilation, time interval between development of shock and death, and the time needed for shock reversal. We also monitored the occurrence of complications after admission to the ICU, including nosocomial pneumonia, acute respiratory distress syndrome (ARDS), pulmonary edema, GI bleeding, disseminated intravascular coagulation (DIC), and sepsis-associated CNS, renal, and hepatic failure. Gastrointestinal bleeding was diagnosed, if there was evidence of hematemesis, coffee-ground gastric content, or melena. Pulmonary edema was diagnosed if clinical suspicion of acute pulmonary edema with increased A-a gradient and chest radiograph compatible with pulmonary edema. We measured platelet count, prothrombin time, and fibrinogen and fibrin degradation products for the DIC score from the International Society on Thrombosis and Haemostasis subcommittee. A score of 5 or more is considered to be compatible with DIC; whereas a score less than 5 was considered to be non-DIC (18). Treatments administered during the period of persistent shock were also examined.

The ratio of positive results in blood, sputum, and urine cultures and presence of fungus in any relevant specimens were recorded. The presence of *Acinetobacter baumannii* and multiple drug–resistant (MDR) bacteria were determined. Multiple drug–resistant bacteria were defined as the following: methicillin-resistant *Staphylococcus aureus* (MRSA), ceftazidime-, or imipenem-resistant *Pseudomonas aeruginosa, A. baumannii*, extended-spectrum β-lactamase-producing gram-negative bacilli, and *Stenotrophomonas maltophilia* (19).

Statistical analysis

Descriptive statistics were used to examine the demographic characteristics of the study population. Data were expressed as mean ± SD. The baseline characteristics, and disease and laboratory variables between the patients assigned to goal-directed therapy and to non–goal-directed therapy were compared using the two-tailed Student t test and chi-square test for continuous and categorical variables, respectively. $P < 0.05$ is considered statistically significant. All of the analyses were performed using SPSS software version 10.0 (Chicago, Ill).

RESULTS

Baseline characteristics

During the study period, 241 patients were eligible for this study, of whom 224 were enrolled; 17 (7.1%) were excluded or did not consent to participate. Therefore, a total of 224 patients were included in the final analysis. The reasons of patients excluded from this study were as follows: do-not-resuscitate status (n = 5), refusal to participate (n = 4), uncured cancer (n = 3), acute pulmonary edema (n = 2), seizure (n = 2), and acute coronary syndrome (n = 1). About one-third (86/224) of the patients were transferred from the emergency department whereas the others were from the medical wards. The distributions of patient source were similar in both groups (Table 1). The baseline characteristics of the enrolled patients are summarized in Table 1.

TABLE 2. **Vital signs and laboratory data on inclusion**

Variable	Protocol (n = 108)	No protocol (n = 116)
Vital signs		
Temperature (°C)	37.0 ± 1.0	36.7 ± 1.2
Respiratory rate (f_R, breaths/min)	22.4 ± 6.5	22.2 ± 6.9
Heart rate (beats/min)	101.7 ± 21.6	109.6 ± 27.5
MAP (mmHg)	55.6 ± 8.6	55.9 ± 8.8
Arterial blood gas		
pH	7.32 ± 0.13	7.31 ± 0.11
Base deficit (mmol L^{-1})	9.1 ± 2.4	8.5 ± 2.1
PaO_2/FiO_2	223.6 ± 104.4	236.1 ± 129.9
Hematology		
White blood cell count (per mm^3)	15269 ± 10258	13472 ± 6405
Hemoglobin (g dL^{-1})	9.5 ± 2	10.2 ± 2.3
Platelet ($\times 1000$ μL^{-1})	233 ± 126.9	210.5 ± 111.8
PT (s)	18.8 ± 11.3	17.1 ± 4.2
aPTT (s)	39.6 ± 16.6	36 ± 13.6
Blood biochemistry		
Lactate (mmol L^{-1})	6.9 ± 4.1	7.2 ± 5.1
AST (ì L^{-1})	70 ± 124.2	53.5 ± 54.6
Total bilirubin (mg dL^{-1})	1.5 ± 3.3	1.2 ± 1.3
Albumin (g dL^{-1})	2.4 ± 0.5	2.3 ± 0.4
Blood urea nitrogen (mg dL^{-1})	53.9 ± 43.6	55.1 ± 49.6
Creatinine (mg dL^{-1})	2.6 ± 2.2	2.1 ± 1.6
Sodium (mEq L^{-1})	134.8 ± 9.2	136.9 ± 9.1
Potassium (mEq L^{-1})	4.5 ± 1.5	4.2 ± 1.1

Values are expressed as mean ± SD.
aPTT indicates activated partial thromboplastin time; AST, aspartate aminotransferase; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in arterial blood; PT, prothrombin time.

TABLE 3. **Bacterial studies and primary origin of infection**

Variables	Protocol (n = 108)	No protocol (n = 116)	P*
Blood culture positive	10 (9.3)	18 (15.5)	0.317
Sputum culture positive	76 (70.4)	76 (65.5)	0.583
Urine culture positive	18 (16.7)	21 (18.1)	0.778
Fungus culture positive	8 (7.4)	13 (11.2)	0.438
Presence of *A. baumannii*	57 (54.6)	61 (52.6)	0.977
Presence of MDR bacteria	62 (57.4)	74 (63.8)	0.371
Adequate antibiotic therapy	102 (94.4)	107 (92.2)	0.510

Values are expressed as no. (%).
*P for chi-square test in the case of categorical variables, and for two-tailed independent t test in the case of quantitative variables.

There were no significant differences between groups regarding demographic variables, APACHE III scores, Glasgow Coma Scale score, CVP values, chronic coexisting conditions, or primary origin of sepsis. Vital signs, arterial blood gas values, and hematological and blood biochemical variables were also similar between groups at baseline (Table 2).

Microorganism variables

The results of bacterial studies are summarized in Table 3. The percentage of positive culture resulting from any relevant specimens were similar between the goal-directed therapy and non–goal-directed therapy group (77.8% and 77.6%, respectively, $P = 0.751$). There was no significant difference between groups in the incidence of fungus, *A. baumannii*, and MDR bacteria in culture results. Moreover, the initially administered broad-spectrum antibiotics in the two groups were similarly adequate in matching the *in vitro* sensitivities of the identified microorganisms (94.4% vs. 92.2%, goal-directed therapy versus non–goal-directed therapy, respectively, $P = 0.51$).

Clinical outcomes and complications

The combined hemodynamic goals for CVP, MAP, and urine output (with adjustment for patients with end-stage renal failure) were achieved in 98.1% (106/108) of the goal-directed therapy group. The time to reverse shock was much less in patients with goal-directed therapy (47 ± 22.8 h) compared with that of patients with non–goal-directed therapy (65.4 ± 32.1 h, $P < 0.01$) (Table 5). During the hospital stay, 53.7% (58/108) of the patients in the goal-directed therapy group died versus 71.6% (83/116) of the patients in the non–goal-directed therapy group ($P = 0.006$ by chi-square test) (Table 5). The ICU mortality rate of patients receiving goal-directed therapy was significantly less than that of patients receiving non–goal-directed therapy (50% vs. 67.2%; respectively, $P = 0.009$). In consideration of the patient source of recruitment, the mortality rates of patients receiving goal-directed therapy were lower than those receiving non–goal-directed therapy in patients transferred from either the emergency department (32.5% vs. 54.3%, $P = 0.042$) or medical wards (60.3% vs. 75.7%, $P = 0.05$). Most patients transferred from medical wards to the ICU had received prior antibiotics ($P < 0.0001$) and had more diabetes ($P = 0.034$), chronic renal insufficiency ($P = 0.04$), severity of illness (indicated by APACHE III score, $P = 0.016$) or higher incidence of nosocomial infection ($P < 0.0001$) compared with those transferred from the emergency department (Table 4). Patients receiving goal-directed therapy had shorter length of ICU stay (14.3 ± 11.7 days) than that of the non–goal-directed therapy group (20.3 ± 16.6 days, $P = 0.003$), whereas the length of total hospital stay were similar in both groups (36.6 ± 22.9 vs. 33.8 ± 23.1 days; goal-directed therapy versus non–goal-directed therapy respectively, $P = 0.358$). The duration of mechanical ventilation in patients receiving non–goal-directed therapy (18.8 ± 17.1 days) was longer than in the goal-directed therapy group (12.9 ± 11.5 days, $P = 0.003$). The interval between the onset of shock and death was increased in the non–goal-directed therapy group (17.4 ± 11.8 days) when compared with the goal-directed therapy group (12.9 ± 11.3 days, $P = 0.033$).

The incidence of the development of sepsis-associated CNS and renal failure was significantly decreased in patients receiving goal-directed therapy (18.5% and 38.9%, respectively) compared with patients receiving non–goal-directed therapy (36.2% and 55.2%, $P = 0.003$ and $P = 0.015$, respectively). In contrast, there was no significant difference between the two groups in other complications, including hepatic failure, ARDS, nosocomial pneumonia, cardiopulmonary edema, DIC, and GI bleeding episodes (Table 5). The mortality rate in the ICU caused by multiorgan failure was significantly higher in the non–goal-directed therapy group than in the goal-directed therapy group ($P = 0.009$). The mortality rate caused by sudden cardiovascular collapse was similar in both treatment groups ($P = 0.288$).

Administered treatments

The average waiting times for first i.v. fluid bolus after development of shock were similar between the groups (Table 6). In contrast, patients in the goal-directed therapy group waited

TABLE 4. **Clinical characteristics of patients transferred from the emergency department and medical wards**

Variable	Transferred from emergency department (n = 86)	Transferred from medical wards (n = 138)	P
Age (y)	69.9 ± 13.9	66.5 ± 14.6	0.83
Female sex	38 (44.2)	56 (43.1)	0.591
APACHE III score	56.4 ± 17.3	63.9 ± 17.2	0.016
Nosocomial infection	2 (2.3)	97 (70.3)	<0.0001
Prior antibiotic administration	4 (4.7)	107 (77.5)	<0.0001
Comorbidities			
Diabetes mellitus	19 (18.6)	49 (35.5)	0.034
Congestive heart failure	22 (25.6)	30 (21.7)	0.508
Chronic renal insufficiency	8 (9.3)	25 (18.1)	0.040
History of malignancy	11 (12.8)	15 (10.9)	0.735

Values are expressed as mean SD or no. (%).

TABLE 5. **Clinical outcomes and complications**

Variable	Protocol (n = 108)	No protocol (n = 116)	*P*
Outcomes			
ICU mortality rate			
Whole cohort	54 (50)	78 (67.2)	0.009
Transfer from emergency department	13/40 (32.5)	25/46 (54.3)	0.042
Transfer from medical ward	41/68 (60.3)	53/70 (75.7)	0.050
Length of hospital stay	36.6 ± 22.9	33.8 ± 23.1	0.358
Length of ICU stay	14.3 ± 11.7	20.3 ± 16.6	0.003
Duration between shock and death	12.9 ± 11.3	17.4 ± 11.8	0.033
Duration of mechanical ventilation	12.9 ± 11.5	18.8 ± 17.1	0.003
Complications			
Sepsis-associated CNS failure	20 (18.5)	42 (36.2)	0.003
Sepsis-associated renal failure	42 (38.9)	64 (55.2)	0.015
Sepsis-associated hepatic failure	24 (22.2)	32 (27.6)	0.354
ARDS	2 (1.9)	7 (6)	0.331
Nosocomial pneumonia	56 (51.9)	54 (46.6)	0.575
Cardiopulmonary edema	5 (4.6)	10 (8.6)	0.537
DIC	14 (13)	21 (18.1)	0.176
GI bleeding	19 (17.6)	16 (13.8)	0.256
Causes of death			
Sudden cardiovascular collapse	38/54 (70.4)	39/78 (50)	0.288
Multiorgan failure	11/54 (20.4)	33/78 (42.3)	0.009

Values are expressed as mean ± SD, no. (%), or in days.

for significantly shorter duration to receive vasopressor support than those in the non–goal-directed group (78 ± 22.2 vs. 104.4 ± 29 min, respectively, $P = 0.001$). The selection of vasopressors (dopamine or norepinephrine) and policy of dosage adjustment were the same in the two groups. Vasopressors administration was aimed at a MAP of 65 to 90 mmHg in both groups, and their doses were decreased with decrements of 2.5 $\mu g\ kg^{-1}\ min^{-1}$ until zero to maintain a minimum MAP of 65 mmHg. The selection of dopamine or norepinephrine and dose of vasopressors were similar between the two groups (Table 6). The duration of antibiotic therapy was decreased in patients assigned to goal-directed therapy (11.9 ± 5.7 days) compared with patients receiving non–goal-directed therapy (16.1 ± 5.4 days, $P = 0.033$). More rapid reversal of shock status was observed in the subjects receiving goal-directed therapy than in the non-goal-directed therapy group (47 ± 22.8 and 65.4 ± 32.1 h, respectively, $P = 0.006$). Patients assigned to goal-directed therapy received more fluid on average during the period of persistent shock when compared with patients assigned to non–goal-directed therapy (136.2 ± 119 mL h^{-1} and 88.6 ± 57.7 mL h^{-1}, respectively, $P = 0.034$). However, the incidences of relative adrenal insufficiency were similar between groups. Blood transfusion was given to all the patients with hemoglobulin less than 10 g dL^{-1}. Blood transfusion was given to 36.6% of patients in the whole cohort. The incidences of patients who received blood transfusion were similar between the two groups (39/108 [36.1%] vs. 43/116 [37.1%], $P = 0.679$). Dobutamine was administrated if the patient had clinical suspicion of low cardiac output or decreased cardiac index detected by Swan-Ganz catheterization. A similar percentage of patients in both groups received dubutamine treatment.

DISCUSSION

Our investigation demonstrated that implementation of a modified goal-directed protocol without $ScVO_2$ monitoring improved the clinical outcomes of patients with septic shock, including ICU mortality, in-hospital mortality, length of ICU stay, and duration of mechanical ventilation. Patients receiving goal-directed therapy had a decreased risk of developing sepsis-associated CNS and renal dysfunction when compared with patients assigned to the non–goal-directed treatment group. In comparison with patients receiving non–goal-directed therapy, patients assigned to goal-directed therapy received significantly larger amounts of fluid, less delay in vasopressor administration, and shorter duration of antibiotic treatment. Our results provide evidence that implementation of a goal-directed protocol, even without continuous monitoring of $ScVO_2$, has a positive impact on survival and other clinical outcomes in patients with septic shock in the ICU.

TABLE 6. **Treatment administered**

Variable	Protocol (n = 108)	No protocol (n = 116)	*P**
Time from shock to bolus fluid administration (min)	42 ± 29.1	48.7 ± 26.6	0.364
Time from shock to vasopressor administration (min)	78.5 ± 22.2	104.4 ± 29.0	0.001
Time needed for shock reversal (h)	47 ± 22.8	65.4 ± 32.1	0.006
Duration of antibiotics (days)	11.9 ± 5.7	16.1 ± 5.4	0.033
Duration of vasopressor (h)	2.2 ± 2.6	2.4 ± 1.9	0.660
Prior antibiotic administration	52 (48.1)	61 (52.6)	0.507
Hydrocortisone for adrenal insufficiency	32 (29.6)	25 (21.6)	0.189
Vasopressor administration	80 (74.1)	81 (69.8)	0.480
Dopamine administration	64 (80)	62 (76.5)	0.595
Norepinephrine administration	21 (26.3)	23 (28.4)	0.760
Dobutamine administration	13 (12.0)	16 (13.8)	0.733
Total fluid amount (mL)	5180 ± 4026	5011 ± 2872	0.838
Mean fluid amount (mL h^{-1})	136.2 ± 119	88.6 ± 57.7	0.034
Total dopamine dose (mg)	220.7 ± 222	226.6 ± 141.5	0.890
Mean dopamine dose ($\mu g\ kg^{-1}\ h^{-1}$)	83 ± 57.2	73 ± 40.9	0.396
Total norepinephrine dose (mg)	4.7 ± 8.8	8.7 ± 9.4	0.311
Mean norepinephrine dose ($\mu g\ kg^{-1}\ h^{-1}$)	2.1 ± 6.5	6.8 ± 7.1	0.943

Values are expressed as mean ± SD or no. (%).
*P for chi-square test in the case of categorical variables, and for two-tailed independent t test in the case of quantitative variables.

The benefits of our clinical pathways in terms of clinical outcomes are multifactorial. In the present study, patients assigned to goal-directed therapy received more fluid resuscitation during the period of persistent shock and experienced less delay in administration of vasopressor when compared with patients assigned to non–goal-directed therapy. The combination of adequate fluid resuscitation and less delay in vasopressor administration may contribute to rapid shock reversal among these patients. Large fluid deficits exist in patients with septic shock. Volume repletion in these patients produces significant improvement in cardiac function and systemic oxygen delivery, thereby enhancing tissue perfusion and decreasing mortality (20). Experimental and clinical studies of septic shock have supported the concept that persistent shock has an adverse impact on survival in a time-dependent manner (4–6). The results of Han et al. (7) disclosed that early shock reversal by adequate fluid resuscitation was associated with improved outcome and each hour of delay in resuscitation was associated with a 50% increased odds of mortality. Another study also showed that aggressive fluid resuscitation early in the treatment course led to a decreased occurrence of persistent shock and subsequently improved survival of patients with septic shock without an increase in risk of cardiopulmonary edema or ARDS (21).

Our study has demonstrated that goal-directed therapy may decrease the incidence of the development of sepsis-associated CNS and renal failure when compared with the non–goal-directed therapy group. Evidence has revealed that sepsis-associated impairment of tissue perfusion leads to multiple organ system failure (22). About half of patients with septic shock die of multiple organ system failure (23). Rapid hemodynamic optimization caused by aggressive fluid resuscitation and less delayed vasopressor administration in our goal-directed therapy group may therefore prevent the development of major organ dysfunction, such as CNS and renal failure. Central nervous system failure, manifested as delirium (2) or consciousness disturbance, has been reported to be associated with grave impact on the survival of patients with sepsis (24). Patients with delirium have a longer stay in the ICU and need a longer duration of mechanical ventilator support (2). The combination of acute renal failure and sepsis is associated with 70% mortality rate, as compared with 45% mortality rate among patients with acute renal failure alone (25). The protective effects against organ failure by goal-directed therapy may contribute to the reduction of mortality rate and improvement in clinical outcomes among patients with septic shock. The presence of myocardial suppression was seen in about 12% of patients with sepsis and required the use of dobutamine in this study. This group of patients may have a low $ScVO_2$ when all other end points are met. A recent retrospective study has revealed that $ScVO_2$ levels independently predicted mortality rate in medical ICU patients with septic shock (32). In this study, $ScVO_2$ was not measured as that in the Rivers et al. (9) study. Had $ScVO_2$ been used, tissue dysoxia may have been detected and outcome may have been improved further.

Evidence reveals that sepsis causes disruption of the hemeostatic balance between inflammation and coagulation (26, 27). The pathogenesis of organ failure caused by sepsis is associated with the formation of sepsis-induced DIC, leading to the development of organ microcirculation failure and subsequent failure of the organ itself (28, 29). Previous study has shown that endotoxemia induced a rapid formation of microthrombi in the hepatic circulation and subsequently caused multiple fibrin clots resulting in focal areas of hypoperfusion and tissue necrosis, and the development of multiple organ dysfunction (28). In the present study, the development of sepsis-associated hepatic failure, ARDS, cardiopulmonary edema, nosocomial pneumonia, DIC, and GI bleeding was unaffected by implementation of the goal-directed protocol. Because most of these complications were caused by markedly enhanced inflammatory response or imbalance between coagulation and fibrinolysis, therefore, rapid hemodynamic optimization by this protocol may not be enough to correct sepsis-induced inflammation and imbalance between coagulation and fibrinolysis. Thus, the incidences of these complications were not decreased by this protocol.

In our study, the mortality rate of the whole cohort was higher than the EGDT study. The high percentage of patients transferred from the medical wards may be responsible for the poor outcome. Compatible with previous reports (14), our results demonstrated that the mortality rate of patients with sepsis recruited from the medical wards was higher than those from the emergency department. The increase in illness severity, comorbidity, and nosocomial infection among patients transferred from the medical wards may account for the high mortality rate. In addition, our study showed that the mortality rate of patients transferred from the emergency department in goal-directed therapy group was similar to that in the EGDT study. Most patients transferred from the medical wards to the ICU had received prior antibiotics and had more comorbid illnesses, greater severity of illness, and higher incidence of nosocomial infection compared with those transferred from the emergency department. The high percentage of patients transferred from the medical wards may contribute to the high rates of MDR bacteria in this study. The blood culture positive rate (12.5%, 28/224) of this study is lower than that of previous reports (9, 30). In the present study, 60% of the patients were admitted because of pneumonia. The range of positive blood culture of a pathogen in pneumonia was reported to be from 7% to 16% (31–33). Thus, a high percentage of patients with pneumonia in this study may decrease the rate of positive blood culture.

Our study was limited by the potential effect of its unblinded design. However, it was not feasible to conduct the study in a strictly blinded fashion for comparing goal- and non–goal-directed groups in the same ICU. This introduces the potential for bias as a result of treating clinicians altering their practices, particularly in the non–goal-directed group. It is possible that some physicians might have changed their management of patients because they knew the goals in the goal-directed therapy. We believe that the bias may actually favor the non-goal therapy group rather than the goal-directed therapy group; however, the survival benefit of goal-directed therapy was so striking that statistical significance was attained despite the appearance of this bias.

In conclusion, goal-directed therapy for patients with septic shock targeting CVP, MAP, and urine output has significant benefit in decreasing mortality rate, and shortening the length of ICU stay and duration of mechanical ventilator support and antibiotic administration. These benefits seem to arise from rapid reversal of shock caused by adequate fluid resuscitation and less delayed vasopressor administration, and the resultant protection of major organ function. Our study confirms that hemodynamic optimization is an important therapeutic goal in the management of patients with septic shock in the medical ICU. For medical ICUs without facility to monitor $ScVO_2$%, this modified therapeutic protocol provides an alternative that reduces mortality, ICU stay, ventilator support duration, and tissue hypoperfusion–associated major organ dysfunction. However, with $ScVO_2$ measurement to detect tissue perfusion, the clinical outcome may be further improved.

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