EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

ABSTRACT

Background Goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit.

Methods We randomly assigned patients who arrived at an urban emergency department with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment. In-hospital mortality (the primary efficacy outcome), end points with respect to resuscitation, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were obtained serially for 72 hours and compared between the study groups.

Results Of the 263 enrolled patients, 130 were randomly assigned to early goal-directed therapy and 133 to standard therapy; there were no significant differences between the groups with respect to base-line characteristics. In-hospital mortality was 30.5 percent in the group assigned to early goal-directed therapy, as compared with 46.5 percent in the group assigned to standard therapy ($P=0.009$). During the interval from 7 to 72 hours, the patients assigned to early goal-directed therapy had a significantly higher mean (±SD) central venous oxygen saturation (70.4±10.7 percent vs. 65.3±11.4 percent), a lower lactate concentration (3.0±4.4 vs. 3.9±4.4 mmol per liter), a lower base deficit (2.0±6.6 vs. 5.1±6.7 mmol per liter), and a higher pH (7.40±0.12 vs. 7.36±0.12) than the patients assigned to standard therapy ($P\leq0.02$ for all comparisons). During the same period, mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0±6.3 vs. 15.9±6.4, $P<0.001$).

Conclusions Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock. (N Engl J Med 2001;345:1368-77.)

THE systemic inflammatory response syndrome can be self-limited or can progress to severe sepsis and septic shock.[1] Along this continuum, circulatory abnormalities (intravascular volume depletion, peripheral vasodilatation, myocardial depression, and increased metabolism) lead to an imbalance between systemic oxygen delivery and oxygen demand, resulting in global tissue hypoxia or shock.[2] An indicator of serious illness, global tissue hypoxia is a key development preceding multiorgan failure and death.[2] The transition to serious illness occurs during the critical "golden hours," when definitive recognition and treatment provide maximal benefit in terms of outcome. These golden hours may elapse in the emergency department,[3] hospital ward,[4] or the intensive care unit.[5]

Early hemodynamic assessment on the basis of physical findings, vital signs, central venous pressure,[6] and urinary output[7] fails to detect persistent global tissue hypoxia. A more definitive resuscitation strategy involves goal-oriented manipulation of cardiac preload, afterload, and contractility to achieve a balance between systemic oxygen delivery and oxygen demand.[2] End points used to confirm the achievement of such a balance (hereafter called resuscitation end points) include normalized values for mixed venous oxygen saturation, arterial lactate concentration, base deficit, and pH.[8] Mixed venous oxygen saturation has been shown to be a surrogate for the cardiac index as a target for hemodynamic therapy.[9] In cases in which the insertion of a pulmonary-artery catheter is impractical, venous oxygen saturation can be measured in the central circulation.[10]

Whereas the incidence of septic shock has steadily increased during the past several decades, the associated mortality rates have remained constant or have decreased only slightly.[11] Studies of interventions such as immunotherapy,[12] hemodynamic optimization,[9,13] or pulmonary-artery catheterization[14] enrolled patients up to 72 hours after admission to the intensive care unit. The negative results of studies of the use of hemodynamic variables as end points ("hemodynamic

From the Departments of Emergency Medicine (E.R., B.N., J.R., A.M., B.K., M.T.), Surgery (E.R.), Internal Medicine (B.N.), and Biostatistics and Epidemiology (S.H., E.P.), Henry Ford Health Systems, Case Western Reserve University, Detroit. Address reprint requests to Dr. Rivers at the Department of Emergency Medicine, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, MI 48202, or at erivers1@hfhs.org.

*The members of the Early Goal-Directed Therapy Collaborative Group are listed in the Appendix.

optimization"), in particular, prompted suggestions that future studies involve patients with similar causes of disease[13] or with global tissue hypoxia (as reflected by elevated lactate concentrations)[15] and that they examine interventions begun at an earlier stage of disease.[16,17]

We examined whether early goal-directed therapy before admission to the intensive care unit effectively reduces the incidence of multiorgan dysfunction, mortality, and the use of health care resources among patients with severe sepsis or septic shock.

METHODS

Approval of Study Design

This prospective, randomized study was approved by the institutional review board for human research and was conducted under the auspices of an independent safety, efficacy, and data monitoring committee.

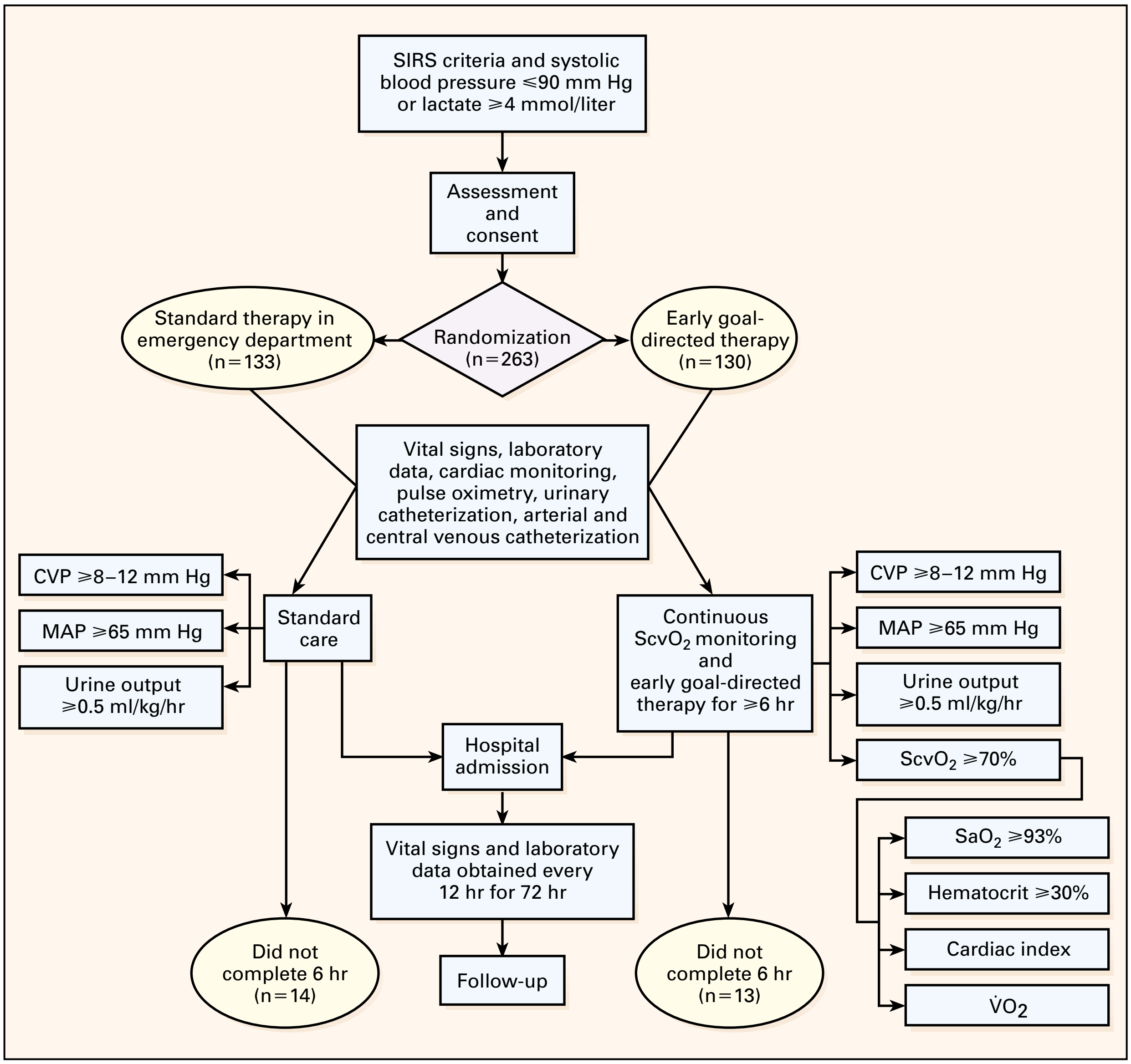

Figure 1. Overview of Patient Enrollment and Hemodynamic Support.

SIRS denotes systemic inflammatory response syndrome, CVP central venous pressure, MAP mean arterial pressure, $ScvO_2$ central venous oxygen saturation, SaO_2 arterial oxygen saturation, and $\dot{V}O_2$ systemic oxygen consumption. The criteria for a diagnosis of SIRS were temperature greater than or equal to 38°C or less than 36°C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 breaths per minute or partial pressure of arterial carbon dioxide less than 32 mm Hg, and white-cell count greater than 12,000 per cubic millimeter or less than 4000 per cubic millimeter or the presence of more than 10 percent immature band forms.

Eligibility

Eligible adult patients who presented to the emergency department of an 850-bed academic tertiary care hospital with severe sepsis, septic shock, or the sepsis syndrome from March 1997 through March 2000 were assessed for possible enrollment according to the inclusion[18,19] and exclusion criteria (Fig. 1). The criteria for inclusion were fulfillment of two of four criteria for the systemic inflammatory response syndrome and a systolic blood pressure no higher than 90 mm Hg (after a crystalloid-fluid challenge of 20 to 30 ml per kilogram of body weight over a 30-minute period) or a blood lactate concentration of 4 mmol per liter or more. The criteria for exclusion from the study were an age of 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), contraindication to central venous catheterization, active gastrointestinal hemorrhage, seizure, drug overdose, burn injury, trauma, a requirement for immediate surgery, uncured cancer (during chemotherapy), immunosuppression (because of organ transplantation or systemic disease), do-not-resuscitate status, or advanced directives restricting implementation of the protocol.

The clinicians who assessed the patients at this stage were unaware of the patients' treatment assignments. After written informed consent was obtained (in compliance with the Helsinki Declaration[20]), the patients were randomly assigned either to early goal-directed therapy or to standard (control) 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.

Treatment

The patients were treated in a nine-bed unit in the emergency department by an emergency physician, two residents, and three nurses.[3] The study was conducted during the routine treatment of other patients in the emergency department. After arterial and central venous catheterization, patients in the standard-therapy group were treated at the clinicians' discretion according to a protocol for hemodynamic support[21] (Fig. 1), with critical-care consultation, and were admitted for inpatient care as soon as possible. Blood, urine, and other relevant specimens for culture were obtained in the emergency department before the administration of antibiotics. Antibiotics were given at the discretion of the treating clinicians. Antimicrobial therapy was deemed adequate if the in vitro sensitivities of the identified microorganisms matched the particular antibiotic ordered in the emergency department.[22]

The patients assigned to early goal-directed therapy received a central venous catheter capable of measuring central venous oxygen saturation (Edwards Lifesciences, Irvine, Calif.); it was connected to a computerized spectrophotometer for continuous monitoring. Patients were treated in the emergency department according to a protocol for early goal-directed therapy (Fig. 2) for at least six hours and were transferred to the first available inpatient beds. Monitoring of central venous oxygen saturation was then discontinued. Critical-care clinicians (intensivists, fellows, and residents providing 24-hour in-house coverage) assumed the care of all the patients; these physicians were unaware of the patients' study-group assignments. The study investigators did not influence patient care in the intensive care unit.

The protocol was as follows. A 500-ml bolus of crystalloid was given every 30 minutes to achieve a central venous pressure of 8 to 12 mm Hg. If the mean arterial pressure was less than 65 mm Hg, vasopressors were given to maintain a mean arterial pressure of at least 65 mm Hg. If the mean arterial pressure was greater than 90 mm Hg, vasodilators were given until it was 90 mm Hg or below. If the central venous oxygen saturation was less than 70 percent, red cells were transfused to achieve a hematocrit of at least 30 percent. After the central venous pressure, mean arterial pressure, and hematocrit were thus optimized, if the central venous oxygen saturation was less than 70 percent, dobutamine administration was started at a dose of 2.5 μg per kilogram of body weight per minute, a dose that was increased by 2.5 μg per kilogram per minute every 30 minutes until the central venous oxygen saturation was 70 percent or higher or until a maximal dose of 20 μg per kilogram per minute was given. Dobutamine was decreased in dose or discontinued if the mean arterial pressure was less than 65 mm Hg or if the heart rate was above 120 beats per minute. To decrease oxygen consumption, patients in whom hemodynamic optimization could not be achieved received mechanical ventilation and sedatives.

Outcome Measures

The patients' temperature, heart rate, urine output, blood pressure, and central venous pressure were measured continuously for the first 6 hours of treatment and assessed every 12 hours for 72 hours. Arterial and venous blood gas values (including central venous oxygen saturation measured by in vitro co-oximetry; Nova Biomedical, Waltham, Mass.), lactate concentrations, and coagulation-related variables and clinical variables required for determination of the Acute Physiology and Chronic Health Evaluation (APACHE II) score (on a scale from 0 to 71, with higher scores indicating more severe organ dysfunction),[23] the Simplified Acute Physiology Score II (SAPS II, on a scale from 0 to 174, with higher scores indicating more severe organ dysfunction),[24] and the Multiple Organ Dysfunction Score (MODS, on a scale from 0 to 24, with higher scores indicating more severe organ dysfunction)[25] were obtained at base line (0 hours) and at 3, 6, 12, 24, 36, 48, 60, and 72 hours.[2,26] The results of laboratory tests required only for purposes of the study were made known only to the study investigators. Patients were followed for 60 days or until death. The consumption of health care resources (indicated by the duration of vasopressor therapy and mechanical ventilation and the length of the hospital stay) was also examined.

Statistical Analysis

In-hospital mortality was the primary efficacy end point. Secondary end points were the resuscitation end points, organ-dysfunction scores, coagulation-related variables, administered treatments, and the consumption of health care resources. Assuming a rate of refusal or exclusion of 10 percent, a two-sided type I error rate of 5 percent, and a power of 80 percent, we calculated that a sample size of 260 patients was required to permit the detection of a 15 percent reduction in in-hospital mortality. Kaplan–Meier estimates of mortality, along with risk ratios and 95 percent confidence intervals, were used to describe the relative risk of death. Differences between the two groups at base line were tested with the use of Student's t-test, the chi-square test, or Wilcoxon's rank-sum test. Incremental analyses of the area under the curve were performed to quantify differences during the interval from base line to six hours after the start of treatment. For the data at six hours, analysis of covariance was used with the base-line values as the covariates. Mixed models were used to assess the effect of treatment on prespecified secondary variables during the interval from 7 to 72 hours after the start of treatment.[27] An independent, 12-member external safety, efficacy, and data monitoring committee reviewed interim analyses of the data after one third and two thirds of the patients had been enrolled and at both times recommended that the trial be continued. To adjust for the two interim analyses, the alpha spending function of DeMets and Lan[28] was used to determine that a P value of 0.04 or less would be considered to indicate statistical significance.

RESULTS

Base-Line Characteristics

We evaluated 288 patients; 8.7 percent were excluded or did not consent to participate. The 263 patients enrolled were randomly assigned to undergo either standard therapy or early goal-directed therapy; 236 patients completed the initial six-hour study period.

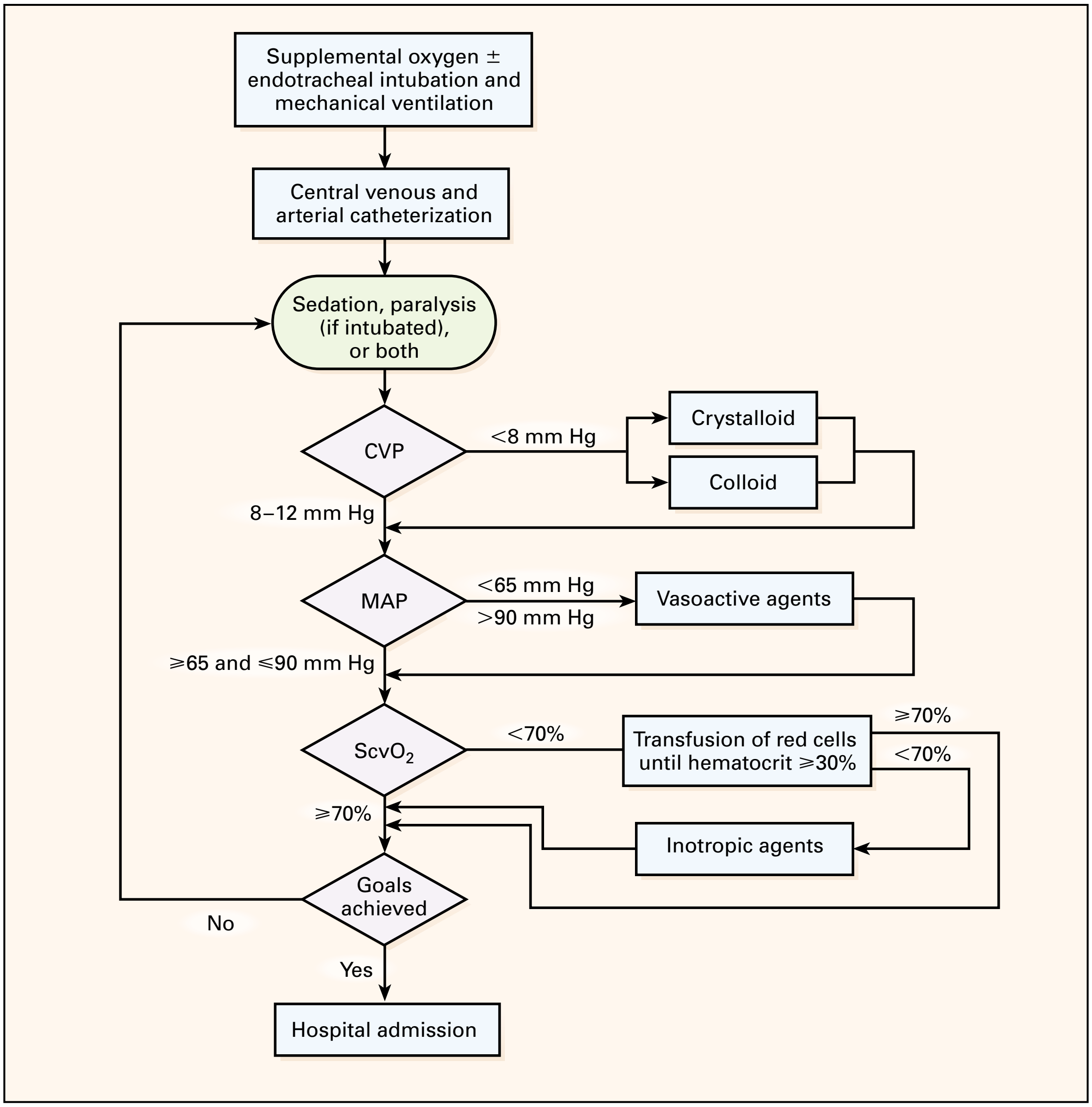

Figure 2. Protocol for Early Goal-Directed Therapy.
CVP denotes central venous pressure, MAP mean arterial pressure, and $ScvO_2$ central venous oxygen saturation.

All 263 were included in the intention-to-treat analyses. The patients assigned to standard therapy stayed a significantly shorter time in the emergency department than those assigned to early goal-directed therapy (mean [±SD], 6.3±3.2 vs. 8.0±2.1 hours; $P<0.001$). There was no significant difference between the groups in any of the base-line characteristics, including the adequacy and duration of antibiotic therapy (Table 1). Vital signs, resuscitation end points, organ-dysfunction scores, and coagulation-related variables were also similar in the two study groups at base line (Table 2).

Twenty-seven patients did not complete the initial six-hour study period (14 assigned to standard therapy and 13 assigned to early goal-directed therapy), for the following reasons: discontinuation of aggressive medical treatment (in 5 patients in each group), discontinuation of aggressive surgical treatment (in 2 patients in each group), a need for immediate surgery (in 4 patients assigned to standard therapy and in 3 assigned to early goal-directed therapy), a need for interventional urologic, cardiologic, or angiographic procedures (in 2 patients in each group), and refusal to continue participation (in 1 patient in each group) ($P=0.99$ for all comparisons). There were no significant differences between the patients who completed

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)
Age (yr)	64.4±17.1	67.1±17.4
Sex (%)		
Female	49.6	49.2
Male	50.4	50.8
Time from arrival at emergency department to enrollment		
Mean (hr)	1.5±1.7	1.3±1.5
Median (min)	50.5	59.0
Entry criteria		
Temperature (°C)	36.6±2.3	35.9±3.2
Heart rate (beats/min)	114±27	117±31
Systolic blood pressure (mm Hg)	109±34	106±36
Respiratory rate (breaths/min)	30.2±10.6	31.8±10.8
Partial pressure of carbon dioxide (mm Hg)	30.6±15.1	31.5±15.7
White-cell count (per mm^3)	14,200±9,600	13,600±8,300
Lactate (mmol/liter)	6.9±4.5	7.7±4.7
Base-line laboratory values		
Anion gap (mmol/liter)	21.4±8.5	21.7±7.6
Creatinine (mg/dl)	2.6±2.0	2.6±2.0
Blood urea nitrogen (mg/dl)	45.4±33.0	47.1±31.3
Total bilirubin (mg/dl)	1.9±3.0	1.3±1.7
γ-Glutamyltransferase (U/liter)	123±130	117±159
Albumin (g/dl)	2.8±0.7	2.8±0.7
Chronic coexisting conditions (%)†		
Alcohol use	38.7	38.5
Congestive heart failure	30.2	36.7
Coronary artery disease	23.5	26.5
Chronic obstructive pulmonary disease or emphysema	13.4	18.0
Diabetes	31.9	30.8
Human immunodeficiency virus infection	1.7	4.3
Hypertension	66.4	68.4
Liver disease	23.5	23.1
History of cancer	10.1	12.8
Neurologic disease	31.9	34.2
Renal insufficiency	21.9	21.4
Smoking	31.1	29.9
Diagnosis (%)†		
Medical condition	93.3	90.6
Pneumonia	39.5	38.5
Urosepsis	27.7	25.6
Peritonitis	4.2	3.4
Other	21.9	23.1
Surgical condition	6.7	9.4
Intraabdominal process	5.9	7.7
Abscess of the arms or legs	0.8	1.7
Types and features of sepsis (%)		
Severe sepsis	48.7	45.3
Septic shock	51.3	54.7
Sepsis syndrome	71.4	75.2
Culture positive	76.5	76.1
Culture negative	23.5	23.9
Blood culture positive	36.1	34.2
Antibiotic therapy		
Antibiotics given in the first 6 hr (%)	92.4	86.3
Antibiotics adequate (%)	94.3	96.7
Duration (days)	11.3±15.8	11.7±16.2

*Plus–minus values are means ±SD. There were no significant differences between groups in any of the variables. To convert the values for creatinine to micromoles per liter, multiply by 88.4; to convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357; and to convert the values for total bilirubin to micromoles per liter, multiply by 17.1.

†Values sum to more than 100% because patients could have more than one condition.

TABLE 2. VITAL SIGNS, RESUSCITATION END POINTS, ORGAN-DYSFUNCTION SCORES, AND COAGULATION VARIABLES.*

VARIABLE AND TREATMENT GROUP	BASE LINE (0 hr)	HOURS AFTER START OF THERAPY		
		6	0–6†	7–72‡
Heart rate (beats/min)				
Standard therapy	114±27	105±25	108±23	99±18
EGDT	117±31	103±19	105±19	96±18
P value	0.45	0.12	0.25	0.04
Central venous pressure (mm Hg)				
Standard therapy	6.1±7.7	11.8±6.8	10.5±6.8	11.6±6.1
EGDT	5.3±9.3	13.8±4.4	11.7±5.1	11.9±5.6
P value	0.57	0.007	0.22	0.68
Mean arterial pressure (mm Hg)				
Standard therapy	76±24	81±18	81±16	80±15
EGDT	74±27	95±19	88±16	87±15
P value	0.60	<0.001	<0.001	<0.001
Central venous oxygen saturation (%)				
Standard therapy	49.2±13.3	66.0±15.5	65.4±14.2	65.3±11.4
EGDT	48.6±11.2	77.3±10.0	71.6±10.2	70.4±10.7
P value	0.49	<0.001	<0.001	<0.001
Lactate (mmol/liter)				
Standard therapy	6.9±4.5	4.9±4.7	5.9±4.2	3.9±4.4
EGDT	7.7±4.7	4.3±4.2	5.5±4.2	3.0±4.4
P value	0.17	0.01	0.62	0.02
Base deficit (mmol/liter)				
Standard therapy	8.9±7.5	8.0±6.4	8.6±6.0	5.1±6.7
EGDT	8.9±8.1	4.7±5.8	6.7±5.6	2.0±6.6
P value	0.81	<0.001	0.006	<0.001
Arterial pH				
Standard therapy	7.32±0.19	7.31±0.15	7.31±0.12	7.36±0.12
EGDT	7.31±0.17	7.35±0.11	7.33±0.13	7.40±0.12
P value	0.40	<0.001	0.26	<0.001
APACHE II score				
Standard therapy	20.4±7.4	17.6±6.2	—	15.9±6.4
EGDT	21.4±6.9	16.0±6.9	—	13.0±6.3
P value	0.27	<0.001		<0.001
SAPS II				
Standard therapy	48.8±11.1	45.5±12.3	—	42.6±11.5
EGDT	51.2±11.1	42.1±13.2	—	36.9±11.3
P value	0.08	<0.001		<0.001

VARIABLE AND TREATMENT GROUP	BASE LINE (0 hr)	HOURS AFTER START OF THERAPY		
		6	0–6†	7–72‡
MODS				
Standard therapy	7.3±3.1	6.8±3.7	—	6.4±4.0
EGDT	7.6±3.1	5.9±3.7	—	5.1±3.9
P value	0.44	<0.001		<0.001
Hematocrit (%)				
Standard therapy	34.7±8.5	32.0±6.9	—	30.1±4.1
EGDT	34.6±8.3	33.3±4.8	—	32.1±4.2
P value	0.91	0.03		<0.001
Prothrombin time (sec)				
Standard therapy	16.5±6.3	17.5±8.1	—	17.3±6.1
EGDT	15.8±5.0	16.0±3.6	—	15.4±6.1
P value	0.17	0.02		0.001
Partial-thromboplastin time (sec)				
Standard therapy	32.9±12.0	37.6±21.0	—	37.0±14.2
EGDT	33.3±20.4	32.6±8.7	—	34.6±14.1
P value	0.17	0.01		0.06
Fibrinogen (mg/dl)				
Standard therapy	361±198	319±142	—	358±134
EGDT	370±209	300±157	—	342±134
P value	0.51	0.01		0.21
Fibrin-split products (μg/dl)				
Standard therapy	39.0±61.6	54.9±84.0	—	62.0±71.4
EGDT	44.8±71.3	45.8±66.0	—	39.2±71.2
P value	0.76	0.13		<0.001
D-Dimer (μg/ml)				
Standard therapy	3.66±8.45	5.48±11.95	—	5.65±9.06
EGDT	4.46±10.70	3.98±9.41	—	3.34±9.02
P value	0.71	0.05		0.006
Platelet count (per mm³)				
Standard therapy	205,000±110,000	164,000±84,000	—	144,000±84,000
EGDT	220,000±135,000	156,000±90,000	—	139,000±82,000
P value	0.65	0.001		0.51

*Plus–minus values are means ±SD. EGDT denotes early goal-directed therapy, APACHE II Acute Physiology and Chronic Health Evaluation, SAPS II Simplified Acute Physiology Score II, and MODS Multiple Organ Dysfunction Score.

†For the period from base line (0 hours) to 6 hours, the area under the curve was calculated, except for noncontinuous variables (as indicated by dashes).

‡For the period from 7 to 72 hours, the adjusted mean value was obtained from a mixed model.

the initial six-hour study period and those who did not in any of the base-line characteristics or base-line vital signs, resuscitation end points, organ-dysfunction scores, or coagulation-related variables (data not shown).

Vital Signs and Resuscitation End Points

During the initial six hours after the start of therapy, there was no significant difference between the two study groups in the mean heart rate (P=0.25) or central venous pressure (P=0.22) (Table 2). During this period, the mean arterial pressure was significantly lower in the group assigned to standard therapy than in the group assigned to early goal-directed therapy (P<0.001), but in both groups the goal of 65 mm Hg or higher was met by all the patients. The goal of 70 percent or higher for central venous oxygen saturation was met by 60.2 percent of the patients in the standard-therapy group, as compared with 94.9 percent of those in the early-therapy group (P<0.001). The combined hemodynamic goals for central venous pressure, mean arterial pressure, and urine output (with adjustment for patients with end-stage renal failure) were achieved in 86.1 percent of the standard-therapy group, as compared with 99.2 percent of the early-therapy group (P<0.001). During this period, the patients assigned to standard therapy had a significantly lower central venous oxygen saturation (P<0.001) and a greater base deficit (P=0.006) than those assigned to early goal-directed therapy; the two groups had similar lactate concentrations (P=0.62) and similar pH values (P=0.26).

During the period from 7 to 72 hours after the start of treatment, the patients assigned to standard therapy had a significantly higher heart rate (P=0.04) and a significantly lower mean arterial pressure (P<0.001) than the patients assigned to early goal-directed therapy; the two groups had a similar central venous pressure (P=0.68). During this period, those assigned to standard therapy also had a significantly lower central venous oxygen saturation than those assigned to early goal-directed therapy (P<0.001), as well as a higher lactate concentration (P=0.02), a greater base deficit (P<0.001), and a lower pH (P<0.001).

Organ Dysfunction and Coagulation Variables

During the period from 7 to 72 hours, the APACHE II score, SAPS II, and MODS were significantly higher in the patients assigned to standard therapy than in the patients assigned to early goal-directed therapy (P<0.001 for all comparisons) (Table 2). During this period, the prothrombin time was significantly greater in the patients assigned to standard therapy than in those assigned to early goal-directed therapy (P=0.001), as was the concentration of fibrin-split products (P<0.001) and the concentration of D-dimer (P=0.006). The two groups had a similar partial-thromboplastin time (P=0.06), fibrinogen concentration (P=0.21), and platelet count (P=0.51) (Table 2).

Mortality

In-hospital mortality rates were significantly higher in the standard-therapy group than in the early-therapy group (P=0.009), as was the mortality at 28 days (P=0.01) and 60 days (P=0.03) (Table 3). The difference between the groups in mortality at 60 days primarily reflected the difference in in-hospital mortality. Similar results were obtained after data from the 27 patients who did not complete the initial six-hour study period were excluded from the analysis (data not shown). The rate of in-hospital death due to sudden cardiovascular collapse was significantly higher in the standard-therapy group than in the early-therapy group (P=0.02); the rate of death due to multiorgan failure was similar in the two groups (P=0.27).

Administered Treatments

During the initial six hours, the patients assigned to early goal-directed therapy received significantly more fluid than those assigned to standard therapy (P<0.001) and more frequently received red-cell transfusion (P<0.001) and inotropic support (P<0.001), whereas similar proportions of patients in the two groups required vasopressors (P=0.62) and mechanical ventilation (P=0.90) (Table 4). During the period from 7 to 72 hours, however, the patients assigned to standard therapy received significantly more fluid than those assigned to early goal-directed therapy (P=0.01) and more often received red-cell transfusion (P<0.001) and vasopressors (P=0.03) and underwent mechanical ventilation (P<0.001) and pulmonary-artery catheterization (P=0.04); the rate of use of inotropic agents was similar in the two groups (P=0.14) (Table 4). During the overall period from base line to 72 hours after the start of treatment, there was no significant difference between the two groups in the total volume of fluid administered (P=0.73) or the rate of use of inotropic agents (P=0.15), although a greater proportion of the patients assigned to standard therapy than of those assigned to early goal-direct-

TABLE 3. KAPLAN–MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.*

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	0.03
Causes of in-hospital death‡				
Sudden cardiovascular collapse	25/119 (21.0)	12/117 (10.3)	—	0.02
Multiorgan failure	26/119 (21.8)	19/117 (16.2)	—	0.27

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.

†Percentages were calculated by the Kaplan–Meier product-limit method.

‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

TABLE 4. TREATMENTS ADMINISTERED.*

TREATMENT	HOURS AFTER THE START OF THERAPY		
	0–6	7–72	0–72
Total fluids (ml)			
Standard therapy	3499±2438	10,602±6,216	13,358±7,729
EGDT	4981±2984	8,625±5,162	13,443±6,390
P value	<0.001	0.01	0.73
Red-cell transfusion (%)			
Standard therapy	18.5	32.8	44.5
EGDT	64.1	11.1	68.4
P value	<0.001	<0.001	<0.001
Any vasopressor (%)†			
Standard therapy	30.3	42.9	51.3
EGDT	27.4	29.1	36.8
P value	0.62	0.03	0.02
Inotropic agent (dobutamine) (%)			
Standard therapy	0.8	8.4	9.2
EGDT	13.7	14.5	15.4
P value	<0.001	0.14	0.15
Mechanical ventilation (%)			
Standard therapy	53.8	16.8	70.6
EGDT	53.0	2.6	55.6
P value	0.90	<0.001	0.02
Pulmonary-artery catheterization (%)‡			
Standard therapy	3.4	28.6	31.9
EGDT	0	18.0	18.0
P value	0.12	0.04	0.01

*Plus–minus values are means ±SD. Because some patients received a specific treatment both during the period from 0 to 6 hours and during the period from 7 to 72 hours, the cumulative totals for those two periods do not necessarily equal the values for the period from 0 to 72 hours. EGDT denotes early goal-directed therapy.

†Administered vasopressors included norepinephrine, epinephrine, dopamine, and phenylephrine hydrochloride.

‡All pulmonary-artery catheters were inserted while patients were in the intensive care unit.

ed therapy received vasopressors (P=0.02) and mechanical ventilation (P=0.02) and underwent pulmonary-artery catheterization (P=0.01), and a smaller proportion required red-cell transfusion (P<0.001). Though similar between the groups at base line (P=0.91), the mean hematocrit during this 72-hour period was significantly lower in the standard-therapy group than in the early-therapy group (P<0.001). Despite the transfusion of red cells, it was significantly lower than the value obtained at base line in each group (P<0.001 for both comparisons) (Table 2).

Consumption of Health Care Resources

There were no significant differences between the two groups in the mean duration of vasopressor therapy (2.4±4.2 vs. 1.9±3.1 days, P=0.49), the mean duration of mechanical ventilation (9.0±13.1 vs. 9.0±11.4 days, P=0.38), or the mean length of stay in the hospital (13.0±13.7 vs. 13.2±13.8 days, P=0.54). However, of the patients who survived to hospital discharge, those assigned to standard therapy had stayed a significantly longer time in the hospital than those assigned to early goal-directed therapy (18.4±15.0 vs. 14.6±14.5 days, P=0.04).

DISCUSSION

Severe sepsis and septic shock are common and are associated with substantial mortality and substantial consumption of health care resources. There are an estimated 751,000 cases (3.0 cases per 1000 population) of sepsis or septic shock in the United States each year, and they are responsible for as many deaths each year as acute myocardial infarction (215,000, or 9.3 percent of all deaths).[29] In elderly persons, the incidence of sepsis or septic shock and the related mortality rates are substantially higher than those in younger persons. The projected growth of the elderly population in the United States will contribute to an increase in incidence of 1.5 percent per year, yielding an estimated 934,000 and 1,110,000 cases by the years 2010 and 2020, respectively.[29] The present annual cost of this disease is estimated to be $16.7 billion.[29]

The transition from the systemic inflammatory response syndrome to severe sepsis and septic shock involves a myriad of pathogenic changes, including circulatory abnormalities that result in global tissue hypoxia.[1,2] These pathogenic changes have been the therapeutic target of previous outcome studies.[12] Although this transition occurs over time, both out of the hospital and in the hospital, in outcome studies interventions have usually been initiated after admission to the intensive care unit.[12] In studies of goal-directed hemodynamic optimization, in particular, there was no benefit in terms of outcome with respect to normal and supranormal hemodynamic end points, as well as those guided by mixed venous oxygen saturation.[9,13] In contrast, even though we enrolled patients with lower central venous oxygen saturation and lower central venous pressure than those studied by Gattinoni et al.[9] and with a higher lactate concentration than those studied by Hayes et al.,[13] we found significant benefits with respect to outcome when goal-directed therapy was applied at an earlier stage of disease. In patients with septic shock, for example, Hayes et al. observed a higher in-hospital mortality rate with aggressive hemodynamic optimization in the intensive care unit (71 percent) than with control therapy (52 percent), whereas we observed a lower mortality rate in patients with septic shock assigned to early goal-directed therapy (42.3 percent) than in those assigned to standard therapy (56.8 percent).

The benefits of early goal-directed therapy in terms of outcome are multifactorial. The incidence of death due to sudden cardiovascular collapse in the standard-therapy group was approximately double that in the group assigned to early goal-directed therapy, suggesting that an abrupt transition to severe disease is an important cause of early death. The early identification of patients with insidious illness (global tissue hypoxia accompanied by stable vital signs) makes possible the early implementation of goal-directed therapy. If sudden cardiovascular collapse can be prevented, the subsequent need for vasopressors, mechanical ventilation, and pulmonary-artery catheterization (and their associated risks) diminishes. In addition to being a stimulus of the systemic inflammatory response syndrome, global tissue hypoxia independently contributes to endothelial activation and disruption of the homeostatic balance among coagulation, vascular permeability, and vascular tone.[30] These are key mechanisms leading to microcirculatory failure, refractory tissue hypoxia, and organ dysfunction.[2,30] When early therapy is not comprehensive, the progression to severe disease may be well under way at the time of admission to the intensive care unit.[16] Aggressive hemodynamic optimization and other therapy[12] undertaken thereafter may be incompletely effective or even deleterious.[13]

The value of measurements of venous oxygen saturation at the right atrium or superior vena cava (central venous oxygen saturation) instead of at the pulmonary artery (mixed venous oxygen saturation) has been debated,[31] in particular, when saturation values are above 65 percent. In patients in the intensive care unit who have hyperdynamic septic shock, the mixed venous oxygen saturation is rarely below 65 percent.[32] In contrast, our patients were examined during the phase of resuscitation in which the delivery of supplemental oxygen is required (characterized by a decreased mixed venous oxygen saturation and an increased lactate concentration), when the central venous oxygen saturation generally exceeds the mixed venous oxygen saturation.[33,34] The initial central venous oxygen saturation was less than 50 percent in both study groups. The mixed venous oxygen saturation is estimated to be 5 to 13 percent lower in the pulmonary artery[33] and 15 percent lower in the splanchnic bed.[35] Though not numerically equivalent, these ranges of values are pathologically equivalent and are associated with high mortality.[32,36] Among all the patients in the current study in whom the goals with respect to central venous pressure, mean arterial pressure, and urine output during the first six hours were met, 39.8 percent of those assigned to standard therapy were still in this oxygen-dependent phase of resuscitation at six hours, as compared with 5.1 percent of those assigned to early goal-directed therapy. The combined 56.5 percent in-hospital mortality of this 39.8 percent of patients, who were at high risk for hemodynamic compromise, is consistent with the results of previous studies in the intensive care unit.[32,36]

In an open, randomized, partially blinded trial, there are unavoidable interactions during the initial period of the study. As the study progressed, the patients in the standard-therapy group may have received some form of goal-directed therapy, reducing the treatment effect. This reduction may have been offset by the slight but inherent bias resulting from the direct influence of the investigators on the care of the patients in the treatment group. The potential period of bias was 9.9 ± 19.5 percent of the overall hospital stay in the standard-therapy group and 7.2 ± 12.0 percent of that in the group assigned to early goal-directed therapy ($P=0.20$). This interval was minimal in comparison with those in previous studies[9,13] because the clinicians who assumed responsibility for the remainder of hospitalization were completely blinded to the randomization order.

We conclude that goal-directed therapy provided at the earliest stages of severe sepsis and septic shock, though accounting for only a brief period in comparison with the overall hospital stay, has significant short-term and long-term benefits. These benefits arise from the early identification of patients at high risk for cardiovascular collapse and from early therapeutic intervention to restore a balance between oxygen delivery and oxygen demand. In the future, investigators conducting outcome trials in patients with sepsis should consider the quality and timing of the resuscitation before enrollment as an important outcome variable.

Supported by the Henry Ford Health Systems Fund for Research, a Weatherby Healthcare Resuscitation Fellowship, Edwards Lifesciences (which provided oximetry equipment and catheters), and Nova Biomedical (which provided equipment for laboratory assays).

We are indebted to the nurses, residents, senior staff attending physicians, pharmacists, patient advocates, technicians, and billing and administrative personnel of the Department of Emergency Medicine; to the nurses and technicians of the medical and surgical intensive care units; and to the staff members of the Department of Respiratory Therapy, Department of Pathology, Department of Medical Records, and Department of Admitting and Discharge for their patience and their cooperation in making this study possible.

APPENDIX

The following persons participated in the study: **External Safety, Efficacy, and Data Monitoring Committee:** A. Connors (Charlottesville, Va.), S. Conrad (Shreveport, La.), L. Dunbar (New Orleans), S. Fagan (Atlanta), M. Haupt (Portland, Oreg.), R. Ivatury (Richmond, Va.), G. Martin (Detroit), D. Milzman (Washington, D.C.), E. Panacek (Palo Alto, Calif.), M. Rady (Scottsdale, Ariz.), M. Rudis (Los Angeles), and S. Stern (Ann Arbor, Mich.); **the Early-Goal-Directed-Therapy Collaborative Group:** B. Derechyk, W. Rittinger, G. Hayes, K. Ward, M. Mullen, V. Karriem, J. Urrunaga, M. Gryzbowski, A. Tuttle, W. Chung, P. Uppal, R. Nowak, D. Powell, T. Tyson, T. Wadley, G. Galletta, K. Rader, A. Goldberg, D. Amponsah, D. Morris, K. Kumasi-Rivers, B. Thompson, D. Ander, C. Lewandowski, J. Kahler, K. Kralovich, H. Horst, S. Harpatoolian, A. Latimer, M. Schubert, M. Fallone, B. Fasbinder, L. Defoe, J. Hanlon, A. Okunsanya, B. Sheridan, Q. Rivers, H. Johnson, B. Sessa-Boji, K. Gunnerson, D. Fritz, K. Rivers, S. Moore, D. Huang, and J. Farrerer (Henry Ford Hospital, Detroit).

REFERENCES

1. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study. JAMA 1995;273:117-23.

2. Beal AL, Cerra FB. Multiple organ failure syndrome in the 1990s: systemic inflammatory response and organ dysfunction. JAMA 1994;271:226-33.

3. Nguyen HB, Rivers EP, Havstad S, et al. Critical care in the emergency department: a physiologic assessment and outcome evaluation. Acad Emerg Med 2000;7:1354-61.

4. Lundberg JS, Perl TM, Wiblin T, et al. Septic shock: an analysis of outcomes for patients with onset on hospital wards versus intensive care units. Crit Care Med 1998;26:1020-4.
5. Lefrant JY, Muller L, Bruelle P, et al. Insertion time of the pulmonary artery catheter in critically ill patients. Crit Care Med 2000;28:355-9.
6. Rady MY, Rivers EP, Nowak RM. Resuscitation of the critically ill in the ED: responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate. Am J Emerg Med 1996;14:218-25.
7. Cortez A, Zito J, Lucas CE, Gerrick SJ. Mechanism of inappropriate polyuria in septic patients. Arch Surg 1977;112:471-6.
8. Elliott DC. An evaluation of the end points of resuscitation. J Am Coll Surg 1998;187:536-47.
9. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 1995;333:1025-32.
10. Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM. Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand. Chest 1989;95:1216-21.
11. Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time. Crit Care Med 1998;26:2078-86.
12. Opal SM, Cross AS. Clinical trials for severe sepsis: past failures, and future hopes. Infect Dis Clin North Am 1999;13:285-97.
13. Hayes MA, Timmins AC, Yau EHS, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717-22.
14. Connors AFJ, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 1996;276:889-97.
15. Haupt MT. Goal-oriented hemodynamic therapy. N Engl J Med 1996;334:799.
16. Hinds C, Watson D. Manipulating hemodynamics and oxygen transport in critically ill patients. N Engl J Med 1995;333:1074-5.
17. Shoemaker WC. Goal-oriented hemodynamic therapy. N Engl J Med 1996;334:799-800.
18. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-74.
19. Sands KE, Bates DW, Lanken PN, et al. Epidemiology of sepsis syndrome in 8 academic medical centers. JAMA 1997;278:234-40.
20. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2000;284:3043-5.
21. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. Crit Care Med 1999;27:639-60.
22. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462-74.
23. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
24. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957-63. [Erratum, JAMA 1994;271:1321.]
25. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple Organ Dysfunction Score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638-52.
26. Pittet D, Thievent B, Wenzel RP, Li N, Gurman G, Suter PM. Importance of pre-existing co-morbidities for prognosis of septicemia in critically ill patients. Intensive Care Med 1993;19:265-72.
27. Rutter CM, Elashoff RM. Analysis of longitudinal data: random coefficient regression modelling. Stat Med 1994;13:1211-31.
28. DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. Stat Med 1994;13:1341-56.
29. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303-10.
30. Karimova A, Pinsky DJ. The endothelial response to oxygen deprivation: biology and clinical implications. Intensive Care Med 2001;27:19-31.
31. Edwards JD, Mayall RM. Importance of the sampling site for measurement of mixed venous oxygen saturation in shock. Crit Care Med 1998;26:1356-60.
32. Krafft P, Steltzer H, Hiesmayr M, Klimscha W, Hammerle AF. Mixed venous oxygen saturation in critically ill septic shock patients: the role of defined events. Chest 1993;103:900-6.
33. Lee J, Wright F, Barber R, Stanley L. Central venous oxygen saturation in shock: a study in man. Anesthesiology 1972;36:472-8.
34. Scheinman MM, Brown MA, Rapaport E. Critical assessment of use of central venous oxygen saturation as a mirror of mixed venous oxygen in severely ill cardiac patients. Circulation 1969;40:165-72.
35. Dahn MS, Lange MP, Jacobs LA. Central mixed and splanchnic venous oxygen saturation monitoring. Intensive Care Med 1988;14:373-8.
36. Heiselman D, Jones J, Cannon L. Continuous monitoring of mixed venous oxygen saturation in septic shock. J Clin Monit 1986;2:237-45.