Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy

A Randomized Clinical Trial

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Context Goal-directed resuscitation for severe sepsis and septic shock has been reported to reduce mortality when applied in the emergency department.

Objective To test the hypothesis of noninferiority between lactate clearance and central venous oxygen saturation ($ScvO_2$) as goals of early sepsis resuscitation.

Design, Setting, and Patients Multicenter randomized, noninferiority trial involving patients with severe sepsis and evidence of hypoperfusion or septic shock who were admitted to the emergency department from January 2007 to January 2009 at 1 of 3 participating US urban hospitals.

Interventions We randomly assigned patients to 1 of 2 resuscitation protocols. The $ScvO_2$ group was resuscitated to normalize central venous pressure, mean arterial pressure, and $ScvO_2$ of at least 70%; and the lactate clearance group was resuscitated to normalize central venous pressure, mean arterial pressure, and lactate clearance of at least 10%. The study protocol was continued until all goals were achieved or for up to 6 hours. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment.

Main Outcome Measure The primary outcome was absolute in-hospital mortality rate; the noninferiority threshold was set at Δ equal to –10%.

Results Of the 300 patients enrolled, 150 were assigned to each group and patients were well matched by demographic, comorbidities, and physiological features. There were no differences in treatments administered during the initial 72 hours of hospitalization. Thirty-four patients (23%) in the $ScvO_2$ group died while in the hospital (95% confidence interval [CI], 17%-30%) compared with 25 (17%; 95% CI, 11%-24%) in the lactate clearance group. This observed difference between mortality rates did not reach the predefined –10% threshold (intent-to-treat analysis: 95% CI for the 6% difference, –3% to 15%). There were no differences in treatment-related adverse events between the groups.

Conclusion Among patients with septic shock who were treated to normalize central venous and mean arterial pressure, additional management to normalize lactate clearance compared with management to normalize $ScvO_2$ did not result in significantly different in-hospital mortality.

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THE RATE OF SEVERE SEPSIS HOSpitalizations has doubled during the last decade with estimates indicating that at least 750 000 persons are affected annually in the United States.[1-3] Approximately, 500 000 patients with severe sepsis in the United States annually are initially treated in emergency departments.[4] The Surviving Sepsis Campaign international consensus guidelines recommend protocol-driven treatment that uses quantitative resuscitation for emergency department patients with severe sepsis and septic shock.[5]

Quantitative resuscitation refers to the use of an explicit protocol that targets predefined physiological or laboratory goals to be achieved within the first several hours. This concept was pioneered by Shoemaker et al[6] to treat high-risk surgical patients. Results of a recent meta-analysis indicated a survival benefit associated with the use of

See also p 777 and Patient Page.

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an early and quantitative resuscitation strategy applied to heterogeneous populations of patients with sepsis.[7]

The optimal goals for quantitative resuscitation of sepsis remain uncertain. It is generally accepted that hemodynamic targets should include some measure of the adequacy of cardiac preload, such as central venous pressure, and perfusion pressure, such as mean arterial pressure.[8] A more controversial issue is the method of determining tissue oxygen delivery. Citing a single-center study, the Surviving Sepsis Campaign guidelines recommend the use of central venous oxygen saturation ($ScvO_2$) or mixed venous oxygen saturation to assess the balance of tissue oxygen delivery and consumption[9]; however, since its publication in 2001 a substantial amount of controversy about this single-center study has been generated in the scientific community.[10-12] Additionally, recently published practice surveys have indicated that the time, expertise, and specialized equipment required to measure $ScvO_2$ collectively pose a major barrier to the implementation of protocol-driven quantitative resuscitation programs.[13,14] In contrast, lactate clearance, derived from calculating the change in lactate concentration from 2 blood specimens drawn at different times, potentially represents a more accessible method to assess tissue oxygen delivery.[15,16]

To address the potential utility of lactate clearance as a substitute for $ScvO_2$, we conducted a multicenter, randomized trial among patients presenting to the emergency department with severe sepsis and septic shock, with the primary hypothesis that early resuscitation targeting lactate clearance as the marker of adequacy of oxygen delivery was noninferior to the currently recommended $ScvO_2$ monitoring for the outcome of in-hospital mortality.

METHODS

Study Design

This study was a prospective randomized, parallel group, nonblinded, clinical trial designed to assess the noninferiority of lactate clearance vs $ScvO_2$ as the protocol goal that evaluated adequacy of oxygen delivery during early quantitative resuscitation of severe sepsis and septic shock. The trial took place from January 2007 to January 2009 in the emergency departments of 3 large urban medical centers in the United States. The research protocol was approved by the local institutional review boards and performed in accordance with Good Clinical Practice guidelines.

Participants

Patients with severe sepsis or septic shock were assessed for inclusion, which required that patients be older than 17 years with confirmed or presumed infection, have 2 or more systemic inflammatory response criteria,[17] and have hypoperfusion evidenced by either a systolic blood pressure lower than 90 mm Hg after a minimum of 20 mL/kg rapid volume challenge or a blood lactate concentration of at least 36 mg/dL (4 mmol/L). The criteria for exclusion from the study were pregnancy, any primary diagnosis other than sepsis, suspected requirement for immediate surgery within 6 hours of diagnosis, an absolute contraindication to chest or neck central venous catheterization, cardiopulmonary resuscitation, transfer from another institution with a sepsis-specific resuscitative therapy underway, and advanced directive orders that would restrict the study procedure. Using a 24-hour day, 7-day-week method that was previously established for the routine clinical care of sepsis patients at each of the participating institutions, an alert was sent to inform clinical care resources when patients were identified as candidates for early aggressive resuscitation. This alert was also received by study staff who responded and screened the patients for study enrollment. Each enrolled patient or the patient's legally authorized next of kin provided written informed consent prior to collection of data. Patients or family members self-identified their race.

Treatment Assignment

Patients were randomly assigned to 1 of 2 groups (eFigure, available at http://www.jama.com). Each group received structured quantitative resuscitation while in the emergency department. The $ScvO_2$ group was resuscitated by sequentially providing therapy needed to meet thresholds of central venous pressure, followed by mean arterial pressure, and then $ScvO_2$. The lactate clearance group had similarly targeted thresholds in central venous pressure, followed by mean arterial pressure, and then lactate clearance instead of $ScvO_2$. Standard measures were used to ensure appropriate concealment of group assignment until after informed consent was obtained. The group assignment sequence was generated by an independent statistician using a parallel design, balanced randomization schedule (1:1 ratio of cases and controls), using the PROC PLAN function in SAS incorporating a sample size of 300, block size equal to 10, with a seed of 6 457 149 (SAS Institute Inc, Cary, North Carolina). After written informed consent was obtained, study staff opened an opaque sealed envelope containing the randomization assignment. Study staff then enforced the study protocol. By design, the clinical staff in the emergency departments could not be blinded to group assignment; however, the clinical staff (physicians and nurses) who assumed subsequent care of the patients in the intensive care units (ICUs) were unaware of group assignment. Prior to entry in the study, patients were cared for by emergency physicians, who provided basic care processes according to participating institutional standards.

Treatment Interventions

Appropriate specimens were taken for culture, and antibiotics were administered as soon as practical. Blood pressure was monitored by either noninvasive automated cuff sphygmomanometer or arterial catheter according to the clinical team's preference. All patients received chest or neck central venous catheter capable of measuring continuous $ScvO_2$ (PreSep, Edwards Lifesciences, Irvine, California).

Patients randomized to the $ScvO_2$ group had their central venous cath-

eters connected to a computerized spectrophotometer (Edwards Lifesciences) that displayed continuous $Scv\overline{O}_2$ readings. The patients were then cared for according to the prespecified treatment plan. First, isotonic crystalloid was administered in boluses to achieve a central venous pressure of 8 mm Hg or higher. Second, the mean arterial pressure goal of 65 mm Hg or higher, if not achieved with fluid administration, was targeted by initiating and titrating vasopressors (dopamine or norepinephrine) to achieve this desired blood pressure goal. Finally, the $Scv\overline{O}_2$ goal of 70% or higher was targeted after central venous and mean arterial pressure goals were met. If the $Scv\overline{O}_2$ was lower than 70% and the hematocrit was lower than 30%, packed red blood cells were transfused to achieve a hematocrit of at least 30%. If the $Scv\overline{O}_2$ remained lower than 70% after the hematocrit was 30% or higher, dobutamine was initiated and titrated in attempts to achieve an $Scv\overline{O}_2$ of at least 70%.

Patients randomized to the lactate clearance group received an identical central venous catheter capable of measuring continuous $Scv\overline{O}_2$. The primary intervention consisted of the act of not connecting the catheter to the computerized spectrophotometer thus preventing display of $Scv\overline{O}_2$ at any time in the emergency department. These patients were cared for according to an identical prespecified treatment plan for central venous and mean arterial pressure targets as outlined for the $Scv\overline{O}_2$ group. However, in the lactate clearance group, clinicians used lactate clearance instead of $Scv\overline{O}_2$ as the last resuscitation goal in the protocol and targeted a lactate clearance of at least 10%.[15,16] The lactate clearance was defined by the equation $[(\text{lactate}_{\text{initial}} - \text{lactate}_{\text{delayed}})/\text{lactate}_{\text{initial}}] \times 100\%$, for which *lactate initial* was the measurement at the start of the resuscitation and *lactate delayed* was another measurement after a minimum of 2 hours after resuscitation was initiated. If the lactate clearance was not at least 10% at the first delayed measurement and the hematocrit was less than 30%, packed red blood cells were transfused to achieve a hematocrit of at least 30%. If the lactate clearance remained lower than 10% after the hematocrit was at least 30%, dobutamine was initiated and titrated in attempts to achieve a lactate clearance of at least 10%. When treatment was continued due to lactate clearance less than 10%, subsequent lactate measurements were performed at a minimum of 1-hour intervals and repeat lactate clearance calculated. Lactate measurements were performed using venous whole blood samples using US Food and Drug Administration–approved devices performed either at the point of care or in the central hospital laboratory, according to participating institutional standards.[18] The lactate clearance goal was met by a lactate clearance of at least 10% or if both the initial and delayed lactate concentrations were not elevated (≤18 mg/dL [2 mmol/L]).

Study patients were treated in the emergency department during the entire study treatment period, from randomization to either of the 2 study termination criteria: all treatment goals were achieved or 6 hours had elapsed. Patients were then transferred to an ICU where the critical care physicians, unencumbered by the study protocol in any way, assumed the care of all patients. The study investigators did not provide care for the patients or influence their care in the ICU.

As a safety measure, clinical physicians could elect study group crossover. For patients assigned to the $Scv\overline{O}_2$ group, clinicians could order a second lactate concentration to calculate the lactate clearance. In the lactate clearance group, the clinician could request to connect the central venous catheter to monitor $Scv\overline{O}_2$. To execute 1 of these options, the clinician was required to indicate clinical deterioration based on 1 of the following criteria: (1) falling systolic blood pressure or inadequate urine output (<0.5 mL/kg per hour); (2) worsening ventilatory status based on either clinical (respiratory rate, oxygen saturation, or oxygen requirement), arterial blood gas, or mechanical ventilator parameters; or (3) worsened mental status. Patients for whom the clinicians enacted the study group crossover methods were assessed using an intent-to-treat analysis of the original group assignment.

Assessments and Outcome Measures

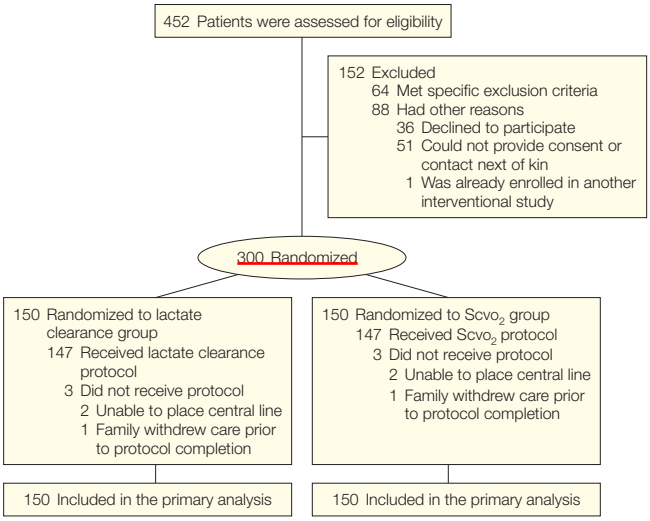
During the study resuscitation treatment period, the patient's physiological parameters were measured routinely. All data needed to calculate the Simplified Acute Physiology Score (SAPS) II,[19] Sequential Organ Failure Assessment (SOFA) score,[20] and the Mortality in Emergency Department Sepsis[21] were collected. After ICU admission, patients were assessed daily for 72 hours and detailed data were collected. Patients were followed up until hospital discharge or death.

The primary end point was absolute in-hospital mortality rate. Secondary end points were ICU length of stay, hospital length of stay, ventilator-free days, and new onset multiple organ failure. Other end points assessed were the number of resuscitative goals achieved, administered treatments, and predefined protocol-related serious adverse events.

Statistical Analysis

The sample size calculation and primary analytical plan centered on the hypothesis of noninferiority of lactate clearance vs $Scv\overline{O}_2$. For the sample size estimate, previously published data suggested a 25% primary outcome event rate for the $Scv\overline{O}_2$ group; we predicted no difference between the groups for the primary outcome event rate, and we set the noninferiority margin (Δ) at –10%.[22-24] The –10% margin was chosen because it represented a two-thirds proportion of the active comparator's ($Scv\overline{O}_2$ group) established superiority in a similar clinical trial[9] and large databases indicate that the mortality rate for severe sepsis can be expected to vary up to 10% between both state-of-the art medical facilities and regions of the United States.[25] Using a 1-sided test of noninferiority, assuming a control group mortality rate of 25% and $\alpha = .05$, a sample size of 150 per group gave 71% power to deter-

Figure. Study Flow Diagram



$ScvO_2$ indicates central venous oxygen saturation.

mine the intervention did not increase mortality by more than 10%.

When appropriate, categorical data were compared using a χ^2 test or Fisher exact test and continuous variables were compared with a Mann-Whitney U test or unpaired *t* test, 2-sided with $P < .05$ considered significant (StatsDirect v 2.7.7, Cheshire, England). Two preplanned blinded interim safety analyses were performed after one-third and two-thirds of the participants were enrolled, and these results were reviewed by an independent safety monitor who had the authority to terminate the study for safety concerns. No sample size adjustments were planned during the interim analyses. We planned both intent-to-treat and per-protocol analyses after study completion.

RESULTS

Of 452 patients who underwent screening for eligibility, 300 underwent randomization (FIGURE). Of these 300 patients, the same pattern of protocol noncompletion was observed in each group: 2 because a chest or neck central venous catheter could not be placed and 1 because family members had decided to withdraw support before the research procedure was completed. One patient in the lactate clearance group had the crossover enacted by a physician after all study goals had been met. The $ScvO_2$ value in this patient was normal, so no treatment changes were made. Because the study treatment period had ended, this patient was analyzed in the lactate clearance group for both the intent-to-treat and per-protocol analyses. None were lost to follow-up or voluntarily withdrew from the study, leaving 150 patients in each group for the intent-to-treat analysis and 147 in each group for the per-protocol analysis.

The baseline characteristics of the 2 groups are shown in TABLE 1 and in TABLE 2. There were no significant differences between the groups in demographics, comorbid conditions, severity of illness scores, or suspected site of infection. The lungs were the most common source of infection, and 38% of patients had a blood specimen that yielded growth of bacteria, whereas 84% had at least 1 culture specimen that was positive. The median time from emergency department triage to eligibility was 111 minutes (interquartile range [IQR], 56-192 minutes) in the lactate clearance group and 105 minutes (IQR, 60-175 minutes) in the $ScvO_2$ group ($P = .67$); the median time from eligibility to study entry was 14 minutes (IQR, 1-48 minutes) in the lactate clearance group and 13 minutes (IQR, 1-55 minutes) in the $ScvO_2$ group ($P = .72$). Prior to enrollment in the study, the mean (SD) amount of intravenous fluid administered was 2.3 L (1.4 L) in the lactate clearance group and 2.4 L (1.4 L) in the $ScvO_2$ group ($P = .37$).

TABLE 3 shows the physiological and severity of illness variables during the first 72 hours of hospitalization. During the first 24 hours, both groups of patients tended to show a trend toward slightly worsening severity of illness in the form of lower systolic blood pressures and higher SOFA scores. The mean initial lactate concentrations were 35.1 mg/dL (3.9 mmol/L) in the lactate clearance group and 37.8 mg/dL (4.2 mmol/L) in the $ScvO_2$ group ($P = .39$). The mean (SD) lactate concentration measured at 2 hours in the lactate clearance group was 23.4 (23.3) mg/dL (2.6 [2.59] mmol/L) and the median lactate clearance at 2 hours was 40% (IQR, 18%-64%). After the initial 24 hours, survivors in both groups manifested improvements in their physiological and severity of illness scores. We observed that lactate measurements did not worsen over the initial 72 hours (Table 3), suggesting that the initial lactate levels were often the most abnormal.

There were no differences in the administered treatments through the initial 72 hours of hospitalization as shown in TABLE 4. During the emergency department–based 6-hour resuscitation period, patients received approximately 4.5 L of crystalloid, 221 patients (74%; 95% confidence interval [CI], 68%-79%) required vasopressors for hypotension, and 79 patients (26%; 95% CI, 21%-32%) required mechanical ventilation. Notably, only 29 patients (10%; 95% CI, 7%-14%) required either dobutamine infusion or packed red blood cell transfusion during the initial 6 hours of treatment. Activated protein C administration was only administered in 5 patients (2%; 95% CI, 1%-4%).

Among the 294 (147 per group) patients included in the per-protocol analy-

sis, the central venous pressure goal was achieved in 133 patients (91%; 95% CI, 85%-95%) in the lactate clearance group and 133 (91%; 95% CI, 85%-95%) in the $ScvO_2$ group ($P=.99$); the mean arterial pressure goal was achieved in 142 patients (97%; 95% CI, 92%-99%) in the lactate clearance group and 142 (97%; 95% CI, 92%-99%) in the $ScvO_2$ group ($P=.99$); and the lactate clearance goal was met in 139 patients (95%; 95% CI, 90%-98%) in the lactate clearance group and the $ScvO_2$ goal was met in 136 (93%; 95% CI, 87%-96%) patients in the $ScvO_2$ group ($P=.67$). The median time from patient triage in the emergency department to first antibiotic administration was 115 (IQR, 62-180) minutes in the lactate clearance group and 115 (IQR, 66-170) minutes in the $ScvO_2$ group ($P=.98$).

The primary and secondary study outcome analysis is outlined in TABLE 5. In the intent-to-treat analysis the in-hospital mortality rate was 17% (25 of 150 [95% CI, 11%-24%]) in the lactate clearance group compared with 23% (34 of 150 [95% CI, 17%-30%]) in the $ScvO_2$ group. The difference in these mortality rates was 6% (95% CI, –3% to 15%). The lower limit of this CI is well above the –10% predefined noninferiority threshold, confirming the primary hypothesis of noninferiority between the lactate clearance and $ScvO_2$ groups for in-hospital mortality. These results did not change substantially in the per-protocol analysis.

There were no differences in the observed rates of predefined protocol-related serious adverse events between the lactate clearance (9 of 150 [6%; 95% CI, 3%-11%]) and $ScvO_2$ (11 of 150 [7%; 95% CI, 4%-13%]) groups ($P=.81$).

COMMENT

The results of this large multicenter randomized controlled trial of 2 resuscitation protocols for early sepsis resuscitation indicate that a protocol targeting lactate clearance of at least 10% as evidence of adequate tissue oxygen delivery produces a similar short-term survival rate as a protocol using $ScvO_2$ monitoring. Patients in the group resus-

Table 1. Patient Demographics and Clinical Characteristics[a]

Variable	No. (%) of Patients: Lactate Clearance Group (n = 150)	No. (%) of Patients: $ScvO_2$ Group (n = 150)
Age, mean (SD), y	59.8 (17.6)	61.6 (17.6)
Race		
White	88 (59)	77 (51)
Black	47 (31)	56 (37)
Sex		
Men	83 (55)	80 (53)
Women	67 (45)	70 (47)
Comorbidities		
Diabetes mellitus	45 (30)	57 (38)
Chronic obstructive pulmonary disease	25 (17)	25 (17)
Human immunodeficiency virus infection	12 (8)	13 (9)
End-stage renal disease	15 (10)	14 (9)
Active malignancy	42 (28)	32 (21)
Organ transplant	5 (3)	4 (6)
Indwelling vascular line	6 (4)	10 (7)
Nursing home resident	28 (19)	28 (19)
Disease severity		
SAPS II score	44.8 (18.4)	44.1 (17.3)
SOFA score	6.7 (3.6)	6.6 (3.5)
MEDS score	10.9 (3.9)	10.6 (3.4)
Suspected source of infection		
Pulmonary	48 (32)	54 (36)
Urinary tract	40 (27)	39 (26)
Intra-abdominal	34 (23)	24 (16)
Skin/soft tissue	19 (13)	23 (15)
Blood	8 (5)	9 (6)
Unknown	13 (9)	9 (6)
Features of sepsis		
Lactate ≥4	61 (41)	56 (37)
Shock[b]	121 (81)	123 (82)
Culture positive	123 (82)	127 (85)
Blood culture positive	62 (41)	53 (35)
Gram positive	33 (22)	36 (24)
Gram negative	29 (19)	17 (11)

Abbreviations: MEDS, mortality in emergency department sepsis; SAPS, Simplified Acute Physiology Score; $ScvO_2$, central venous oxygen saturation; SOFA, Sequential Organ Failure Assessment.
[a] Continuous data are compared using an unpaired *t* test; categorical data, using the χ^2 test.
[b] Shock is defined as a systolic blood pressure of 90 mm Hg or less after receiving a 20 mL/kg-fluid bolus.

Table 2. Systemic Inflammatory Response Criteria and Dysfunctional Organ Systems

Variable	No. (%) of Patients: Lactate Clearance Group (n = 150)	No. (%) of Patients: $ScvO_2$ Group (n = 150)
SIRS criteria		
Abnormal white blood cell count	117 (78)	104 (69)
Elevated heart rate	100 (67)	108 (72)
Elevated respiratory rate	96 (64)	89 (59)
Abnormal body temperature	61 (41)	64 (43)
Organ dysfunction		
Respiratory	85 (57)	86 (57)
Liver	43 (29)	43 (29)
Neurological	47 (31)	58 (39)
Coagulation	51 (34)	39 (26)
Cardiovascular	132 (88)	128 (85)
Renal	110 (73)	109 (73)

Abbreviations: $ScvO_2$, central venous oxygen saturation; SIRS, systemic inflammatory response syndrome.

citated to a lactate clearance of 10% or higher had 6% lower in-hospital mortality than those resuscitated to an $ScvO_2$ of at least 70% (95% CI for this difference, –3% to 15%) exceeding the –10% predefined noninferiority threshold. These data support the substitution of lactate measurements in peripheral venous blood as a safe and efficacious alternative to a computerized spectrophotometric catheter in the resuscitation of sepsis. To our knowledge, this is the largest randomized trial of emergency department–based early quantitative resuscitation for sepsis conducted to date and the first such trial to investigate the relative value of different goals of early, emergency department–resuscitation strategies.

Table 3. Physiological and Severity of Illness Measurements

Variable by Study Time Point, h[a]	Lactate Clearance Group (n = 150)	$ScvO_2$ Group (n = 150)	*P* Value[b]
Systolic blood pressure, mm Hg			
0	91 (24.6)	92 (21.0)	.62
24	73 (20.8)	79 (15.3)	.01
48	94 (22.1)	95 (21.3)	.91
72	103 (19.9)	103 (19.1)	.87
Heart rate, beats/min			
0	103 (23.6)	106 (24.4)	.36
24	117 (23.6)	119 (21.9)	.37
48	106 (19.7)	107 (20.5)	.51
72	105 (22.1)	103 (20.1)	.56
Central venous pressure, mm Hg			
0	11 (6.5)	11 (6.2)	.55
24	16 (7.8)	15 (6.6)	.47
48	13 (6.4)	14 (6.5)	.45
72	12 (6.5)	14 (8.3)	.14
Central venous oxygen saturation, %			
0		74 (12.3)	
24	65 (19.9)	64 (13.1)	.71
48	70 (16.6)	68 (14.8)	.53
72			
Lactate level, mg/dL[c]			
0	35.1 (28.1)	37.8 (27.7)	.39
24			
48			
72	35.1 (30.3)	36.9 (29.6)	.67
SOFA score, median (IQR)			
0	6 (4-9)	6 (4-9)	.71
24	8 (5-11)	7 (5-11)	.98
48	4 (2-7)	5 (2-7)	.90
72	3 (1-6)	3 (1-6)	.62
SAPS II score			
0	44.8 (18.4)	44.1 (17.3)	.69
24			
48			
72	33.4 (14.1)	34.6 (17.2)	.54
MEDS score			
0	10.9 (3.9)	10.6 (3.4)	.46
24			
48			
72	8.4 (4.2)	8.4 (4.5)	.93
Glasgow coma scale			
0	13 (4.1)	13 (3.7)	.67
24	12 (4.3)	12 (3.9)	.68
48	13 (3.7)	13 (3.5)	.91
72	15 (3.1)	14 (4.0)	.04

Abbreviations: IQR, interquartile range; MEDS, Mortality in Emergency Department Sepsis; SAPS, Simplified Acute Physiology Score; $ScvO_2$, central venous oxygen saturation; SOFA, Sequential Organ Failure Assessment.
SI conversion factor: to convert lactate concentration from mg/dL to mmol/L, multiply by 0.111.
[a] Values represent the mean (SD) measurements at enrollment (0) and the most abnormal values at each hour of measurement, except for the SOFA score. Lactate values and SAPS and MEDS scores were not recorded at 24 and 48 hours.
[b] Continuous data are compared using an unpaired *t* test; categorical variables, using the χ^2 test.
[c] Lactate levels at 72 hours represent worst value over the initial 72 hours of hospitalization.

The physiological basis for lactate clearance presumes that circulatory shock causes inadequate oxygen delivery, resulting in mitochondrial hypoxia. Under hypoxic conditions, mitochondrial oxidative phosphorylation fails, and energy metabolism becomes dependent on anaerobic glycolysis.[26] Anaerobic glycolysis sharply increases the production of cellular lactate, which diffuses into the blood during prolonged cell hypoxia. In patients with a clinical picture of severe infection, the blood lactate concentration varies in proportion to the ongoing deficit in tissue oxygenation, and the ability of the patient to reduce the blood lactate concentration indicates restoration of oxygen delivery with resuscitation.[27] Previous work has found that a lactate clearance of 10% or more predicts survival from septic shock, providing the rationale for this goal.[15,16] In addition, we constructed the protocol to consider 2 normal lactate levels (≤18 mg/dL [2 mmol/L]) at least 2 hours apart as evidence of ongoing adequate tissue oxygenation. The rationale for including this criterion was that clinically it would make no sense to attempt to clear a value that is already normal and that 2 normal values provide a reasonable clinical signal that effective resuscitation has prevented worsening of tissue oxygenation and anaerobic metabolism.

We have previously documented that many clinicians perceive a significant degree of technical difficulty associated with the use of computerized spectrophotometric catheters to monitor $ScvO_2$.[28] These devices require equipment and expertise that are not available in many tertiary care emergency departments.[13] Use of $ScvO_2$ monitoring catheters requires preplanned train-

ing and real-time calibration and troubleshooting that can divert attention from the patient.[28] We thus submit that the need exists for a simpler and more generalizable method to monitor the adequacy of tissue oxygen delivery as a research imperative in the treatment of patients with severe infection. Our results address this unmet need by providing data that justify the use of lactate clearance instead of continuous $Scvo_2$ monitoring.

The sample size assumed a mortality rate of 25% in the active comparator ($Scvo_2$) group. The observed mortality was 23% in the $Scvo_2$ group, indicating that we maintained approximately 80% power to detect a true difference. Although our observed overall mortality rate (20%) is lower than the 37% overall rate reported in the sentinel emergency department–based resuscitation study,[9] it is nearly identical to mortality rates that both individual investigators from our group[22-24] and others[29] have previously reported in effectiveness studies conducted in more heterogeneous populations. We believe that that the mortality rate represents a contemporaneous and accurate estimate of the true mortality rate for patients with severe sepsis and septic shock treated with an early quantitative resuscitation protocol in the emergency department.

Several limitations of our study warrant discussion. By its design, the groups could not be blinded, allowing for possible treatment bias. Our protocol was designed with safeguards to minimize this potential effect. For example, every participant received identical central venous catheters so that group assignment would not be easily identifiable. Also, investigators involved with the study were not allowed to provide care for the participants or influence their care in the ICU. Second, we did not have a method to assess whether an indicated therapeutic action was performed in response to a parameter below the intended goal (eg, if central venous pressure was 4 mm Hg, we did not record whether a fluid bolus was given). Rather, we only assessed for compliance with individual treatment goals during the study treatment period. Third, this study was conducted at 3 institutions that had established emergency department–based quantitative resuscitation programs for sepsis prior to initiation of the study. Therefore, our results may not be generalizable to centers that do not routinely perform early quantitative resuscitation. Fourth, if other influences on care were ignored, it could be suggested that the potential difference in protocol actions directly attributable to using lactate clearance vs $Scvo_2$ was small, because only 10% of patients went on to receive dobutamine or packed red blood cell transfusion. Fifth, we did not have a mechanism to query ICU admission for potentially missed cases; thus, we may have missed patients who met criteria because a clinical alert was not activated. Finally,

Table 4. Administered Treatments and Resuscitation Goals

Intervention, h	No. (%) of Patients: Lactate Clearance Group (n = 150)	No. (%) of Patients: $Scvo_2$ Group (n = 150)	*P* Value[a]
Crystalloid volume, mean (SD), L			
0-<6	4.5 (2.36)	4.3 (2.21)	.55
6-72	12.4 (6.15)	11.8 (6.41)	.44
Vasopressor administration			
0-<6	108 (72)	113 (75)	.60
6-72	100 (67)	108 (72)	.45
Dobutamine administration			
0-<6	5 (3)	8 (5)	.57
6-72	10 (7)	13 (9)	.66
PRBC transfusion			
0-<6	11 (7)	5 (3)	.20
6-72	35 (23)	31 (21)	.78
Mechanical ventilation			
0-<6	40 (27)	39 (26)	.99
6-72	69 (46)	75 (50)	.56
Activated protein C			
0-<6	0	0	
6-72	3 (2)	2 (1)	.68
Parenteral corticosteroids			
0-<6	18 (12)	26 (17)	.25
6-72	59 (39)	51 (34)	.40

Abbreviations: PRBC, packed red blood cell; $Scvo_2$, central venous oxygen saturation.
[a] Continuous variables are compared using unpaired *t* test; categorical variables, using χ^2 test except activated protein C which was analyzed using Fisher exact test.

Table 5. Hospital Mortality and Length of Stay

Variable	Lactate Clearance Group (n = 150)	$Scvo_2$ Group (n = 150)	Proportion Difference (95% Confidence Interval)	*P* Value[b]
In-hospital mortality, No. (%)[a]				
Intent to treat	25 (17)	34 (23)	6 (–3 to 15)	
Per protocol	25 (17)	33 (22)	5 (–3 to 14)	
Length of stay, mean (SD), d				
ICU	5.9 (8.46)	5.6 (7.39)		.75
Hospital	11.4 (10.89)	12.1 (11.68)		.60
Hospital complications				
Ventilator-free days, mean (SD)	9.3 (10.31)	9.9 (11.09)		.67
Multiple organ failure, No. (%)	37 (25)	33 (22)		.68
Care withdrawn, No. (%)	14 (9)	23 (15)		.15

Abbreviations: ICU, intensive care unit; $Scvo_2$, central venous oxygen saturation.
[a] Primary study end point.
[b] Continuous data are compared using an unpaired *t* test; categorical variables, using the χ^2 test.

it is possible that knowledge of the study prompted clinical care providers to have a heightened awareness and provide differential treatment patterns (ie, a Hawthorne-like effect).

In conclusion, in this randomized trial, we found no difference in mortality for patients with severe sepsis and septic shock resuscitated with a protocol that used lactate clearance compared with a protocol that used $ScvO_2$ as the method of measuring total body oxygen metabolism.

Author Contributions: Dr Jones had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Jones, Shapiro, Trzeciak, Kline.
Acquisition of data: Jones, Shapiro, Trzeciak, Arnold, Claremont, Kline.
Analysis and interpretation of data: Jones, Shapiro, Trzeciak, Kline.
Drafting of the manuscript: Jones, Kline.
Critical revision of the manuscript for important intellectual content: Jones, Shapiro, Trzeciak, Arnold, Claremont, Kline.
Statistical analysis: Jones, Kline.
Obtained funding: Jones, Kline.
Administrative, technical, or material support: Jones, Shapiro, Arnold, Claremont, Kline.
Study supervision: Jones, Kline.
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Disassembling Goal-Directed Therapy for Sepsis

A First Step

Roger J. Lewis, MD, PhD

In this issue of *JAMA*, Jones et al[1] report the results of a randomized, noninferiority trial comparing 2 strategies for guiding the use of inotropes and red blood cell transfusions during early goal-directed therapy for patients with severe sepsis or septic shock. Early goal-directed therapy is a multifaceted strategy for titrating intravenous fluids, pressors, inotropes (ie, dobutamine), and transfusions to rapidly correct the physiological derangements associated with severe sepsis. In a single-center randomized trial, the use of early goal-directed therapy was associated with a decrease in mortality from 46.5% to 30.5%.[2] Early goal-directed therapy is a key element of the treatment bundle suggested by the Surviving Sepsis Campaign, is widely believed to be effective, and has been implemented to varying degrees in emergency departments across the country.[3-6] However, the validity of the initial trial has been questioned by some, and the benefits of early goal-directed therapy and its components are currently being re-evaluated in a number of large prospective clinical trials.[7]

Conceptually, early goal-directed therapy tailors the intensity of fluid resuscitation and pharmacological therapy to address 3 sequential physiological targets, specifically: (1) using intravenous fluids to achieve a central venous pressure of between 8 and 12 mm Hg; (2) using pressors to achieve a mean arterial pressure of at least 65 mm Hg; and (3) using dobutamine or red blood cell transfusions to restore tissue oxygen delivery, as assessed by central venous oxygen saturation using a target of at least 70%.[2] The trial conducted by Jones et al evaluated a strategy in which this last resuscitation target was guided by clearance of serum lactate rather than central venous oxygen saturation. Central venous oxygen saturation is commonly measured using a specialized central venous catheter; this may explain why early goal-directed therapy is not more widely used. If a lactate-based strategy were found to be equally effective, the authors suggest that early goal-directed therapy may be more widely used.

Overall, Jones et al[1] observed a mortality of 23% among patients receiving central venous oxygen saturation–guided treatment and a mortality of 17% among those receiving lactate-guided treatment. These results support the noninferiority of the lactate-guided approach, even when assessed using a conservative 2-tailed 95% confidence interval (a traditional noninferiority hypothesis would be evaluated using a 1-tailed 95% confidence interval).[8]

Interpretation of the study results is somewhat complicated because only 10% of enrolled patients received dobutamine or transfusions, the only treatments influenced by the resuscitation targets being compared. With only a small fraction of enrolled patients receiving the therapies potentially altered by the third resuscitation target, it might seem implausible, in retrospect, that a change in this resuscitation target could increase mortality by 10%, the noninferiority margin selected for the trial. Nevertheless, the data support the noninferiority of the lactate guidance strategy.

The use of early goal-directed therapy is resource intensive, and the relative contributions of the individual components to the overall treatment effect are not well characterized. Thus, there is substantial interest in identifying the key components responsible for the efficacy of the strategy, with the goal of reducing the burden of implementation without loss of benefit. The study by Jones et al is a step in this direction. However, early goal-directed therapy is a complex bundle of treatments, and an investigative strategy based on conducting a series of controlled clinical trials, each evaluating a single component of early goal-directed therapy in isolation is extremely costly, time-consuming, and unlikely to identify successfully the optimal combination of treatment goals for these critically ill patients. Although early goal-directed therapy is guided by 3 resuscitation targets—central venous pressure, mean arterial pressure, and central venous oxygen saturation—addressing these resuscitation targets is not an all-or-nothing proposition. Instead, each resuscitation target is quantitative (eg, targeting a central venous pressure of 8-12 mm Hg); thus, each resuscitation goal has a numerical target that must be carefully chosen, a task analogous to choosing a dose in a phase 2 dose-finding trial of a pharmacological agent.

See also p 739.

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The task of evaluating the independent contribution of each component of early goal-directed therapy and selecting the optimal target for each intervention is daunting. For example, there are 12 potential treatment groups, assuming 4 possible target values (no target, a less aggressive target, the current target, and a more aggressive target) and the 3 targets. Using traditional clinical trial designs to identify the single best strategy among these many options would be inefficient and impractical, especially considering that each component is likely to have a smaller treatment effect than the overall strategy, and interactions may exist between the treatment effects of different components. Thus, a new conceptual framework is needed for the design of clinical trials aiming to identify the optimal and most efficient configuration for complex treatment bundles. Recent advances in the design and conduct of adaptive, dose-finding trials may help fill this void.[9]

In a traditional clinical trial, all key design elements (eg, the doses to be compared, number of treatment groups, randomization ratios) are defined prior to initiation and held fixed throughout the trial. However, in an adaptive clinical trial, key design elements are modified during the conduct of the trial in response to the accumulating data, to efficiently address scientific, clinical, and ethical goals.[9-11] Elements that may be varied include the treatment groups to which patients are randomized, dosing levels within each treatment group, and randomization ratios.[9] For example, patients may be randomized to a higher dosing level only after a lower dose has proved safe,[12] or patients may be preferentially randomized to a treatment group associated with better outcomes to improve the outcomes of patients in the current study. Improving the outcomes of patients within the trial is especially important for patients who are enrolled under an emergency exception from informed consent.[13] Because such designs are inherently complex, their performance parameters (eg, false-discovery rates, required sample sizes, and power) are best evaluated using numerical simulation. Recently, there has been increasing interest in adaptive clinical trials within the pharmaceutical industry, the US Food and Drug Administration, and the National Institutes of Health.[11]

An adaptive clinical trial might begin by enrolling patients in a standard early goal-directed therapy group, 3 modified groups in which 1 treatment goal, such as central venous pressure, mean arterial pressure, or central venous oxygen saturation, is less aggressive, and 3 modified groups in which 1 of the treatment goals is more aggressive. Although such a 7-group trial might be expected to require an unmanageable sample size, dose-response modeling can be used to integrate the information from all treatment groups to achieve practical data requirements. Treatments found to be underperforming could be stopped, and, similarly, treatments found to be performing well could lead to the opening of additional treatment groups. For example, if a higher central venous pressure goal is associated with better outcomes, a new treatment group with an even higher goal could be added. Conversely, if a less-aggressive goal for central venous oxygen saturation is found to be noninferior to the standard target, then a treatment group could be added in which central venous oxygen saturation is not used as a goal. By closing poorly performing treatment groups and opening new ones, an adaptive trial could efficiently identify the least burdensome approach that is either maximally effective or at least noninferior to current early goal-directed therapy.

The challenges associated with conducting such a clinical trial are substantial but not insurmountable. Such a study would need to be conducted in a large, multicenter research network to enroll a sufficient number of patients. Implementing response-adaptive allocation requires the use of centralized randomization, the rapid capture of patient outcomes, and the real-time implementation of the adaptive algorithm. Trials with these requirements have been successfully completed.[14]

How should physicians proceed in the initial management of the adult patient with severe sepsis or septic shock? There are really 2 questions to be considered: first, should early goal-directed therapy be used whenever possible, and, second, if so, what should the resuscitation targets be? The available evidence does not yet support unequivocal answers to either question. Regarding the use of early goal-directed therapy, 1 study provides direct evidence,[2] whereas several studies offer indirect evidence suggesting that it decreases mortality.[15] The primary randomized trial was weakened by high mortality in the control group.[2] The studies providing indirect evidence often used before-and-after experimental designs of multifaceted interventions (eg, evaluating the effect of implementing a sepsis treatment bundle including early goal-directed therapy as a component).[15] This approach may yield false-positive conclusions when secular improvements occur in other aspects of patient care. A recent study[16] demonstrated improved outcomes from a program aiming to increase the use of early goal-directed therapy as part of a treatment bundle, despite only a small fraction of patients receiving all elements. These improved outcomes remained stable after the use of early goal-directed therapy returned to preintervention levels. Thus, uncertainty remains about the true benefit of early goal-directed therapy. This uncertainty provides motivation for ongoing trials and allows the ethical randomization of patients between early goal-directed therapy and other treatments within closely monitored clinical trials. Until the results of those trials are available, however, the current best evidence suggests that early goal-directed therapy is beneficial and should be used when it is practical and safe to do so.

When early goal-directed therapy is initiated, what resuscitation targets should be used? Without new trials evaluating the effects of using alternative targets, clinicians should use the original central venous pressure target of between 8 and 12 mm Hg and a mean arterial pressure target of at

least 65 mm Hg. The data from the report by Jones et al[1] demonstrate that the third resuscitation target can be either a central venous oxygen saturation of at least 70% or a lactate clearance of at least 10%. Although using the lactate clearance does not obviate the need for a central venous catheter, it does allow the use of a nonspecialized catheter and does eliminate the need for the associated electronic instrumentation.

In summary, the study by Jones et al is an important first step to identifying less burdensome approaches to the initial management of critically ill patients with severe sepsis and septic shock. Substantial further progress most likely will depend on appropriately designed, rigorously conducted clinical trials (requiring novel strategies, such as adaptive design) that can efficiently and practically address the complicated questions inherent in identifying the optimal and least burdensome combination of resuscitation targets.

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