Prognostic Value and Agreement of Achieving Lactate Clearance or Central Venous Oxygen Saturation Goals During Early Sepsis Resuscitation

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Abstract

Objectives—Lactate clearance (LC) and central venous oxygen saturation ($ScvO_2$) have been proposed as goals of early sepsis resuscitation. The authors sought to determine the agreement and prognostic value of achieving $ScvO_2$ or LC goals in septic shock patients undergoing emergency department (ED) based early resuscitation.

Methods—This was a preplanned analysis of a multicenter ED randomized controlled trial of early sepsis resuscitation targeting three variables: central venous pressure, mean arterial pressure, and either $ScvO_2$ or LC. Inclusion criteria included suspected infection, two or more systemic inflammation criteria, and either systolic blood pressure <90 mmHg after intravenous fluid bolus or lactate > 4 mM. Both $ScvO_2$ and LC were measured simultaneously. The $ScvO_2$ goal was defined as ≥70%. Lactate was measured at enrollment and every two hours until the goal was reached, or up to six hours. LC goal was defined as a decrease of ≥ 10% from initial measurement. The primary outcome was in-hospital mortality.

Results—Two hundred three subjects were included, with an overall mortality of 19.7%. Achievement of the $ScvO_2$ goal only was associated with a mortality rate of 41% (9/22), while achievement of the LC goal only was associated with a mortality rate of 8% (2/25; proportion difference 33%; 95% CI = 9% to 55%). No agreement was found between goal achievement (κ = −0.02), and exact test for matched pairs demonstrated no significant difference between discordant pairs (p = 0.78).

Conclusions—No agreement was found between LC and $ScvO_2$ goal achievement in early sepsis resuscitation. Achievement of a $ScvO_2$ ≥70% without LC ≥10% was more strongly associated with mortality than achievement of LC ≥10% with failure to achieve $ScvO_2$ ≥70%.

INTRODUCTION

Severe sepsis hospitalizations affect at least 750,000 persons annually in the United States.[1,2] Estimates suggest that 500,000 patients with severe sepsis are treated annually in

U.S. emergency departments (ED).[3] The Surviving Sepsis Campaign (SSC) currently recommends early structured resuscitation targeting specific values of central venous pressure, mean arterial pressure, and central venous oxygen saturation ($ScvO_2$).[4] While early quantitative resuscitation protocols have been demonstrated to improve outcomes in patients with severe sepsis,[5-7] there remains significant debate regarding the relative value of early sepsis resuscitation goals,[8,9] particularly the value of $ScvO_2$. Lactate clearance (LC) has been shown to be non-inferior to $ScvO_2$ as the final goal during early sepsis resuscitation.[10] However, to our knowledge no prospective study has directly compared $ScvO_2$ and LC values measured simultaneously in the same patient during the resuscitative phase of septic shock.

The need for personnel, training, and equipment for $ScvO_2$ measurement has been cited as a barrier to implementation for quantitative resuscitation protocols.[11] Measurement of LC is potentially less invasive and requires fewer resources to perform; however, it is still unclear if these physiologic goals are complimentary or if there is unique value of each as a resuscitation goal. Our primary aim was to measure the agreement between the achievement of LC and $ScvO_2$ goals. We also sought to compare the relative prognostic value of achieving $ScvO_2$ or LC goals in septic shock patients undergoing an early resuscitation protocol in the ED. Our hypothesis was that there would be very good agreement ($\kappa \geq 0.8$) between LC and $ScvO_2$ goal achievement, and that attainment of the LC and $ScvO_2$ goals would have similar ability to predict mortality.

METHODS

Study Design

We conducted a preplanned analysis of a prospective, parallel group randomized clinical trial designed to assess the non-inferiority of LC versus $ScvO_2$ as the protocol endpoint that evaluated the adequacy of oxygen delivery during ED-based early quantitative resuscitation of sepsis. The trial was registered (NCT00372502) and the methods for this study were published previously.[10] The study was approved by the institutional review board at each institution, and all participants or their surrogate provided written informed consent for participation.

Study Setting and Population

The trial took place from January 2007 to January 2009 at Carolinas Medical Center, Charlotte, North Carolina; Beth Israel Deaconess Medical Center, Boston, Massachusetts; and Cooper University Hospital, Camden, New Jersey, all of which are large, urban, tertiary-care hospitals staffed by emergency medicine resident physicians supervised by board certified emergency physicians with established quantitative resuscitation protocols for severe sepsis. Consecutive patients presenting to one of the participating EDs were eligible for enrollment if they were older than 17 years, and had confirmed or suspected infection, two or more systemic inflammatory response criteria,[13] and hypoperfusion evidenced by hypotension after fluid challenge or a blood lactate concentration of at least 4 mmol/L.

Randomization—After enrollment, patients were randomly assigned to one of two groups. Study group assignment sequence was generated by an independent statistician using a parallel design, balanced randomization schedule (1:1 ratio of cases and controls).

Study Protocol

Both groups received structured resuscitation in the ED targeting central venous pressure, mean arterial pressure, and either LC or $ScvO_2$ based on treatment group assignment. The

study protocol was continued until all endpoints were achieved, or a maximum of six hours. The published results of this study showed a 6% (95% confidence intervals [CI] = −3% to 14%) in-hospital mortality difference between the two study groups, confirming the primary hypothesis of non-inferiority between the two resuscitation endpoints.[10]

Patients assigned to the $ScvO_2$ arm had $ScvO_2$ measurements made using a central venous catheter capable of continuous $ScvO_2$ measurements (PreSep, Edwards LifeSciences, Irvine, CA). Patients randomized to the lactate clearance group received an identical central venous catheter capable of measuring continuous $ScvO_2$. Lactate clearance was defined by the equation $[(\text{lactate}_{initial} - \text{lactate}_{delayed})/\text{lactate}_{initial}] \times 100\%$, for which *lactate initial* was the measurement at the start of the resuscitation, and *lactate delayed* was another measurement after a minimum of two hours after resuscitation was initiated. Lactate measurements were repeated every two hours until the patient met the LC goal, or the six-hour resuscitation period was complete.

Blinding—As a part of the study protocol, research staff were instructed to perform blinded measurements of LC if patients were randomized to the $ScvO_2$ arm and blinded $ScvO_2$ measurements if patients were randomized to the LC arm. Blinded lactate and blinded spot $ScvO_2$ measurements were performed by the research coordinator on a bedside point-of-care device, and results were printed onto a hard-copy that was immediately gathered by the research coordinator. Measurements were performed using a deidentified patient ID number, which did not synchronize with the electronic medical record, and the treating clinicians had no way to access the data. If the patient was assigned to the LC group, a relative LC was calculated by the research coordinator and shared with the clinical care providers and at the same time a spot $ScvO_2$ measurement was performed and was not shared with the clinical care providers. If the patient was assigned to the $ScvO_2$ group, blinded lactate measurements were performed, and a LC was calculated. This data was not shared with the clinical care team, but was recorded on the case report form.

At the suggestion of our hospital regulatory board, the simultaneous blinded measurements were encouraged, but not mandated, and therefore we expected they would not be performed on all subjects. Final data analysis was performed on all patients who received both sets of measurements (Figure 1).

Outcome Measurements

The primary outcome was in-hospital mortality. Patients were categorized based on achievement of predefined $ScvO_2$ and LC goals. The $ScvO_2$ goal achievement was defined as $ScvO_2 \geq 70\%$ recorded at any time during the resuscitation. LC goal achievement was defined as: a) if initial lactate > 2 mM, a decrease of ≥10% from initial; or b) both initial and repeat levels <2.0 mM. For the purposes of this analysis, patients achieving the $ScvO_2$ or LC goal at any time point within the 6-hour resuscitation period were considered equivalent.

Data Analysis

Baseline characteristics of included and excluded patients were compared to assess for the possibility of systematic bias. Baseline characteristics and clinical outcomes of patients achieving the $ScvO_2$ goal versus those achieving the LC goal were compared using descriptive analysis. To test if failure to achieve each of these goals has clinical significance, a subgroup analysis was performed to measure outcome of patients who achieved the $ScvO_2$ goal but not the LC goal, compared with patients who achieved the LC but not the $ScvO_2$ goal.

Continuous data were tested for normality by Wilks-Shapiro and visual inspection of histograms. Continuous data are presented as means and standard deviations, or medians and inter-quartile ranges (IQR) as appropriate. Categorical data are presented as proportions. Results were compared using t-tests or Mann-Whitney tests for continuous data, and chi-square or Fisher exact tests for categorical data, as appropriate. We tested for association between achievement of $ScvO_2$ and lactate clearance goals using Cohen's kappa, and tested for differences in discordant pairs using an exact test for matched pairs.[12] All statistical tests were two-sided with $p < 0.05$ considered significant and no adjustment for multiple comparisons.

RESULTS

Simultaneous $ScvO_2$ and LC were measured in 203 patients, and 93 patients were excluded due to lack of concurrent LC and $ScvO_2$ data (Figure 1). Baseline demographics, co-morbidities, initial vital signs, and percentage of patients achieving the LC or $ScvO_2$ goals were similar between included and excluded patients, with few exceptions. Excluded patients were slightly older (63 vs. 59 years, $p = 0.047$), had a higher incidence of diabetes mellitus (33% vs. 22%, $p = 0.049$), and a presented with a lower initial heart rate (97 vs. 108, $p = 0.026$).

Of the included patients, the median initial $ScvO_2$ was 80% (IQR 74% to 88%), and the median initial lactate was 3.4 mM (IQR 1.8 to 5.9 mM). The proportion of patients treated with the LC arm versus the $ScvO_2$ arm of the study was similar (93/203 (46%) vs. 110/203 (54%), percent difference: 8%; 95% CI = −1% to 20%; Figure 1). The $ScvO_2$ goal was achieved in 175 (86%), and the LC goal was achieved in 178 (88%) patients. Overall in-hospital mortality rate was 19.7%. Baseline demographics, clinical characteristics, physiological parameters, and severity of illness variables are shown in Table 1. There were no differences in co-interventions administered between those patients who achieved the $ScvO_2$ or LC goals, including transfusion of packed red blood cells or administration of dobutamine (Table 2).

There was no significant agreement between goal achievement ($\kappa = -0.02$, 95% CI = −11.5 to 17.4), with an observed agreement of 76.85% and expected agreement of 77.29%. An exact test for matched pairs demonstrated no significant difference between discordant pairs ($p = 0.78$), suggesting that the discordant pairs were randomly distributed (Table 3). Among those who met the LC goal, 30 of 178 (17%) died, and among those who met $ScvO2$ goal, 37 of 175 (21%) died (difference of 4%, 95% CI = −4% to 13%). One hundred fifty-three of 203 subjects met both the $ScvO_2$ and LC goals, and the mortality in this group was 18.3%.

In the subgroup analysis, 22 out of 203 (11%) met only the $ScvO_2$ but not the LC goal, and 25 out of 203 (12%) met only the LC but not the $ScvO_2$ goal. Baseline demographics, clinical characteristics, physiological parameters, and severity of illness variables between these subgroups are shown in Table 4. There were no differences in co-interventions administered between those patients who achieved the $ScvO_2$ or LC goals, including transfusion of packed red blood cells or administration of dobutamine (Table 5). If the only the $ScvO_2$ goal (but not the LC goal) was met mortality was 9 of 22 (41%), as opposed to 2 of 25 (8%) if the only the LC goal (but not the $ScvO_2$ goal) was met (proportion difference 33%; 95% CI = 9% to 55%). There were only three patients in which neither goal was met, one of whom died.

DISCUSSION

In this study, we found no significant agreement in the achievement of $ScvO_2$ and LC goals beyond what would be expected by chance, and also found that achievement of only a $ScvO_2$ of 70% or more was more strongly associated with mortality than achievement of only an LC of 10% or more. These data suggest that if only one goal is achieved, failure to achieve an LC of 10% has a worse prognosis than failure to achieve an $ScvO_2$ of 70% during early sepsis resuscitation.

Our group recently completed a prospective, parallel group randomized clinical trial designed to assess the non-inferiority of LC versus $ScvO_2$ as the protocol endpoint to evaluate the adequacy of oxygen delivery during ED-based early quantitative resuscitation of sepsis.[10] The study demonstrated the non-inferiority of using LC instead of continuous $ScvO_2$ as the final goal of a resuscitation strategy for septic shock. The current analysis is unique in that it is the first study of which we are aware in which simultaneous $ScvO_2$ values and LC measurements were performed in patients undergoing early quantitative resuscitation for septic shock. Our data suggest that successful achievement of an $ScvO_2$ of 70% or more, but failure to achieve an LC of 10%, is more strongly associated with mortality in patients with septic shock than is failure to achieve a $ScvO_2$ of 70% or higher while successfully achieving a lactate clearance of 10% or more. These data represent an important contribution to the ongoing controversy surrounding the optimal endpoints of early sepsis resuscitation.

Since the initial adoption of early goal directed therapy as described by Rivers et al.[14] into Surviving Sepsis Campaign recommendations, several implementation studies have demonstrated reductions in mortality from septic shock.[5-7] Despite success associated with the implementation of the early sepsis quantitative resuscitation, the relative value of specific resuscitation goals, particularly $ScvO_2$, remain uncertain.[8,9] The present study adds to the available data regarding the relative value of resuscitation goals. Specifically, the failure to achieve LC during early sepsis resuscitation is associated with higher in-hospital mortality than failure to achieve $ScvO_2$, suggesting that if a clinician had to choose between the two goals, LC may be the preferred goal to target.

We found no agreement between $ScvO_2$ and LC goal achievement in this study, suggesting that these tests may be measuring and/or providing data about physiologically distinct processes. The physiologic processes measured by $ScvO_2$ and serum lactate are complex, and are influenced by numerous factors. Generally speaking, however, a decreased $ScvO_2$ results from an imbalance of oxygen consumption and oxygen delivery.[15] As oxygen delivery decreases, in order to maintain consumption and prevent tissue hypoxia, oxygen extraction increases, resulting in central venous desaturation. This imbalance provides the rationale for interventions aimed at increasing oxygen supply and decreasing oxygen demand in patients with low $ScvO_2$. Hyperlactatemia is also well recognized in the setting of acute infection, and is usually attributed to anaerobic metabolism as a consequence of hypoperfusion and tissue hypoxia. The true source of hyperlactatemia in sepsis is probably multi-factorial, and the contribution of catechol-stimulated aerobic lactate production might be a viable source in some patients.[16] This corroborates the clinical observation of hyperlactatemia in hemodynamically stable patients without clinical evidence of tissue hypoperfusion, suggesting in some situations that hyperlactatemia is a marker of metabolic stress rather than true occult hypoperfusion.

LIMITATIONS

This study has several limitations that deserve consideration. First, all three of the hospital systems have considerable experience with early quantitative resuscitation protocols, and

our results may not be generalizable to hospitals without such protocols. Second, all measurements and comparisons of $ScvO_2$ and LC were obtained within the first six hours of ED resuscitation, and our results may not be generalizable to resuscitation taking place at later time points in the intensive care unit. Third, treating clinicians had access to either $ScvO_2$ or LC data based on treatment group assignment, not both, and we do not know how this additional data may have affected clinical care. Fourth, all patients in this study had central venous pressure and mean arterial pressure goals targeted prior to $ScvO_2$ or LC goals. Therefore, we cannot draw any conclusions regarding the relative value of targeting those goals from this study, nor the value of targeting specific values of $ScvO_2$ or LC in the absence of central venous pressure and mean arterial pressure optimization. Fifth, while we did not find a significant difference in the ability of $ScvO_2$ or LC goal achievement to predict mortality, it is possible that a larger study may result in a different conclusion. Sixth, we chose in-hospital mortality as an endpoint for this study and it is possible that another endpoint (such as an organ dysfunction score) may be associated with different results. Finally, our data can only describe associations and not cause and effect between the variables and outcomes.

CONCLUSIONS

In septic shock patients treated with an early aggressive resuscitation protocol, we found no agreement between lactate clearance and central venous oxygen saturation goal achievement. Achieving central venous oxygen saturation of 70% or more without achieving a lactate clearance of 10% or more was more strongly associated with mortality than achievement of a lactate clearance 10% or more with failure to achieve central venous oxygen saturation of 70% or more.

Acknowledgments

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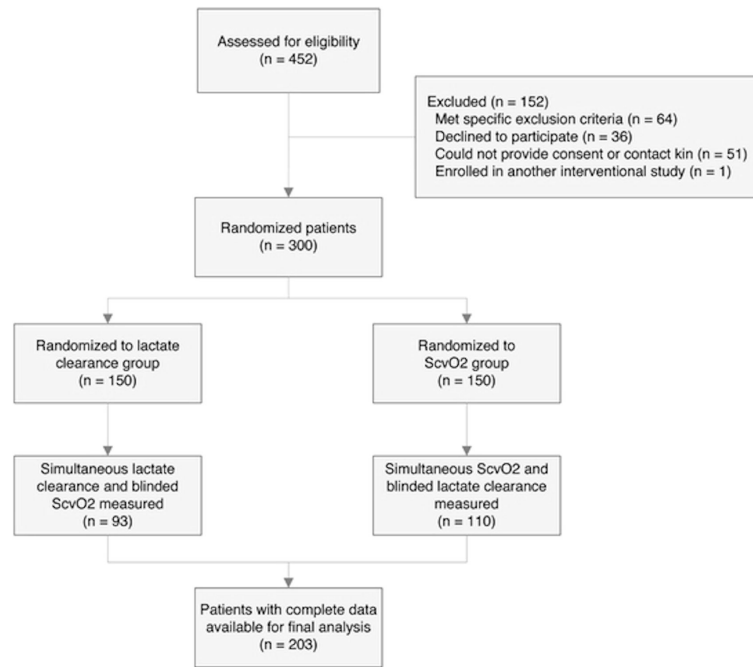
Figure 1.
Study flow diagram.

Table 1

Patient demographics and clinical characteristics.

Variable	Entire cohort (N = 203)	Met ScvO$_2$ goal (n = 175)	Met LC goal (n = 178)
Age in years, mean (±SD)	59.4 (±17.3)	58.6 (±17.4)	59.8 (±17.6)
Race, n (%)			
White	105 (51.7)	91 (52.0)	90 (50.6)
Black or African American	80 (39.4)	69 (39.4)	71 (40.0)
Hispanic	15 (7.4)	13 (7.4)	15 (8.4)
Other	3 (1.5)	2 (1.1)	2 (1.1)
Sex, n (%)			
Male	110 (54.2)	95 (54.3)	95 (53.4)
Female	93 (45.8)	80 (45.7)	83 (46.6)
Co-morbidities, n (%)			
Diabetes mellitus	67 (33.0)	53 (30.3)	57 (32.0)
Chronic obstructive pulmonary disease	33 (16.3)	31 (17.8)	30 (16.9)
Human immunodeficiency virus	17 (8.4)	16 (9.1)	14 (7.9)
End stage renal disease	18 (8.9)	17 (9.7)	17 (9.6)
Active malignancy	52 (25.6)	45 (25.8)	42 (23.6)
Organ transplant	9 (4.4)	9 (5.1)	8 (4.5)
Indwelling vascular line	33 (16.3)	23 (13.1)	30 (16.9)
Nursing home resident	35 (17.2)	28 (13.5)	29 (16.3)
Do not resuscitate	5 (2.5)	3 (1.7)	5 (2.7)
Disease severity, ^ median (IQR)			
SAPS II score	42 (32-56)	42 (31-55)	41 (30-54)
SOFA score	6 (4-9)	6 (4-9)	6 (4-9)
MEDS score	11 (8-13)	11 (8-13)	11 (8-13)
Suspected Source of Infection, n (%)			
Pulmonary	69 (33.4)	58 (33.1)	62 (34.8)
Urinary tract	55 (27.1)	44 (25.1)	49 (27.5)
Intra-abdominal	34 (16.7)	30 (17.1)	25 (14.0)
Skin/soft tissue	23 (11.3)	20 (11.4)	21 (11.8)
Blood	15 (7.4)	14 (8.0)	14 (7.9)
Unknown	39 (19.2)	36 (20.6)	35 (19.7)
>1 identified source	28 (13.8)	23 (13.1)	24 (13.5)
Initial physiologic measurements, median (IQR)			
Systolic blood pressure (mmHg)	88 (78-102)	89 (78-103)	90 (79-104)
Heart rate (beats/minute)	108 (88-122)	109 (87-122)	107 (86-122)
Respiratory rate (breaths/minute)	22.5 (18-28)	22.5 (18-28)	22 (18-28)
Glasgow Coma Scale	15 (13-15)	15 (13-15)	15 (13-15)
Lactate level (mmol/liter)	3.4 (1.8-5.9)	3.4 (1.8-5.9)	3.4 (1.6-6.1)
Central venous pressure (mmHg)	10 (6-15)	10 (7-14.5)	9 (6-14)

Variable	Entire cohort (N = 203)	Met ScvO$_2$ goal (n = 175)	Met LC goal (n = 178)
ScvO$_2$	80 (74-88)	82 (78-89)	80.5 (74-88)

IQR = interquartile range; SAPS = simple acute physiology score; SOFA = Sequential Organ Failure Assessment; MEDS = Mortality in Emergency Department Sepsis; ScvO2= central venous oxygen saturation; LC = lactate clearance

^
Disease severity scores calculated at time of enrollment

Table 2

Administered treatments and resuscitation endpoints.

Intervention	Entire cohort (N = 203)	Met ScvO$_2$ goal (n = 175)	Met LC goal (n = 178)
Total crystalloid volume (L)[*]	4.6 (3.0-6.0)	4.6 (3.0-6.0)	4.6 (3.0-6.0)
Parenteral corticosteroids[+]	38 (18.7)	35 (20.0)	33 (18.5)
Time to initial antibiotics[^]	119 (65-176)	119 (65-185)	117 (63-185)
Mechanical ventilation	65 (32.0)	53 (30.3)	52 (29.2)
Activated Protein C	2 (1.0)	1 (0.6)	2 (1.1)
Dobutamine administered	9 (4.4)	6 (3.4)	8 (4.5)
PRBC administered	10 (4.9)	8 (4.6)	8 (4.5)

Abbreviations: ScvO$_2$ = central venous oxygen saturation; LC = lactate clearance; L = liters;

PRBC = packed red blood cells

Values are reported as either n (%) or median (IQR)

[*] 0-6 hours, additional intravenous crystalloid volume administered after initial 2L fluid challenge

[+] 0-6 hours

[^] Time from ED triage to initiation of antibiotics, in minutes

Table 3

Concordance between reaching central venous oxygen saturation and lactate clearance goals.

	Met LC goal	Failed to meet LC goal	Total
Met ScvO$_2$ goal	153	22	175
Failed to meet ScvO$_2$ goal	25	3	28
Total	178	25	203

ScvO$_2$ = central venous oxygen saturation; LC = lactate clearance

Table 4

Patient demographics and clinical characteristics of the subgroup of patients who only met one of the two goals

Variable	Only met ScvO$_2$ goal (n = 22)	Only met LC goal (n = 25)
Age in years, mean (±SD)	1 55.1 (±15.4)	63.9 (±17.0)
Race (%)		
White	13 (59.1)	12 (48.0)
Black or African American	8 (36.4)	10 (40.0)
Hispanic	0 (0.0)	2 (8.0)
Other	1 (4.5)	1 (4.0)
Sex (%)		
Male	12 (54.5)	12 (48)
Female	10 (44.5)	13 (52)
Co-morbidities (%)		
Diabetes mellitus	8 (36.4)	12 (48.0)
Chronic obstructive pulmonary disease	3 (13.6)	2(8.0)
Human immunodeficiency virus	3 (13.6)	1 (4.0)
End stage renal disease	1 (4.5)	1(4.0)
Active malignancy	9 (40.9)	6 (24.0)
Organ transplant	1 (4.5)	0 (0.0)
Indwelling vascular line	3 (13.7)	10 (40.0)
Nursing home resident	5 (22.7)	6 (24.0)
Do not resuscitate	0 (0.0)	2 (8.0)
Disease severity,[*] median (IQR)		
SAPS II score	53 (35-75)	41 (33-65)
SOFA score	8 (5-11)	7 (5-9)
MEDS score	8 (6-13)	11 (9-14)
Suspected Source of Infection (%)		
Pulmonary	6 (27.7)	10 (40.0)
Urinary tract	6 (27.7)	11 (44.0)
Intra-abdominal	7 (31.8)	2 (8.0)
Skin/soft tissue	2 (9.1)	3 (12.0)
Blood	1 (4.5)	1 (4.0)
Unknown	4 (18.2)	3 (12.0)
>1 identified source	4 (18.2)	5 (20.0)
Initial physiologic measurements, median (IQR)		
Systolic blood pressure (mmHg)	73 (67-85)	86 (73-94)
Heart rate (beats/minute)	111 (95-124)	104 (92-120)
Respiratory rate (breaths/minute)	24 (20-28)	24 (19-31)
Glasgow Coma Scale	14 (10-15)	15 (13-15)
Lactate level (mmol/liter)	3.2 (2.5-5.3)	3.8 (1.9-6.8)

Variable	Only met ScvO$_2$ goal (n = 22)	Only met LC goal (n = 25)
Central venous pressure (mmHg)	14 (8-17)	8 (6-14.5)
ScvO$_2$	81 (77-88)	64 (54-67)

IQR = interquartile range; SAPS = simple acute physiology score; SOFA = Sequential Organ Failure Assessment; MEDS = Mortality in Emergency Department Sepsis; ScvO2 = central venous oxygen saturation; LC = lactate clearance

*
Disease severity scores calculated at time of enrollment

Table 5

Administered treatments and resuscitation endpoints of the subgroup of patients who only met one of the two goals

Intervention	Only met ScvO₂ goal (n = 22)	Only met LC goal (n = 25)
Total crystalloid volume (L)*	4.7 (3.5-5.9)	4.8 (3.7-5.3)
Parenteral corticosteroids^	5 (22.7)	3 (12.0)
Time to initial antibiotics*,+	123 (73-151)	115 (68-140)
Mechanical ventilation	11 (50.0)	10 (40.0)
Activated Protein C	0 (0.0)	1 (4.0)
Dobutamine administered	1 (4.5)	1 (4.0)
PRBC administered	2 (9.1)	4 (16.0)

ScvO2 = central venous oxygen saturation; LC = lactate clearance; L = liters; PRBC = packed red blood cells

Values are reported as either n (%) or median (IQR)

*0-6 hours, additional intravenous crystalloid volume administered after initial 2L fluid challenge

^0-6 hours

+Time from emergency department triage to initiation of antibiotics, in minutes