Updates in Emergency Department Management of Sepsis

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Introduction
Severe sepsis is responsible for more than 750,000 hospitalizations each year in the United States and about 500,000 of these patients will initiate treatment in the emergency department (ED). The significant mortality associated with sepsis and septic shock and the substantial cost and utilization of resources associated with this illness has prompted the development of the Surviving Sepsis Campaign (SSC). The SSC is an international collaboration with the objective of reducing mortality due to sepsis and to stimulate research. The SSC has made recommendations for the management of severe sepsis and septic shock that focus on identification of high-risk patients, early antibiotics and cultures, and early goal-directed therapy. This review addresses the evidence behind early antibiotics in sepsis as well as sepsis severity scores, sepsis biomarkers such as procalcitonin and resuscitation endpoints such as lactate clearance and central venous oxygen saturation (ScvO₂).


The Mortality in Emergency Department Sepsis (MEDS) score is used to evaluate the severity of disease and to predict the mortality of patients with suspected infection in the ED. It was derived from 2,070 patients using nine historical, examination, and laboratory findings to form a point score ranging from 0 to 27. It was validated in 2008 as an accurate prediction tool of 28-day mortality in patients who present to the ED with systemic inflammatory response syndrome (SIRS) and who are admitted to the hospital (Sankoff 2008).

Biomarkers such as procalcitonin (PCT), Interleukin-6 (IL-6), and C-reactive protein (CRP) are commonly used for diagnosis, evaluation of treatment effects, and prognosis of sepsis. The authors of this study hypothesized that the combination of the MEDS score with biomarkers would enhance the ability of risk stratification and prognostic evaluation for patients presenting to the ED with sepsis.

The study was prospective in nature and included 570 patients presenting to a single tertiary care hospital with a suspected infection and at least two SIRS criteria between September 1, 2009 and September 1, 2010. The exclusion criteria were age less than 18 years, operative patients, and patients on immunosuppressive medications. All enrolled patients had blood serum collected immediately upon arrival to the resuscitation room that was preserved for CRP, PCT, and IL-6 analysis. In addition, the MEDS score for each patient was calculated. The primary outcome was the presence of severe sepsis or septic shock. The secondary outcome was 28-day mortality. Health care providers and patients were blinded to the score and biomarker results. Hospital records were followed for 28 days after ED admission or until death. Receiver operating characteristic (ROC) curves of the MEDS score and PCT, IL-6, and CRP levels were compared for the severity of sepsis and 28-day mortality, and the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

The study investigated 570 patients with suspected sepsis. Forty-five patients were excluded because of confirmed noninfectious etiology, and 24 patients had missing data or were lost to follow up. Of the 501 remaining patients, 319 (63.7%) had sepsis, 155 (30.9%) had severe sepsis, and 27 (5.4%) had septic shock. A total of 134 patients failed to survive with a 28-day mortality of 26.7%. The MEDS score had the largest AUC (0.793 for severity of sepsis and 0.776 for 28-day mortality). It also had the highest specificity, PPV, and NPV (85.3%, 70.4% and 79.5%, for severity of sepsis and 81.7%, 55.6%, and 85.7% for 28-day mortality). Logistic regression found that the MEDS score and PCT were the only relevant variables that were statistically significant (p<0.05). A new combination of the MEDS score and PCT was compared with the MEDS score and PCT alone, and found that there was a significant difference in the severity of sepsis (AUC, 0.8952 vs. 0.793; p<0.001) and in 28-day mortality (AUC, 0.813 vs. 0.776; p=0.008). The new combination also found a better sensitivity (63.2% vs. 61.5%), specificity (92.2% vs. 85.3%), PPV (82.1% vs. 70.4%) and NPV (81.4% vs. 79.5%) for evaluating severity and a better sensitivity, (67.2% vs. 62.7%), PPV (56.6% vs. 55.6%), and NPV (87.1% vs. 85.7%) for predicting mortality. Given these results, the authors of this study concluded that including PCT into the MEDS score would make a better scoring system than MEDS alone.

One limitation of this study is that only one biomarker concentration was obtained at the time of ED evaluation. Serial levels were not obtained and controlling for the same time point of all samples was not performed. Furthermore, at this time, PCT is not widely available in most centers. Additionally, this was a relatively small study and was carried out at a single institution. A broader clinical trial with multiple centers is required to prove that these results are applicable to all ED patients presenting with sepsis. With that in mind, the MEDS score combined with PCT appears to enhance the ability of risk stratification and prognostic evaluation for patients presenting to the ED.


The SSC international consensus guidelines recommend initiating broad-spectrum antibiotics within one hour of recognizing severe sepsis and septic shock (Dellinger 2008). The objective of this prospective study was...
to assess if there is an association between the timing of initial antibiotics and mortality in patients presenting to three U.S. EDs with septic shock and treated with an early quantitative resuscitation protocol.

The study was a pre-planned analysis of a previously completed prospective, parallel group, non-blinded randomized clinical trial comparing lactate clearance to ScvO2 as a tool for assessing resuscitation of sepsis. The trial took place between January 2007 and January 2009 at three urban tertiary care hospitals and included patients greater than 17 years old with suspected infection, at least two systemic inflammatory criteria, and evidence of hypoperfusion (either hypotension after fluid challenge or lactate >4mmol/L). All patients received broad-spectrum antibiotic coverage according to local hospital guidelines. The primary outcome evaluated was in-hospital mortality. The study compared outcomes of subjects who received an initial dose of antibiotics to those receiving antibiotics before each hourly increment (up to a maximum of six hours after ED triage). The study also assessed for differences before each hourly increment after shock recognition.

Of the 300 patients enrolled in the study, nine were excluded due to receiving a first dose of antibiotics prior to hospital arrival. One hundred seventy-two (172) of 291 (59%) patients received the initial dose of antibiotics after recognition of shock. Overall mortality was 55 of 291 (18.9%) patients. One hundred (100) of 291 (34.4%) patients grew positive blood cultures for pathologic organisms with a mortality rate of 26.0%. The mortality rate for those with blood culture negative septic shock was 29/191 (15.2%).

The median time from triage to initial antibiotic administration was 115 minutes. The odds ratio (OR) for inpatient mortality was 1.18 (95% CI 0.57-2.46) for the group who received antibiotics within one hour of presentation and 0.71 (95% CI 0.39-1.30) for the group receiving antibiotics between one and two hours from triage. No association was found between in-hospital mortality and the time from ED triage to antibiotic administration. The median time to shock recognition was 89 minutes, and 172 (59%) patients received antibiotics after shock recognition. Those patients who received antibiotics after shock recognition were more likely to die with an OR of 2.35 (95% CI, 1.12-4.53). The study found no increase in mortality with delaying antibiotic administration during the first three hours after shock recognition.

This study found no association between mortality and time from triage to initial antibiotic administration, even when controlling for appropriateness of antibiotics. That said, the data do suggest an increase in mortality if antibiotics are delayed until after shock recognition. However, no increase in mortality was identified if antibiotics were administered within three hours of shock recognition. A major limitation, however, is the near impossible nature of identifying the exact time for onset of septic shock. It is also very difficult to identify those patients at triage who will go on to develop septic shock. It seems logical that early antibiotic administration would decrease mortality from septic shock. The timing of antibiotics was not randomized in this study, but retrospectively analyzed. Furthermore, the design of the study was only able to draw conclusions regarding associations, and not causation. To demonstrate a true benefit from early antibiotic administration, additional randomized control trials are necessary.


Antibiotics are a mainstay of therapy for patients with severe sepsis. Choosing inappropriate antibiotics can have deleterious effects on patient outcomes including death. Recent sepsis guidelines have encouraged empiric combination therapy to cover gram-negative organisms despite there being no evidence to support a clinical advantage for using combination therapy over monotherapy.

This particular study set out to compare combination therapy with two broad-spectrum antibiotics to monotherapy on sepsis related organ dysfunction. Subjects for the study were randomized to either meropenem/moxifloxacin or meropenem alone. The median administration of meropenem in both the combination and monotherapy groups was eight days. The median administration of the moxifloxacin in the combination group was seven days. Of note, the administration of the medications was not blinded. There was also co-administration of other medications such as activated protein C, hydrocortisone, selenium, and prednisolone to some of the study subjects based on clinician discretion.

Data was collected prior to treatment, at the end of treatment, and at day 21 or discharge from the ICU. In this study, an interim analysis was conducted with half of the sample size followed by a confirmatory analysis based on all randomized patients. This allowed for adjustment to the significance level. Per protocol data analyses at the end of the study were based on excluding patients with protocol violations.

The primary outcome was sepsis-related organ dysfunction, which was measured using the Sequential Organ Failure Assessment (SOFA). A SOFA score is based on subscores for 6 organ systems ranging from 0-4. Therefore, the overall SOFA score ranges from 0 to 24 with higher scores indicating increasing organ dysfunction. Patients had a calculated mean daily SOFA score over a period of 14 days or until the end of their ICU stay. Secondary end points included 28-day and 90-day all cause mortality along with several other end points such as SOFA subscores, duration of ICU and hospital stay, clinical and microbiologic treatment response, secondary infection, antibiotic resistant bacteria, adverse events, and intervention-free days with a ventilator, vasopressor, dialysis, or antibiotic.

Between October 2007 and March 2010, 5,607 patients were screened in 44 different academic ICUs in Germany. Six hundred patients were randomized into the study. In 49 of these patients, delayed informed consent could not be obtained and their data could not be included. The two groups were balanced in terms of baseline characteristics.

In terms of the primary end point, there was no significant difference in overall SOFA score for the combination therapy group compared to the monotherapy group: 8.3 and 7.9 respectively (7.9 and 7.6, respectively in the per-protocol analysis). The rates of 28-day and 90-day mortality were not significantly different between the two treatment groups either. At day 28, there were 66 deaths in the combination group and 58 deaths in the monotherapy group. At day 90, there were 96 deaths in the combination
group and 84 deaths in the monotherapy group. The per-protocol analysis also did not demonstrate a significant mortality difference between the combination and monotherapy groups.

After multivariate analysis, it was determined that the risk factors for a higher mean SOFA score at 14 days included SOFA score at enrollment, renal failure at enrollment, and age. In Cox regression analysis, risks for time to death were SOFA score at baseline, renal failure at enrollment, and age. Of note, study therapy, prior antibiotic treatment, and gram-negative pathogens were not associated with higher SOFA scores or hastened time to death.

Overall, there was no benefit to combination therapy of meropenem/ moxifloxacin versus meropenem monotherapy in regard to 14-day mean SOFA score or any other secondary end point in this particular study. It is important to keep in mind that this study tested specific antibiotics and cannot be generalized to the efficacy of other antibiotics. In addition, in this study, most participants received antibiotics within 1.5 hours and this may not be a standard that can be met in clinical practice. More data is needed to determine the best antimicrobial treatment for severe sepsis. However, there are so many antibiotics on the market combined with differing resistance patterns geographically, that it proves difficult to determine a generalizable regimen.


The SSC guidelines recommend monitoring ScvO₂ as a marker of tissue oxygen delivery. However, this is controversial since the recommendation was based on a single center study and ScvO₂ testing requires time, expertise and special equipment that complicates its use in many EDs.

This study is a multicenter, randomized, non-inferiority trial comparing the change in lactate levels versus ScvO₂ for monitoring tissue oxygen delivery in sepsis patients in the ED. The trial enrolled 300 patients from EDs of three large US urban medical centers. Included patients were older than 17 years, met SIRS criteria with hypoperfusion (defined as SBP <90mmHg after a 20cc/kg volume challenge) or had a lactate of >4mmol/L. Exclusion criteria included pregnancy, primary diagnosis that was not sepsis, suspected surgery within 6 hours, cardiopulmonary resuscitation (CPR), contraindication to central venous catheter (CVC) placement, transfer from another institution with sepsis resuscitation already in progress or advanced directives that prevented study protocols. Both groups had mean arterial pressure (MAP) and central venous pressure (CVP) measured and were randomly assigned to either ScvO₂ or lactate measurements. Intention-to-treat analysis was used for patients who crossed over due to clinical necessity. The primary outcome measured was in-hospital mortality rate. Secondary outcomes were ICU length of stay, hospital length of stay, ventilator-free days and new onset multiple organ failure.

All patients received CVCs that could monitor ScvO₂. Patients in both groups were given crystalloid boluses to achieve a goal CVP >8mmHg. The next goal was to keep MAP >65 mmHg by giving fluids and if unsuccessful, vasopressors were started. Once these first two goals were obtained then either ScvO₂ or lactate clearance was checked depending on randomization. In the ScvO₂ group, if ScvO₂ was less than 70% and hematocrit (Hct) was <30% then packed red blood cells (pRBCs) were transfused. If ScvO₂ was still low after achieving Hct >30% then dobutamine was administered and titrated. In the lactate clearance group, lactate was measured at least every two hours and if <10% clearance and Hct <30%, pRBCs were transfused. If Hct >30%, dobutamine was titrated to lactate clearance of 10% when measured each hour. Patients were treated until all treatment goals were achieved or until six hours had elapsed.

The CVP goal was achieved in 133 patients in both groups and the MAP goal in 142 patients in both groups. The lactate clearance goal was met in 139 patients and the ScvO₂ goal met in 136 patients. In-hospital mortality was 23% in the ScvO₂ group with 17% in the lactate clearance group. This difference did not meet the predefined -10% threshold for non-inferiority (95% CI for this difference -3 to 15%). Thus, there was no difference in in-hospital mortality between the two treatment arms. There was also no significant difference in adverse outcomes.

The authors conclude that lactate clearance goals should be used as a substitute for attempts to normalize ScvO₂ in the early goal-directed therapy for sepsis. The rationale behind this is that lactate measurements are easier to perform and do not require special training and equipment that may not be available in many EDs. However, the major limitation of this study was that it was unblinded. Another limitation is that the actual cause of outcome differences may be minimal since only 10% of patients even required dobutamine or pRBCs, which begs the question of whether either parameter actually makes a significant difference in quantitative resuscitation. In the future it would be interesting to see how these various goal-directed therapies compare to placebo. In the meantime, it appears lactate monitoring is at a minimum, non-inferior to ScvO₂ monitoring in the guidance of early sepsis therapy.


Despite the significant morbidity and mortality due to sepsis, the endpoints of adequate resuscitation remain unclear. As discussed above, two such possible markers that have been proposed are lactate clearance and ScvO₂. Elevated lactate in septic patients has been associated with increased mortality and previous studies have demonstrated that a lactate clearance of 10% or more in sepsis resuscitations is associated with improved outcomes. Studies have also suggested that achievement of a goal ScvO₂ >70% in septic shock may be associated with improved survival.

This study is derived from the larger parent study by Jones, et al., discussed above. It is a prospective, non-blinded, randomized trial that enrolled 187 patients from three medical centers. Inclusion criteria were as follows: age >17 years, confirmed or suspected infection, met two or more SIRS criteria and hypotension after a fluid challenge or blood lactate of >4mM or initial lactate >2mM. All patients were resuscitated in the ED with intravenous crystalloid with a goal CVP >8mmHg, followed by

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vasopressors to maintain MAP >65mmHg. Patients were then transfused pRBCs and/or given inotropes, with one group having a goal of lactate clearance of >10% and the other group having a goal of ScvO₂ >70%.

The same protocol for escalation of treatment is described in detail above.

The primary outcome of the study was in-hospital survival. Overall survival was 143 of 187 patients (76.5%). The lactate clearance arm included 98 patients, while the other 89 patients were randomized to the ScvO₂ arm. Of the 187 patients, 68 (36%) normalized their lactate level during the first six hours of resuscitation. Lactate normalization was the best predictor of survival (OR, 6.3; 95% CI, 2.4-17.0), followed by lactate clearance of 50% (OR, 4.3; 95% CI, 1.8-10.2). Differences in mortality rates for patients with initial lactate of 2-4mM compared with >4mM and lactate clearance of 10% were not statistically significant. To control for possible confounding factors due to catecholamine-induced lactate production, a subgroup analysis was performed after exclusion of patients who received vasopressors. The only statistically significant predictor of survival remained a lactate clearance of 50%. Similarly, a second subgroup analysis of patients presenting with hypotension but did not have initial lactate >4mM was performed and found that only lactate normalization and lactate clearance of 50% were significant predictors of survival.

This study found that normalization of lactate to <2mM and lactate clearance of 50% were the best independent predictors of survival in septic shock. In particular, lactate normalization was more closely associated with a favorable prognosis when compared to absolute clearance, relative clearance and rate of clearance. This study represents an extension of the larger parent study and suggests that greater lactate clearance (50% compared to 10% in the original study) may be a superior resuscitation endpoint.

The authors cite several weaknesses to this study and its results. First, the centers from which patients were enrolled had resuscitation protocols in place prior to initiation of the study; therefore the results may not be generalizable to other institutions where such protocols do not exist. Additionally, lactate measurements were made at variable times, about two hours apart (median of 133 minutes), therefore lactate clearance rates may underestimate actual rates, particularly in patients in which repeat measurements were made at a relatively later time.

This study suggests that, in patients presenting with septic shock in the ED, early resuscitation with a goal of lactate normalization provides the highest predictor of survival. Lactate clearance of 50% may also be associated with a favorable prognosis, though further research is needed in this area.

**Conclusion**

Severe sepsis and septic shock represent a considerable burden on the health care system in the United States and worldwide. With about 500 deaths per day in the U.S. due to septic shock, mortality rates due to sepsis now nearly surpass those of out-of-hospital myocardial infarction. The Surviving Sepsis Campaign emphasizes timely identification of high-risk patients, early administration of antibiotics and goal-directed interventions. Despite these recommendations, there are many unanswered questions in the literature regarding methods of identifying these patients, which antibiotics should be administered and within what period of time, and what exact objective measurements should be used to guide resuscitation.

For early identification of sepsis, the Mortality in Emergency Department Sepsis (MEDS) score, particularly when used in combination with the biomarker procalcitonin, appears to aid in risk stratification as well as for prognostic estimation.

Although the literature reviewed found no association between mortality and time from triage to initial antibiotic administration, an increase in mortality was associated with administration of antibiotics after, rather than before, the recognition of shock. Another study which compared dual therapy with meropenem and moxifloxacin to monotherapy with meropenem demonstrated a lack of benefit of combination therapy with regards to sepsis-related organ dysfunction and mortality rates.

Finally, lactate clearance of 10% was found to be equivalent to achievement of ScvO₂ of 70% as a resuscitation goal in septic shock with respect to in-hospital mortality rates. Additional literature suggests that a higher lactate clearance of 50% as well as using lactate normalization as a goal may be more accurate predictors of survival.