Resident Journal Review

Updates in Emergency Department Management of Sepsis

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Severe sepsis is responsible for more than 750,000 hospitalizations each year in the United States, and treatment will be initiated in the emergency department (ED) for about 500,000 of these patients. 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 stimulating 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 score ranging from 0 to 27. It was validated in 2008 as an accurate prediction tool for 28-day mortality in patients who present to the ED with systemic inflammatory response syndrome (SIRS) (Sankoff 2008).

Biomarkers such as procalcitonin (PCT), Interleukin-6 (IL-6), and C-reactive protein (CRP) are commonly used for diagnosis 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.

This was a prospective, blinded study that included 570 patients presenting to a single tertiary care hospital with suspected infection and at least two SIRS criteria. All enrolled patients had blood collected 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. Hospital records were followed for 28 days after ED admission or until death.

Of the 501 enrolled 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, for a 28-day mortality of 26.7%. The MEDS score had the largest area under the curve (AUC) (0.793 for severity of sepsis and 0.776 for 28-day mortality). It also had the highest specificity, positive predictive value (PPV), and negative predictive value (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 had better sensitivity, specificity, PPV, and NPV for both evaluating severity and for predicting mortality.

One limitation of this study is that only one biomarker concentration, rather than serial levels, was obtained at the time of ED evaluation. 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.


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The SSC guidelines recommend initiating broad-spectrum antibiotics within one hour of recognizing severe sepsis and septic shock. 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.

The study was an analysis of a previously completed prospective, non-blinded, randomized clinical trial comparing lactate clearance to Svo₂ as a tool for assessing resuscitation of sepsis. The trial took place at three urban tertiary care hospitals and included patients with age greater than 17 years with suspected infection, at least two SIRS criteria, and evidence of hypoperfusion (either hypotension after fluid challenge or lactate >4mmol/L). All patients received broad-spectrum antibiotic coverage according to 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. 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) out 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) out 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).

This study found no association between mortality and time from triage to initial antibiotic administration. However, the data do suggest an increase in mortality if antibiotics are delayed until after shock recognition, though there was no increase in mortality if they 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. In addition, the timing of antibiotics was not randomized in this study, but retrospectively analyzed. 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. Recent sepsis guidelines have encouraged empiric combination therapy to cover gram-negative organisms despite a lack of evidence to support improved outcomes 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 for a total of seven to eight days. Of note, 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.

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 six 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.

Six hundred patients were randomized into the study from 44 academic ICUs in Germany. Forty-nine patients were excluded due to inability to obtain informed consent. 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). There was also no difference in rates of 28-day continued on next page
and 90-day mortality. 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.

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


The SSC guidelines recommend monitoring ScvO$_2$ as a marker of tissue oxygen delivery. However, this is controversial since the recommendation was based on a single center study and because ScvO$_2$ testing requires time, expertise, and special equipment that complicates its use in many EDs.

All patients received CVCs that could monitor ScvO$_2$. Patients in both groups were given crystalloid boluses to achieve a goal CVP >8mmHg. The next goal was to keep MAP >65mmHg by giving fluids and, if unsuccessful, vasopressors. In the ScvO$_2$ group, if ScvO$_2$ was less 70% and hematocrit (Hct) was <30%, then packed red blood cells (pRBCs) were transfused. If ScvO$_2$ was still low after achieving Hct >30% then dobutamine was administered. In the lactate clearance group, lactate was measured at least every two hours and if <10% clearance and Hct <30%,

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Despite significant morbidity and mortality due to sepsis, the endpoints of adequate resuscitation remain unclear. As discussed above, two 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 has been associated with improved outcomes.

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. Inclusion criteria were as follows: age >17 years, confirmed or suspected infection, 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 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 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. 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.
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 which 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 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 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 the achievement of a ScvO\(_2\) 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.