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Using Early Goal Directed Therapy with MEDS Score

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Abstract

Objectives: To determine if an emergency department Early Goal Directed Therapy (EGDT) protocol differentially affects in-hospital mortality when controlling for severity of illness using Mortality in Emergency Department Sepsis (MEDS) score.

Methods: This study is a retrospective chart review of 243 patients, conducted at an urban tertiary care center, after implementing an EGDT protocol on January 1, 2008. This study compares differences in in-hospital mortality and length of stay (LOS) in the ICU and the ED between the 126 septic patients who were hospitalized the year prior to implementation of an EGDT protocol (control group) and the post-implementation study group (117 septic patients from 7/2008-6/2009), using MEDS score as a risk stratification tool. In-hospital mortality was compared between our pre- and post EGDT groups and adjusted for MEDS score using logistic regression with accompanying odds ratios and 95% confidence intervals. Median ED and ICU LOS were also compared.

Results: The mean age and comorbidities were similar between the two groups. (*p=0.27* and *p=0.87* respectively). Reduction in absolute mortality was 9.9% when EGDT is used (control = 30.4%, study = 20.5%, *p=0.08*). When controlling for illness severity using MEDS score, the relative risk (RR) of death with EGDT was about half that of the control group (RR=0.52, 95% CI [0.27-0.960]). Also, by applying MEDS to risk stratify patients into various groups of illness severity, we found no specific groups where EGDT was more efficacious at reducing the Predicted Probability of death. EGDT lead to a 39.1% reduction in the median LOS in ICU (control=124 hours, study = 75.5 hours, *p=0.03*), without increasing LOS in ED (control = 6 hours, study = 7 hours, *p=0.69*).

Conclusions: EGDT is beneficial in septic patients regardless of their MEDS score. Our data suggests that risk stratification tools such as MEDS score should not be used to determine which patients should or should not receive EGDT.

Keywords: Sepsis; EGDT; MEDS score

Introduction

Severe sepsis and septic shock are associated with high mortality and have been a challenge to diagnose early and treat effectively in the emergency department (ED)[1]. In 2001, a randomized controlled trial examined the use of a systematic approach to treat patients presenting with severe sepsis and septic shock [2]. Their approach, termed early goal directed therapy (EGDT), was designed to aggressively resuscitate patients to achieve specific therapeutic endpoints. These "goals" included a central venous pressure (CVP) between 8-12 mmHg, mean arterial pressure (MAP) greater than or equal to 65 mmHg, urine output greater than or equal to 0.5 mL/kg/hr, or central venous oxygen saturation ($Scvo_2$) or mixed venous oxygen saturation greater than or equal to 70% or 65%, respectively. This was a unique approach to management because all prior studies evaluated the treatment of severe sepsis and septic shock in the intensive care unit (ICU) only. These investigators observed a 16% reduction in absolute mortality when EGDT was used suggesting that the management of severe sepsis is time-sensitive, with better outcomes for earlier initiation of therapy [2].

Although EGDT has been shown to improve mortality in septic patients, there is no evidence to date that delineates the role of using a risk stratification tool to determine which subgroups of patients may have a greater benefit with EGDT. The Mortality in Emergency Department Sepsis (MEDS) Score (Table 1) has been validated as a model to predict mortality in patients with sepsis and is based upon a point scoring system for clinical characteristics among septic presenting to the ED [3-5].

Risk stratification by MEDS risk group has the potential to identify patients who need more aggressive therapy and in turn, avoid aggressive, potentially harmful treatment in patients with lower risk of mortality [6-12]. Since EGDT requires a large amount of financial and human resources, risk stratification by patient presentation to the ED may help guide the efficient and responsible application of this therapy.

The primary objective of our study was to determine if an EGDT protocol differentially affects mortality based on the severity of illness using MEDS score. Secondary goals of this study were to evaluate the effect of EGDT on length of stay in ICU and ED.

Methods

Study design

This study was a retrospective chart review from January 1, 2007 to June 30, 2009, conducted at an academic tertiary care center ED that sees approximately 45,000 patients annually. The review was conducted by the authors for the hospital as a quality improvement measure following implementation of the EGDT protocol. As such, the study was granted exemption status by the Institutional Review Board.

Variables	Points
Terminal illness	6
Tachypnea or hypoxemia	3
Septic shock	3
Platelet count, < 150,000 cells/mm^3	3
Bands > 5%	3
Age, > 65 years	3
Lower respiratory infection	2
Nursing home resident	2
Altered mental status	2

Table 1: MEDS Score (Mortality %); 0-4 = Very Low(0.9%), 5-7 = Low(2%), 8-12 = Moderate (7.9%), 13-15 = High(20%), >15 = Very High (39%).

Study Protocol

An EGDT protocol was implemented on January 1, 2008 (Figure 1) as part of a initiative to improve outcome in septic patients. After implementation, we provided extensive in-service training to ED and ICU physicians and nurses regarding the protocol for a period of six months. This study compares in-hospital mortality, length of stay (LOS) in ICU, and LOS in ED between a control group and a post-implementation study group using MEDS score as a risk stratification tool.

Study population

We included all patients who presented to our ED with a discharge ICD-9 code for sepsis or bacteremia with two or more SIRS criteria on ED presentation: [(1) T > 38.3°C or < 36°C, (2) RR > 20, (3) HR > 90, and (4) WBC count > 12,000, or < 4000, or with > 10% bands], a MAP < 65 mmHg, a SBP < 90 mmHg, or a lactate ≥ 4 mmol/L.

We excluded all patients who presented during the six months of in-service training (from 1/1/08-6/30/08), those younger than 18 years of age, those who died on arrival to the ED, those that expressed wishes of Do Not Resuscitate or Do Not Intubate, those who needed an emergent surgical intervention, or those with comorbidities that actively complicated the initiation of the EGDT protocol. Examples of comorbidities include an acute myocardial infarction, COPD exacerbation, GI bleed, and CHF exacerbation. We also excluded patients who had significant portions of their chart missing, thereby preventing us from collecting critical data for our study.

Our study group consists of septic patients who presented to the ED from 7/1/08 to 6/30/09 and were managed according to our EGDT protocol, with a specific algorithm and specific antibiotics for each source of sepsis. The control group consisted of septic patients who presented to the ED from 1/1/07 to 12/31/07 and were managed according to the individual practices of each physician without any specific protocol. The practice pattern varied within the preimplantation group; however, prior to implementation of our protocol, CVP monitoring was not available in the ED.

Data collection

In total we trained eight data collectors to conduct the chart review and abstract the data in a predesigned standardized database form created in Microsoft® Access. Five of our data collectors were medical students, three were pharmacy students, and one was a pre-medical student. Each data collector had an individualized lecture on sepsis tailored to close any knowledge gaps that each person may have had on the subject matter. Prior to starting data collection, all team members had achieved the same level of background knowledge on the topic required to perform the data collection. Each data collector was then trained individually by the primary author on how to perform the chart review and how to enter the information into the database. Each data collector was then directly supervised by the primary author while performing data collection until he deemed them adequately trained to perform without direct supervision. After that, if the data collectors had any charts with missing data or questions, they would mark it as "incomplete" and leave the chart for the primary author to review and complete on his own. The primary author would also

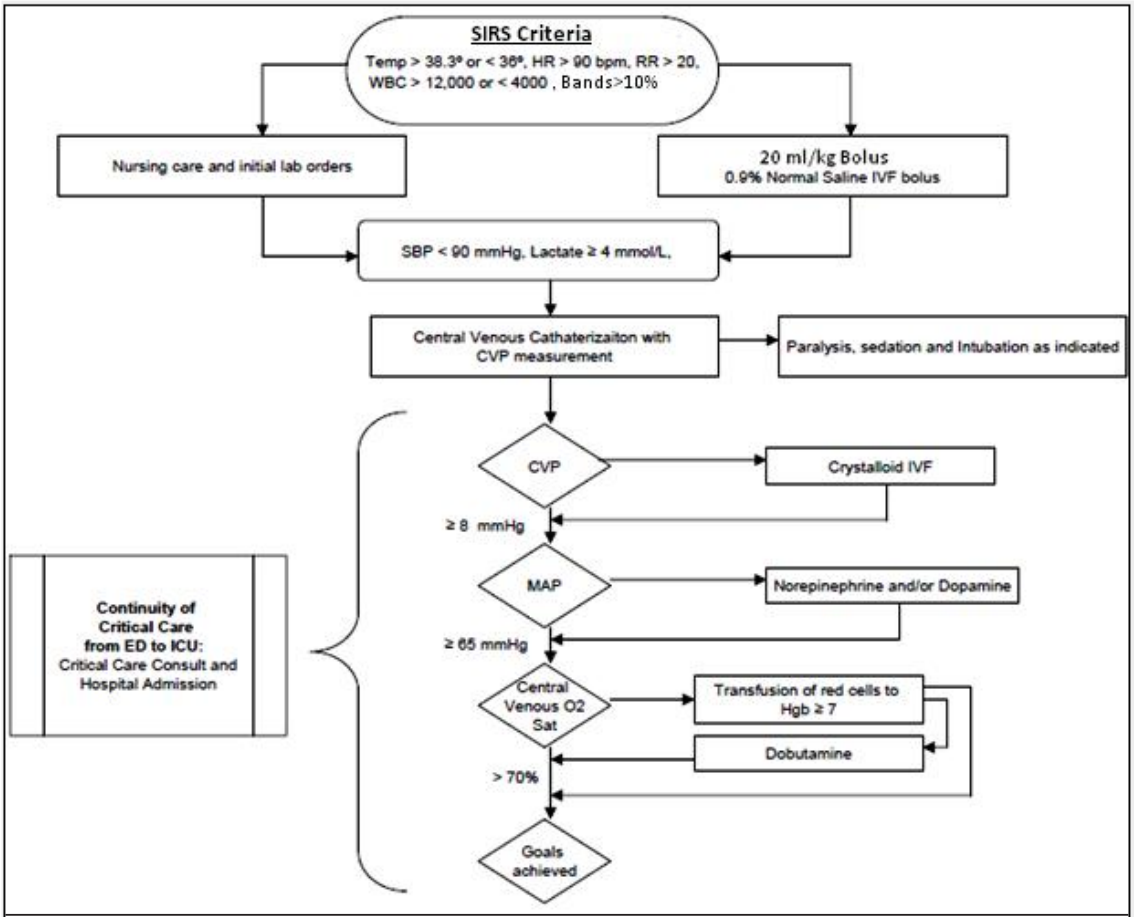

Figure 1: EGDT protocol.

SIRS = Systemic Inflamattory Response Syndrome; MAP = Mean Arterial Pressure; SBP = Systolic Blood Pressure; CVP = Central Venous Pressure

review any chart that either met exclusion criteria or did not meet inclusion criteria. There was no need to blind the data collectors as all data entry variables were objective. The primary author would also perform an internal audit approximately once a month, by randomly selecting charts completed by each trained data collector and perform a second review to ensure accuracy and reliability in the collection. An interrater k-statistic was not calculated as all data collected was objective and there were no data collected where variability should exist.

Data Analysis

Differences in selected continuous and categorical variables were examined between our two primary comparison groups using t-tests and chi-square tests respectively. Differences in mortality between our control and post-implementation groups were compared before and after adjustment for MEDS score using logistic regression. The adjusted odds ratios for dying and the accompanying 95% confidence intervals were calculated in a standard manner. The data collected were analyzed using SAS® software.

Results

In total we identified 622 patients with the ICD codes of sepsis or bacteremia, 379 patients were excluded from our study based on the above inclusion and exclusion criteria, leaving a total sample size of 243 patients (Figure 2). Of these, 117 patients were part of the EGDT study group and 126 patients were part of the control group. Table 2 shows the demographic distribution between the two groups, including the sources of sepsis. The distribution of patients within each group was similar in regards to age, gender, ethnicity, comorbidities, and sources of sepsis.

The absolute mortality in the control group was 30.2% while that of the study group was 20.5% (Figure 3). After controlling for illness severity using MEDS score, the risk (RR) of death with EGDT compared to the control group was 0.52 ([0.28-0.97], *p=0.04*). With subjects risk stratified into groups based on their MEDS score, EGDT was not statistically more efficacious at reducing the Predicted Probability of death in any of the individual stratified groups; however, in every risk group, the EGDT subjects had a reduced odds of dying (Table 3)

Furthermore, use of EGDT was associated with an approximate 40% reduction in the median LOS in the ICU. The median LOS in the ICU in the control group was 124 hours, while that in the study group was 74 hours, with *p=0.03*. The median LOS in the ED in the control group was 6 hours, while that of the study group was 7 hours, with a *p=0.50*.

Variable	Control	Post	*P- Value*
Age	63.3	65.4	0.24
Male (%)	66 (52.4)	63 (53.9)	0.82
Race			0.39
White	80	77	
Black	37	26	
Other	9	12	
Comorbidities	1.33	1.36	0.81
Source of Sepsis			0.46
GI	37	31	
GU	27	23	
Respiratory	48	41	
Soft Tissue	12	16	
Unknown	2	6	

Table 2: Patient demographics and sources of sepsis. Comorbidities include: Congestive heart failure, gastrointestinal bleed, myocardial infarction, diabetes mellitus, COPD (chronic obstructive pulmonary disease), HIV, Cancer, end-stage chronic renal insuffiency, and patient's who underwent organ transplant.

MEDS Score	n	Control	Study	Difference	*P- Value*
Very High (>15)	42	0.623	0.455	0.167	0.649
High (13-15)	53	0.498	0.335	0.163	0.714
Moderate (8-12)	103	0.357	0.219	0.137	0.454
Low (5-7)	30	0.181	0.101	0.080	0.814
Very Low (0-4)	15	0.127	0.069	0.059	0.654

Table 3: Predicted Probability of Death within each MEDS Score Illness Severity Subgroup.

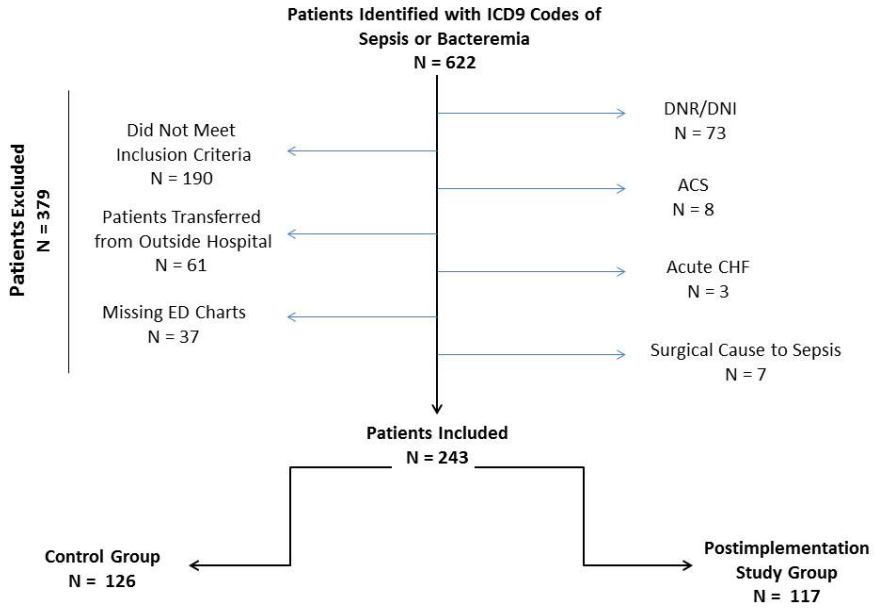

Figure 2: Exclusions Flowchart.

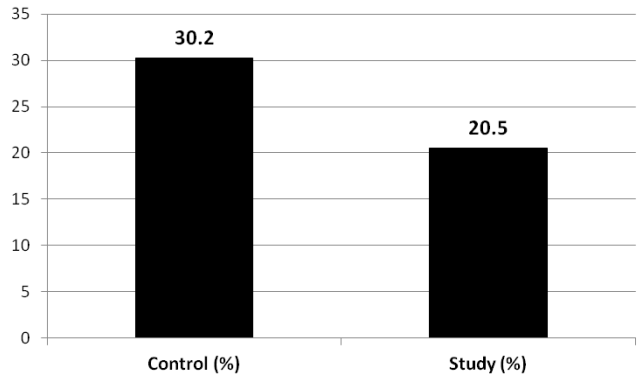

Figure 3: Absolute mortality in percent between the control and study groups without controlling for MEDS score (*p=0.086*).

Discussion

EGDT has been shown to reduce mortality by up to 16% [2], and our results further support this. However, critics of the protocol question its ability to be applied clinically in the ED. The efficacy of initiating an EGDT protocol was reviewed by two other independent studies, both of whom concluded that such an approach is efficacious clinically and that EGDT goals were achievable in a clinical setting [6,13] Our study further confirmed that EGDT reduces mortality, and this is even more evident when controlling for mortality risk.

Although MEDS score is a validated tool used to predict mortality in septic patients, it's utility in risk stratifying which patient may benefit more from EGDT has not been studied [3-5]. Our study has shown that EGDT reduced the predicted probability of death in all subgroups of severity using MEDS score (Table 3). There was no single group where EGDT was found to be more effective. However, those with higher MEDS scores have a higher predicted mortality than those with a very low score, therefore, a reduction in the predicted probability of death may be more evident with an intervention in the sicker patients. A larger study with a larger sample size within each subgroup may show statistically significant differences in the odds of dying between the various subgroups. Nevertheless, our data suggests that risk stratification tools such as MEDS score should not be used to determine which patients should or should not receive EGDT.

We also showed a benefit with EGDT in reducing the median LOS in the ICU. There were no other defined interventions in place by our institution to reduce ICU LOS. Furthermore, some critics of EGDT argue that it will significantly increase LOS in the ED. We observed no significant difference between the median LOS in the ED between the EGDT and control groups. Our institution generally can have long ED boarding times, and this may have impacted all patients LOS by causing them to stay longer in the ED regardless of whether they were started on EGDT or not. This may differ at other EDs where ED boarding is kept at a minimum.

Our study excluded patients who expressed wishes of Do Not Resuscitate or Do Not Intubate. As EGDT involves aggressive fluid resuscitation, placement of central lines, and potentially intubation, we did not want to include patients whose wishes regarding resuscitation could have impacted carrying out the protocol. This could have affected the outcome data we gathered in a retrospective fashion. We also excluded patients who had comorbidities that affected the initiation of EGDT such as acute MI, CHF exacerbation, or patients on hemodialysis. While these patients would be appropriate to include in a prospective study, the retrospective nature of our study makes it difficult for us to include these patients, as their comorbidity may have complicated the initiation or continuation of EGDT. We also excluded patients who were septic from a surgical cause that needed an emergent operative approach. These patients would not primarily benefit from EGDT alone and their outcomes were likely more dependent on the extent of their surgical disease. Also, the perioperative and postoperative complications that may have arisen would have added other confounding factors that would be hard to control for in a retrospective study.

Our study was not without its limitations. Based on the fact that this was a retrospective study at a single medical center, and that we decided to collect data during the year before and after implementation of the EGDT protocol to minimize possible biases and changes in various treatment modalities over time, we were inadequately powered to definitively state that EGDT led to an absolute decrease in the in-hospital death rates. After approximately 60% of possible patients were excluded due to our pre-defined exclusion criteria, we had a final sample size of 243 patients. Based on this available sample, and a pretest mortality rate of approximately 30%, we had a power of 44% to detect a difference in the absolute in-hospital death rate of 10%.

Also, as this review was retrospective, missing data from charts was a limitation of the study as incomplete documentation could have been the result of not adhering to the protocol or to merely not documenting what was in fact done. There were 37 patients identified as septic by their ICD-9 codes that were excluded due to missing ED charts. We have no way of identifying which MEDS score category these patients belonged to. If they were mostly skewed towards one end of the risk stratification, this may have changed the study outcome.

Furthermore, there were some differences in our EGDT protocol compared with the original study by Rivers et al [2]. Specifically, not everyone in the EGDT arm of our protocol received the protocol in its entirety. If they were hypotensive and responded to IVF, CVP monitoring was not performed in the ED. Continuous $ScvO_2$ monitoring was not used. Instead VBGs were drawn off the central line to obtain this measurement. Our threshold for blood transfusion was a Hgb < 7 rather than a Hgb < 10. The decision for this threshold was based on the results of the Transfusion Requirements in Critical Care trial (TRICC) which indicated that an increase in mortality was associated with blood transfusions in critically ill patients with Hgb < 10 as opposed to those with Hgb < 7 [14].

In addition, it is also important to acknowledge that while our results did not show a statistically significant difference in mortality in any of the individual risk groups, there was a reduction in mortality with EGDT in each of the five groups. With larger numbers, it is possible that each of the groups may have shown significant reductions, which would still support the conclusion that EGDT is beneficial across all sepsis patients. It is also noted that the percent reduction in mortality grew progressively larger with higher risk categories. A much larger sample size would be necessary to determine whether there is greater benefit with sicker patients.

We are aware that the results presented in two recent prospective trials [15,16] showed no differences in mortality between EGDT and "standard care"; however, an important point to consider is that protocol-based care, or EGDT, has become the standard of treatment at most clinical sites. Therefore, most physicians' individual practices will probably include elements of EGDT or protocol-based care when managing septic patients, even if they are not randomized to one those arms. This may be why significant differences in the principal study outcomes were not observed in these and other more recent studies. Moreover, a different study concluded that mortality in both sepsis and non-

sepsis patient populations significantly declined over a 12 year period and that this may be due to overall better healthcare, better medications, and understanding of illness for all medical diseases [17]. The study also suggest that in sepsis the trending decrease in mortality overtime was possibly due to more aggressive hydration, broader spectrum antibiotics, and early vasopressor use. Given this and the drastic results we saw at our institution over the span of one year, we believe that EGDT can provide benefit to several important patient outcomes. While we understand that our study has a number of limitations, we believe that it provides relevant information to our understanding of how to better manage patients who develop septic shock. Our findings suggest that employing a EGDT protocol reduced mortality and length of stay in the ICU. We believe that employing such a protocol makes physicians and nurses better at detecting sepsis at an earlier stage, and inasmuch, these health care providers are more aggressive with resuscitation with IV fluids and antibiotics and provide overall better care and awareness of these patients.

In conclusion, our data suggests that risk stratification tools such as MEDS score should not be used to determine which patients should receive EGDT. EGDT appears to be beneficial for all adult patients with severe sepsis or septic shock, regardless of their MEDS score. We found that it leads to reduction in the RR of death both overall and within each risk stratification group. It also resulted in a reduction in LOS in the ICU without affecting LOS in the ED.

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