Research Article

Could a protocol based on early goal-directed therapy improve outcomes in patients with severe sepsis and septic shock in the Intensive Care Unit setting?

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Abstract

Context: Sepsis is a disease with high incidence and mortality. Among the interventions of the resuscitation bundle, the early goal-directed therapy (EGDT) is recommended. **Aims:** The aim was to evaluate outcomes in patients with severe sepsis and septic shock using EGDT in real life compared with patients who did not undergo it in the Intensive Care Unit (ICU) setting. **Settings and Design:** retrospective and observational cohort study at tertiary hospital. **Subjects and Methods:** All the patients admitted to ICU were screened for severe sepsis or septic shock and included in a registry and followed. The patients were allocated in two groups according to submission or not to EGDT. **Results:** A total of 268 adult patients with severe sepsis or septic shock were included. EGDT was employed in 97/268 patients. The general mortality was higher in no early goal-directed therapy (no-EGDT) then in EGDT groups (49.7% vs. 37.1% [$P = 0.04$] in hospital and 40.4% vs. 29.9% [$P = 0.08$] in the ICU, respectively. The general length of stay [LOS] in the no-EGDT and EGDT groups was 45.0 ± 59.8 vs. 29.1 ± 30.1 days [$P = 0.002$] in hospital and 17.4 ± 19.4 vs. 9.1 ± 9.8 days [$P < 0.001$] in the ICU, respectively). **Conclusions:** Our study shows reduced mortality and LOS in patients submitted to EGDT in the ICU setting. A simplified EGDT without central venous oxygen saturation is an important tool for sepsis management.

Keywords: Early goal-directed therapy, outcomes, protocol, sepsis

Introduction

Sepsis is a disease with high incidence, high costs and mortality.[1-3] Angus *et al*. estimated 751,000 cases in the U.S. population per year.[3] The average costs per case were US$22,100, with annual total costs of US$16.7 billion nationally.[3] The mortality from severe sepsis and septic shock ranged from 30% to 40%.[3-5]

There are worldwide initiatives aiming to reduce mortality associated with sepsis, such as the surviving sepsis campaign (SSC).[6-9] Among the interventions of the resuscitation bundle by SSC, the early goal-directed therapy (EGDT) is a cardiovascular support protocol. The EGDT was performed using specific criteria for the early identification of high-risk sepsis patients, verified definitions, and a consensus-derived protocol to reverse the hemodynamic perturbations of hypovolemia, vasoregulation, myocardial suppression, and increased metabolic demands.[10]

Since the publication of the original study of EGDT by Rivers *et al*.[11] and others studies[12-24] had been developed, generating a lot of discussion regarding the concepts underlying the early pathogenesis of

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sepsis, the conceptualization of the study, controversies over the treatment algorithm, the salutary effects of EGDT on morbidity and mortality, as well as the generalization and implementation of EGDT.[10] Rivers *et al*. conducted the EGDT in the emergency department and the time of 6 h of presentation of severe sepsis and septic shock.[11] Currently, EGDT has not yet been implemented fully in actual practice especially in the intensive care setting.[4,5,25]

Therefore, the present study evaluated outcomes in patients with severe sepsis and septic shock who underwent EGDT compared to patients who did not undergo it in the Intensive Care Unit (ICU) setting. We also evaluated the reasons for not employing EGDT and also determined the patients who would be the best candidates for its use according to the severity of their condition. We also conducted an analysis of the reasons for not starting, endpoints and interventions of the EGDT protocol.

Subjects and Methods

Design and setting
A retrospective observational cohort study carried out in the Hospital Mãe de Deus ICU from October 1, 2005 to June 30, 2009. The ICU has 32 beds, with approximately 1700 annual ICU admissions. The Ethics Committee of the Mãe de Deus Hospital approved the study (number 419/10) and waived the need for patients' written informed consent.

Study population
All the patients admitted to ICU were screened by medical staff of the hospital for severe sepsis and septic shock. After admission in the ICU, the medical staff reviewed cases and confirmed the diagnosis severe sepsis or septic shock. All adults (aged 18 years or older), who met the classical severe sepsis or septic shock criteria[6,7,26] were included in a registry and followed.

Exclusion criteria were patients with do-not-resuscitate orders and patients with nonsepsis diagnosis. The patients were allocated in two groups according to submission or not to EGDT (EGDT and no-EGDT groups, respectively) previous judged by medical staff of the ICU. After initial evaluation of patients with severe sepsis and septic shock, the medical staff followed a preestablished protocol [Appendix 1] based on the SCC,[6,7] according to their individual judgment. All the patients included in the no-EGDT group, the interventions were based on the SSC and hemodynamic resuscitation guided by medical staff without protocol. When analyzing EGDT interventions, we divided patients according to

survival at ICU or hospital discharge (survivors [SV] or nonsurvivors [NSV]).

Data collection
For all study patients, the following patient characteristics were recorded: age, sex, site of infection, serum lactate, type of admission (clinical or surgical), time prior to admission in ICU, length of stay (LOS) and mortality in ICU and hospital, and severity of illness using the Acute Physiologic and Chronic Health Evaluation II (APACHE II) score based on the worst values obtained in the first 24 h in the ICU. The reasons for not employing EGDT were observed.

The central venous pressure (CVP), mean arterial pressure (MAP) and central venous oxygen saturation (ScvO$_2$) values were collected during the hemodynamic resuscitation of patients submitted to EGDT. ScvO$_2$ values were recorded hourly by central venous gas analysis performed by laboratory or continuous monitoring (central venous catheter capable of continuous ScvO$_2$ measurement [Edwards Lifesciences]) when available. Implementation and monitoring of EGDT.

After initial evaluation of patients with severe sepsis and septic shock, the medical staff followed a preestablished protocol [Appendix 1] based on the SSC,[6,7] according to their individual judgment. EGDT was applied only if the patient was within the first 6 h of diagnosis of severe sepsis and septic shock. The procedures started as soon as signs of tissue hypoperfusion began demonstrated clinically by arterial hypotension, oliguria, slow capillary bed filling and hyperlactatemia (lactate ≥ 4.0 mmol/L). The resuscitation started with 1000 ml crystalloids in 30 min and faster and larger volumes according to signs of tissue hypoperfusion. The quantities of volume had to be reduced if heart filling pressures increased without improving the hemodynamic status. If blood pressure did not respond to fluids, noradrenaline was initiated.

Hemodynamic resuscitation objectives were: (a) CVP between 8 and 12 mmHg; (b) MAP ≥ 65 mm Hg; (c) diuresis ≥ 0.5 ml/kg/h; (d) ScvO$_2$ ≥ 70%. When this last item did not reach the values recommended, transfusion of red packed blood cells (RPC) had to be considered) if the hematocrit was < 30% l in the first 6 h and also the use of dobutamine infusion until a dose of 20 μg/kg/min.

The following sequence was adopted:
1. Samples were collected within the 1st h after diagnosis of severe sepsis and septic shock: hematocrit,

hemoglobin, $ScvO_2$, and lactate (if not previously collected) were collected by the ICU nursing staff.

2. Monitoring: the nursing staff of the ICU inserted a urinary catheter. Medical staff placed central venous catheterization, always avoiding delays in infusion. Immediately after installing the catheter, chest X-ray was performed. Installation of CVP was conducted immediately after confirmation of the catheter position. MAP monitoring was ideally carried out on patients using vasopressor.

3. The steps were recorded hourly during the first 6 h of hemodynamic resuscitation in the group submitted to EGDT: CVP, oximetry, blood glucose measurement, $ScvO_2$, volume infusions (ml), dosis of noradrenaline and dobutamine, RPC units transfused and diuresis.

Statistical analyses

The results were reported as mean ± standard deviation, numbers and percentages. Student's *t*-test was applied when comparisons were made for parametric data. Nonparametric data were analyzed with the Mann–Whitney U-test. Categorical variables were analyzed using the Chi-square or Fisher's exact tests to find out whether there were differences among groups. All tests were two-tailed, and a $P < 0.05$ was predetermined for statistical significance. Analyses were done using the SPSS 17.0 software package (SPSS, Chicago, IL).

Results

The study population is summarized in Figure 1. Two patients were excluded with differential diagnosis of sepsis (pulmonary embolism and cardiogenic shock). The demographics of the 268 patients included in the study are summarized in Table 1. EGDT was employed in 97/268 patients (36.2% of the sample). The main causes for not submitting patients to EGDT (no-EGDT group) were ICU admission 6 h after the diagnosis of severe sepsis or septic shock (31%), congestive cardiac failure (6.3%), oliguric acute renal failure (3.0%), previous volemic therapy (1.9%), decision by medical staff (1.9%).

For the group submitted to EGDT, mean CVP, MAP and $ScvO_2$ and rates of goals achieved during the 6 h of EGDT are shown in Table 2. The means and rates were calculated separately for SV and NSV in the ICU. There were no significant differences in achieving EGDT goals in SV and NSV subgroups.

The use of fluids, noradrenaline, dobutamine and the RPC units administered in the group submitted to EGDT is shown in Table 3, according to ICU and hospital survival. The hospital NSV group received more fluid than the SV during EGDT (3.290 ± 1.920 vs. 2.540 ± 1.450 ml [$P = 0.04$]).

The general mortality in no-EGDT and EGDT groups was 49.7 vs. 37.1% ($P = 0.04$) in hospital and 40.4 vs. 29.9% ($P = 0.08$) in the ICU, respectively. In the subgroup with an APACHE II score lower than 20, mortality in the no-EGDT compared with EGDT was 42.5 vs. 23.5% ($P = 0.02$) in hospital and 32.5 vs. 17.6% ($P = 0.06$) in the ICU, respectively [Figure 2].

The general LOS in the no-EGDT and EGDT groups was 45.0 ± 59.8 vs. 29.1 ± 30.1 days ($P = 0.002$) in hospital and 17.4 ± 19.4 vs. 9.1 ± 9.8 days ($P < 0.001$) in the ICU, respectively. In the subgroup with an APACHE II score lower than 20, the LOS in the no-EGDT and EGDT groups was 48.4 ± 70.7 vs. 24.6 ± 21.4 days ($P = 0.01$) in hospital and 19.0 ± 23.8 days vs. and 7.5 ± 9.5 days ($P < 0.001$), respectively [Table 4].
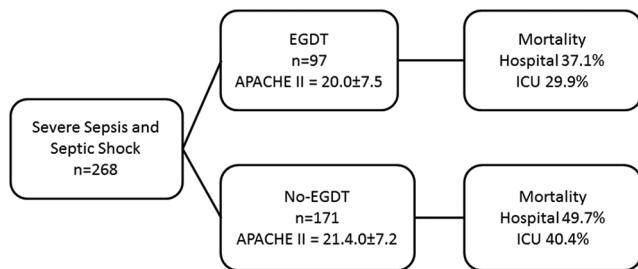

Figure 1: Study population: EGDT: Early goal-directed therapy group; no-EGDT: No Early goal-directed therapy group; APACHE II: Acute Physiologic and Chronic Health Evaluation II; ICU: Intensive Care Unit; This figure shows the patients included in the study with EGDT and no-EGDT groups. Both groups have similar APACHE II scores and the EGDT group has lower mortality
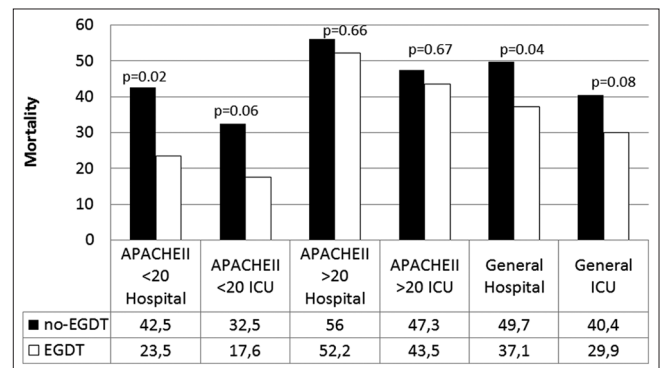

Figure 2: Mortality of the no-EGDT and EGDT groups; Dark = no-EGDT group (no-EGDT); White = EGDT group; EGDT: Early goal-directed therapy; APACHE II: Acute Physiologic and Chronic Health Evaluation II; ICU: Intensive Care Unit; Mortality (%); Chi-square or Fisher's exact test. This figure shows the overall mortality in EGDT and no-EGDT groups. Subgroups were divided according to severity by APACHE II score

Discussion

Our study shows the use of EGDT in the ICU setting, without aiming at the implementation or evaluation of the tool. In our study, the use of EGDT reduced mortality and LOS mainly in less severely ill patients as based on the APACHE II score.

Our study was conducted in single open ICU and was a nonrandomized study. The no-EGDT group of patients was older, with more respiratory infections and with a longer time of hospitalization prior to admission in ICU (although not statistically significant). The apparently worse condition of this group may have biased the medical decision to submit or not the patient to EGDT. Otherwise, there were no differences in the APACHE II score and the first value of lactate between both groups, suggesting that they were similarly critical.

We used the APACHE II score to evaluate whether different subgroups would benefit from EGDT before severe organ dysfunction was established. The mean APACHE II score in our group was 20.8. To choose a cutoff value, we reviewed the mean APACHE II scores of other studies using EGDT and who used this score (Rivers *et al*. was 20.9, Shapiro *et al*. was 22.6, Gao *et al*. was 19.5, Kortgen *et al*. was 33, Trzeciak *et al*. was 23.8, Micek *et al*. was 22.5 and Nguyen *et al*. was 29.8, the mean of all studies was 24.5).[11-13,15-18] and we also evaluated the study that assessed the use of drotrecogin alfa (activated) in patients with severe sepsis at low risk of death, using an APACHE II value of 25 for definition.[27] The objective of this study was to treat patients with established severe organ dysfunction. However, as we wanted to evaluate the use of EGDT before severe organ dysfunction was established the value had to be lower than in this study, and so we arbitrarily defined the value as 20.

Table 1: Baseline characteristics

Characteristic	no-EGDT	EGDT	P
Number of patients	171	97	-
Age, years*	71.0±15.7	64.9±17.8	0.005†
Gender: Male**	50	53	0.93††
APACHE II score*	21.4±7.2	20.0±7.5	0.2†
Clinical/surgical**	77.6/22.4	68.8/31.3	0.3††
Pre-ICU, days*	7.7±14.9	5.1±9.3	0.08†
Lactate*	2.7±2.7	3.0±1.6	0.06†
Infectious sites**			
Respiratory	49.7	40.2	0.001
Urinary	24.6	23.7	0.2
Abdomen	12.9	15.5	0.02
Cutaneous	5.3	7.2	0.6
Other sites	7.6	13.4	0.001

*Values in mean±SD; **Percentage; †Mann-Whitney U-test; ††Chi-square or Fisher's exact test. Baseline characteristics of the EGDT and no-EGDT groups. There are statistically significant differences in age and rate of respiratory and other sites infections. APACHE II: Acute Physiologic and Chronic Health Evaluation II; Pre-ICU: Time prior to admission in Intensive Care Unit; EGDT: Early goal-directed therapy; no-EGDT: No early goal-directed therapy; Others sites: Infective endocarditis, infected catheter, mediastinitis, epiglottitis, meningitis and undefined site infection; SD: Standard deviation

Table 2: Parameters during the EGDT

Parameter	Time of the EGDT (hours)						
	0 h	1 h	2 h	3 h	4 h	5 h	6 h
ScvO2							
NSV†	66.7±10.8	73.0±11.7	73.2±8.5	71.6±7.9	72.3±11.3	69.2±13.5	70.6±15.6
SV†	69.0±10.9	73.0±8.8	74.0±7.8	72.7±8.1	73.6±6.3	71.6±8.4	73.4±9.6
ScvO$_2$ >70%	46.7	64.6	70.0	63.0	68.4	61.1	72.9
CVP							
NSV††	8.3±3.9	8.3±4.7	8.3±4.0	10.4±4.6	9.6±2.8	8.9±2.8	9.9±3.2
SV††	10.1±5.1	9.2±5.2	9.6±5.0	9.7±5.2	9.8±4.4	9.1±4.5	9.5±4.3
CVP >8 mmHg%	64.0	60.7	67.1	63.2	75.6	71.3	76.8
MAP							
NSV††	66.8±15.6	75.7±18.9	74.2±22.5	78.9±21.1	77.3±15.4	77.1±15.8	76.7±13.7
SV††	65.4±13.7	74.0±13.0	75.9±14.1	75.4±15.4	80.5±19.0	81.5±18.1	81.3±13.3
MAP >65 mmHg%	51.7	76.1	80.9	83.7	92.3	90.1	90.8

†Percentage; ††mmHg. The percentage of patients who achieved goals and mean values for goals in NSV and SV groups hourly. EGDT: Early goal-directed therapy; ScvO$_2$: Central venous oxygen saturation; CVP: Central venous pressure; MAP: Mean arterial pressure; NSV: Nonsurvivors Intensive Care Unit; SV: Survivors Intensive Care Unit

Table 3: Interventions during EGDT

Intervention	ICU SV	ICU NSV	P	Hospital SV	Hospital NSV	P
Fluids (ml)	2.615±1.550	3.295±1.900	0.06	2.540±1.450	3.290±1.920	0.04††
Noradrenaline (%)	92.5	93.1	0.9	94.4	91.7	0.6†
Dobutamine (%)	14.5	17.9	0.6	14.0	18.2	0.6†
RPC (units)	0.16±0.5	0.41±9.8	0.2	0.17±0.4	0.36±0.9	0.2††

†Mann-Whitney U-test; ††Chi-square or Fisher's exact test. The different interventions during the implementation of EGDT classified by survival in ICU and hospital the only intervention that was statistically different was the amount of volume that the hospital survivors and NSV received during EGDT. ICU SV: Survivors at Intensive Care Unit discharge; ICU NSV: Nonsurvivors at Intensive Care Unit discharge; Hospital SV: Survivors at hospital discharge; Hospital NSV: Nonsurvivors at hospital discharge; RPC: Red packed blood cells; EGDT: Early goal-directed therapy

Table 4: LOS of the EGDT and no-EGDT groups

	no-EGDT (*n* = 171)	EGDT (*n* = 97)	*P*
Hospital LOS (days)			
General	45.0 ± 59.8	29.1 ± 30.1	0.002
APACHE II <20	48.4 ± 70.7	24.6 ± 21.4	0.01
APACHE II ≥20	41.9 ± 48.4	34.0 ± 37.0	0.13
ICU LOS (days)			
General	17.4 ± 19.4	9.1 ± 9.8	<0.001
APACHE II <20	19.0 ± 23.8	7.5 ± 9.5	<0.001
APACHE II ≥20	15.9 ± 14.5	10.7 ± 9.9	0.02

Mann–Whitney U-test. General LOS of the EGDT and no-EGDT groups. Subgroups were divided according to severity by APACHE II score. ICU and hospital LOS were lower in the whole EGDT group, but there were no differences between groups when APACHE II was higher than 20. EGDT: Early goal-directed therapy; no-EGDT: No early goal-directed therapy; APACHE II: Acute Physiologic and Chronic Health Evaluation II; LOS: Length of stay (days); ICU: Intensive Care Unit

Rivers *et al*. published the first study showing 16% absolute reduction in mortality with the use of EGDT compared with standard care in patients with severe sepsis and septic shock.[11] This study of EGDT was performed in the pre-ICU or ED phase of the disease, within 6 h of the patient's admission. However, the ProCESS and ARISE studies conducted too in the ED showed no differences in outcomes with the use of EGDT protocol-based or protocol-based standard therapy when compared to usual care.[28,29] Our results show the benefits of EGDT in the ICU, even in patients that had not just arrived in hospital with severe sepsis or septic shock, but in patients that may have developed severe sepsis or septic shock in hospital. Others have found results suggesting improvements in outcomes with EGDT compared with historical controls.[12-24] Shapiro *et al*. found a 20.3% reduced mortality in the EGDT group compared with 29.4% in historical controls.[13] Sebat *et al*. showed that the septic subgroup appeared to benefit from the Shock Program. The mortality rate was reduced to 32.6% compared with the septic shock control group whose mortality rate was 46%.[14]

In our study, a reduction of LOS occurred in the EGDT group compared with the traditional group (hospital LOS 29.1 ± 30.1 vs. 45.0 ± 59.8 [*P* = 0.002] and ICU LOS was 9.1 ± 9.8 vs. 17.4 ± 19.4 [*P* < 0.001]). These differences persisted in only in the subgroup of patients with APACHE II lower than 20, suggesting that this subgroup benefits more from EGDT. In the Rivers study, the mean LOS in the hospital was similar in both groups. Jones *et al*. found that the hospital LOS was 1.2 days longer in the EGDT group, whereas the mean ICU LOS was 1.8 days longer in the EGDT group.[19]

Since the publication of the Rivers study, numerous questions have been raised regarding specific components of treatment. In our study, no significant differences were seen between SV and NSV in the end points, suggesting that early treatment may have a greater influence than each goal alone. Trzeciak *et al*. found that all EGDT end points were successfully achieved in 91% of the EGDT cases.[12] Rivers *et al*. showed differences in the goals with the use of EGDT,[11] van Beest *et al*. showed a low incidence of low $ScvO_2$ in septic patients in Dutch ICUs. The mean $ScvO_2$ was 74% compared to 67.8% in our study, 71% in the ProCESS study and 48.9% in the Rivers study.[11,29,30]

Fluids were more used during EGDT in those of our patients who had not survived to hospital discharge (2.540 ± 1.450 vs. 3.290 ± 1.920 L, *P* = 0.04). In contrast, in the Rivers study those who received more fluids had a better outcome.[11] The Rivers study has been considered by some to be a liberal fluid strategy as the EGDT group received significantly more volume therapy and packed RBCs in the first 6 h of treatment. Other studies show that fluid resuscitation in septic shock with positive fluid balance and elevated CVP may be harmful.[31,32] Our study shows a similar use of dobutamine, noradrenaline and RPC between SV and NSV in the EGDT group.

Our study was conducted in the ICU setting and many patients are not selected to undergo EGDT. The main reason for not performing EGDT was the delay of ICU admission (56%). This may have occurred because the medical staff in the ward and the ED was not trained to recognize patients with severe sepsis and septic shock and to perform the EGDT outside the ICU. Our study was conducted in the ICU setting with staff trained in sepsis diagnosis and management with a specific approach protocol. The presence of an expert team with experience in sepsis management may be considered mainly in the ED and general practice medical-surgical floors. To achieve a consistent level of quality, multiple models of sepsis management with EGDT should be implemented, such as a multidisciplinary sepsis response team and model that rapidly transfers the patient to the ICU from the various locations within the hospital.[33] The early identification of a septic patient with an insidious illness allows the early implementation of EGDT and its benefits. These patients were treated quickly and did not suffer microcirculatory failure and the onset of severe organ dysfunction. However, studies showed that the delayed introduction of EGDT was associated with improved outcomes.[34,35]

Despite the failure of some sepsis bundle interventions during the development of better evidence such as recombinant human activate protein C,[36] the EGDT is still important to guide the management of these

patients. Moreover, the external validity of the recent studies is debatable to world reality who developing countries the culture of SSC certainly is not totally incorporate.[28,29] This corroborates that protocols may be useful, however, the individualization performed at the bedside by the professional is best approach the patients with sepsis. Improved recognition and management of sepsis outside the ICU is essential to reduce morbidity and mortality.

Conclusion

Our study shows reduced mortality and LOS in patients submitted to EGDT in an ICU setting. Besides customization, which is necessary to apply EGDT protocol, we think that simplified EGDT without ScvO$_2$ is an important tool for sepsis management.

The crucial point is that to apply this intervention, we need early recognition and management of sepsis. The hospital should have policies that help train the staff in medical and surgical floors in recognition and management of patients with sepsis. It should also enable quicker transfer of patients from the floors to the ICU.

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