The Concept of Early Goal-Directed Therapy in Sepsis Syndrome

HAZEM EL-AKABAWY, M.D.; MERVAT KHALAF, M.D.; FAHEEM RAGAB, M.D. and MICHAEL NAEEM, M.Sc.

The Department of Critical Care, Faculty of Medicine, Cairo University

Abstract

Background: Early goal-directed therapy (EGDT) used in the treatment of sepsis is essentially a comprehensive strategy that involves the early identification of high-risk septic patients and performance of a consensus-derived protocol to reverse the hemodynamic perturbations of hypovolemia, vasoregulation, myocardial suppression, and increased metabolic load by adjustment of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand.

Objective: To evaluate the concept of EGDT; provided at the earliest stages of severe sepsis and septic shock; regarding the clinical course and final outcome.

Methods: A prospective, randomized, single center study were conducted on 60 patients admitted with severe sepsis and septic shock, 30 patients were treated according to the protocol of EGDT which consists of aggressive hemodynamic support during the first 6 hours after sepsis is recognized, to achieve certain physiologic targets, the other 30 patients received only conventional sepsis treatment. Both groups were matched by APACHE IV score (within the 1st 6 hours). MODS and SOFA scores were calculated at baseline and everyday until ICU discharge or death. Clinical outcome (duration of stay in the ICU, need for mechanical ventilation, need for inotropic/vasopressor support, need for haemodialysis, and final outcome of survival/mortality rates) were recorded for all patients.

Results: EGDT, provided at earliest stage of severe sepsis or septic shock, (1) significantly improved patient outcome as indicated by significant reduction of SOFA and MODS scores from the second day of hospital stay (mean 1st day 9.5±3.02 Vs. mean 2nd day 7.8±3.66; p=0.006 for SOFA and mean1st day 7.93±1.75 Vs. mean2nd day 6.86±2.44; p=0.03 in MODS), (2) significantly reduced the length of ICU stay for surviving patients (8.2±3.1 Vs. 39±43 d; p=0.02), (3) significantly reduced the 28 days mortality (40% Vs. 73.3%; p=0.009), (4) non significantly reduced frequency of those needed vasopressor support (p=0.1) and non significantly reduced frequency of those needed MV (p=0.24).

Conclusion: EGDT provide significant benefits in patients with severe sepsis and septic shock.

Key Words: EGDT – Sepsis – APACHE IV – MODS – SOFA.

Introduction

THE systemic inflammatory response syndrome can be self-limited or can progress to severe sepsis and septic shock. Along this continuum, circulatory abnormalities (intravascular volume depletion, peripheral vasodilatation, myocardial depression, and increased metabolism) lead to an imbalance between systemic oxygen delivery and oxygen demand, resulting in global tissue hypoxia or shock which are a key development preceding multiorgan failure or death [1].

The transition to serious illness occurs during the critical “golden hours,” when definitive recognition and treatment provide maximal benefit in terms of outcome. These golden hours may elapse in the emergency department (ED), hospital ward, or the intensive care unit (ICU) [2].

Sepsis, especially severe sepsis and septic shock are complex healthcare problems around the world. There is a large burden of disease and high mortality. Outcomes have; until recently; remained relatively static, and the incidence is increasing. The optimal treatment strategy is constantly evolving and includes initial resuscitation, rapid diagnosis, timely administration of appropriate antibiotics, source identification and control, and meticulous ED and ICU management [3].

A more definitive resuscitation strategy involves goal-oriented manipulation of cardiac preload, afterload, and contractility to achieve a balance between systemic oxygen delivery and oxygen demand. End points include normalized values for mixed venous oxygen saturation, arterial lactate concentration, base deficit, and pH. Mixed venous oxygen saturation has been shown to be a surrogate for the cardiac index as a target for hemodynamic therapy [4].
Aim of the work:

To evaluate the concept of Early Goal Directed Therapy (EGDT); provided at the earliest stages of severe sepsis and septic shock; weather it affects the patients' outcome as regard the clinical course, multiorgan failure, mortality, and overall hospital stay.

Patients and Methods

The study protocol was approved by the local Ethics. A prospective, randomized clinical trial was conducted at Kasr Al-Aini Hospitals, Faculty of Medicine, Cairo University, Egypt.

Out of all patients admitted to the emergency department (ED) and/or during their stay in hospital ward and newly diagnosed as having severe sepsis, and/or septic shock due to variety of etiologies, during the period from March 2010 to February 2011; only 30 patients were selected, met the inclusion criteria and enrolled into the study.

Inclusion criteria: (1) Age ≥ 18 years, (2) Patients admitted to ED and considered as “qualifying for EGDT at triage” if they have an apparent source of infection and one of the followings: Hypotensive in triage and remained so during their initial intravenous fluid resuscitation in the ED (20-30ml/kg over 30-minute period), became hypotensive during the first 60 minutes after triage and that hypotensive reading occurred after adequate initial fluid resuscitation (20-30ml/kg), or Had an elevated serum lactate ≥4mmol/L as a marker of significant tissue hypoperfusion [8], (3) Patients; during their in hospital stay; and were found to have either: (i) Severe sepsis: Sepsis complicated by one organ dysfunction. "Sepsis (ACCP/SCCM criteria) [5]: (a) Clinically suspected infection as per the treating physician or confirmed infection and (b) 2 or more of the following: Temperature >38 °C (100.4 °F) or <36 C (96.8 °F), Heart rate (HR) >90/min, Respiratory rate (RR) >20/min or PaCO2 <32mmHg, White blood cell count > 12,000/mm3 or <4000/mm3 or >10% immature neutrophils. Organ dysfunction: Defined using the definitions used for SOFA score: (a) Change in mental status: GCS <9., (b) PaO2/FiO2 <26.7kpa (200mmHg), (c) Noradrenaline/Adren-aline ≥0.1 µg/kg/min., (c) Acute renal dis- function: Creatinin ≥3.5mg/dL, (d) Total Bilirubin ≥4 mg/dL, (e) Platelet count ≤100,000/mm³, (e) Lactate >3mmol/L." or (ii) Septic Shock: If they have the above criteria of severe sepsis and one of the followings: A systolic blood pressure (SBP) ≤90mm Hg after a fluid challenge of 20 to 30ml/kg over 30 minutes or If their SBP remained at least 40mm Hg below a well-documented baseline SBP after 20-30mL/kg fluid challenge over 30 minutes.

Exclusion criteria included pregnancy, trauma, burn, acute myocardial infarction, acute pulmonary edema, cardiac dysrhythmias (as a primary diagnosis), drug overdose, contraindication to central venous catheterization, overt GIT bleeding and patients with history of autoimmune disease, or immunosuppression (because of organ transplantation or systemic disease).

Patients who met inclusion criteria were followed up for a maximum period of 28 days or till the day of discharge or demise. They received a central venous catheter and treated according to the protocol of EGDT as soon as possible during the first 6 hours of admission and transferred to the first available inpatient ICU bed. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand.

Early goal-directed therapy consists of aggressive hemodynamic support during the first 6 hours after sepsis is recognized, that is aimed at achieving specific physiologic targets including: Central venous pressure (CVP) from 8 to 12mmHg; mean arterial pressure (MAP) greater than 65mmHg; urine output (UO) greater than 0.5mL/kg/hr; and central venous oxygen saturation (ScvO2) ≥ 70% from superior vena cava) greater than 70%. The goal for CVP in patients who are mechanically ventilated or who have increased abdominal pressure is between 12 and 15mmHg. ScvO2 measured by performing blood gas analysis on blood drawn through the distal port of a central venous catheter in the superior vena cava.

Fluid resuscitation was applied according to the Surviving Sepsis Campaign guidelines [6] which recommend administration of fluid challenges of 500 to 1000mL of crystalloids every 30 minutes in patients with suspected hypovolemia; these should be repeated based on the patient’s response (increase in MAP and UO) and tolerance (to achieve a CVP of 8-12mmHg). Fluid challenges are given in addition to the baseline maintenance fluid administration. If a ScvO2 of 70% is not achieved by fluid resuscitation alone, the guidelines recommend transfusion of packed red blood cells to achieve a hematocrit over 30% and/or administering dobutamine intravenously to achieve this goal. Dobutamine used as the agent of choice to increase cardiac output without increasing it above physiologic levels. It was started at a dose of 2.5 µg/kg/min., and was increased by 2.5 µg/kg/min every 30
minutes until the Scvo₂ was 70% or higher or until a maximum dose of 20µg/kg/min was given. An arterial catheter was placed as soon as practically possible. Vasopressors are indicated when fluid challenges do not restore blood pressure and organ perfusion. When used, the vasopressors are titrated to maintain a MAP of 65mmHg or higher. Norepinephrine at doses of 1-20µg/min was the vasopressor of choice used in this study.

Another 30-age matched-patients served as control group received only conventional sepsis treatment which consists of treating or eliminating the source of infection, timely and appropriate usage of antimicrobial agents, hemodynamic optimization, and other physiologic organ supportive measures. They were followed-up from the date of ICU admission until ICU discharge or demise or up to a total of 28 days.

**Evaluation of patients:** All included patients (those subjected to EGDT and the control group) were subjected to the following:

- **Full clinical evaluation:** Including history and physical examination with special emphasis on vital signs (MAP, HR, Temperature, RR, UO and CVP) and GCS; which were evaluated at the day of admission and then followed daily.

- **Laboratory investigations:**


  These routine Labs were withdrawn on study day 1 and subsequently thereafter every day until ICU discharge or demise or up to a total of 28 days.

- **Imaging studies:** Required to identify the source of sepsis e.g. ultrasound and chest X-ray.

  - **Clinical data:** Length of ICU stay, final outcome of survival/mortality rates and need for organ supportive measures (Vaspressors, Mechanical ventilation and/or Hemodialysis) were reported for all patients until ICU discharge or demise.

- **Application scoring systems:**

  APACHE IV ("Acute Physiology and Chronic Health Evaluation IV") score was evaluated on study day 1. APACHE IV score is a successful scoring system assessing severity of illness and prognosis of ICU patients. After admission of a patient to ER, an integer score computed based on several measurements was taken within the first 6 hours for all patients in the study; higher scores imply a more severe disease and a higher risk of death [8].

  The Sequential Organ Failure Assessment score, or just SOFA score was evaluated on study day 1 and serially every day until ICU discharge or demise or up to a total of 28 days. It is one of several ICU scoring systems. It is a six-organ dysfunction/failure score, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems, measuring multiple organ
The Concept of Early Goal-Directed Therapy in Sepsis Syndrome

...dysfunction/failure daily to track a patient's status during the stay in an ICU, and used to determine the extent of a person's organ function or rate of failure. Each organ is graded from 0 (normal) to 4 (the most abnormal), providing a daily score of 0 to 24 points. Both the mean and highest SOFA scores are particularly useful predictors of outcome [9,10].

The Multiple Organ Dysfunction Score (MODS):
Six systems defined the multiple organ dysfunction syndrome: a) the respiratory system (PO2/FIO2 ratio); b) the renal system (serum creatinine concentration); c) the hepatic system (serum bilirubin concentration); d) the hematologic system (platelet count); e) the central nervous system (GCS), and f) the new cardiovascular parameter, the pressure-adjusted heart rate, which is calculated as the product of the HR and the ratio of CVP to MAP. Most abnormal value of each variable were constructed on a scale from 0 to 4 so that a value of 0 represented essentially normal function, whereas a value of 4 represented marked functional derangement. Maximal scores for each variable were summed to yield a MODS (maximum of 24). This score correlates strongly with the ultimate risk of ICU mortality and hospital mortality [11,12].

Statistics:
Data were statistically described in terms of range, mean ± standard deviation (SD), median for quantitative variables, frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparison of quantitative variables between the study groups was done using Student t test for independent samples when normally distributed and Mann Whitney U test for independent samples when not normally distributed. For comparing categorical data, Chi square (c2) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between continuous variables was done using Pearson correlation coefficient. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version XP (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

I- Demographic and baseline clinical data at ICU admission:
Patients’ characteristics on admission as regards age, sex, comorbid conditions, place of admission, source of sepsis and clinical diagnosis as severe sepsis or septic shock in both groups are shown in Table (1).

| Table (1): Demographic and clinical data of the patients entered into the study. |
|--------------------------------------------------|------------------|------------------|------------------|
| Gender                                           | EGDT             | Control          | p value          |
| Males                                           | 20 (66.7%)       | 16 (53.3%)       | NS               |
| Females                                         | 10 (33.3%)       | 14 (46.7%)       | NS               |
| Age                                             | 59.9±22          | 63±14            | NS               |
| Comorbid conditions                              |                  |                  |                  |
| Diabetes                                        | 8 (26.6%)        | 18 (60%)         | NS               |
| Hypertension                                    | 8 (26.6%)        | 20 (66.6%)       | NS               |
| CAD                                             | 2 (6.6%)         | 6 (20%)          | NS               |
| Renal impairment                                | 8 (26.6%)        | 16 (53%)         | NS               |
| Cerebrovascular stroke                          | 8 (26.6%)        | 6 (20%)          | NS               |
| Malignancy                                      | 8 (26.6%)        | 2 (6.6%)         | NS               |
| Chronic liver disease                           | 4 (13.3%)        | 4 (13.3%)        | NS               |
| Chronic lung disease                            | 2 (6.6%)         | 2 (6.6%)         | NS               |
| Source of sepsis                                |                  |                  |                  |
| Respiratory                                     | 20 (66.6%)       | 20 (66.6%)       | NS               |
| Gastrointestinal                                | 8 (26.6%)        | 6 (20%)          | NS               |
| Genitourinary                                   | 4 (13.3%)        | 2 (6.6%)         | NS               |
| Skin/soft tissue                                | 2 (6.6%)         | 4 (13.3%)        | NS               |
| Place of admission                              |                  |                  |                  |
| Emergency room                                  | 14 (46.7%)       | 16 (53%)         | NS               |
| Inpatient ward                                  | 16 (53.3%)       | 14 (46.7%)       | NS               |
| Severe sepsis Vs. septic shock                  |                  |                  |                  |
| Severe sepsis                                   | 19 (63.3%)       | 18 (60%)         | NS               |
| Septic shock                                    | 11 (36.7%)       | 12 (40%)         | NS               |

NS: Non significant.
II- Administered treatment (protocol of EGDT):

- **IV fluids infusion:**

  During the initial six hours, the patients assigned to EGDT received significantly more fluid (colloid and crystalloids) than those of control group (1.5 ± 0.42 L Vs. 0.46±0.35L, with p=0.04 for colloids and 5.13±1.8 Vs. 1.26±1.17L, with p=0.02 for crystalloids).

  IV fluids infusion, either colloids or crystalloids were statistically higher in the first 6 hours of admission in EGDT group and extremely lower in the following days (1.5±0.42L in 1 st 6hrs Vs. 0.36±0.48 L in 2nd day with p<0.001 for colloids and 5.13±1.8L in 1 st 6hrs Vs. 2.86±0.8L in 2nd day with p<0.001). On the other hand, IV fluids infusion were statistically lower in the first 6 hours of admission in control group in relation to those in the following days (0.46±0.35L in 1 st 6hrs Vs. 1.56±0.41L in 2nd day with p<0.001 for colloids and 1.26±1.17L in 1 st 6hrs Vs. 4.2±0.77L in 2nd day with p<0.001).

- **Vasoactive agents:**

  Out of the 30 patients of EGDT group, 18 patients (60%) needed vasopressor support to maintain MAP ≥65mmHg in the first 6 hours of admission while 2 (6.6%) patients, out of 30 patients subjected to conventional therapy, needed vasopressor support, (60% Vs. 6.6% with p<0.001). During the following days, the incidence of patients needed vasopressor support decreased to 23.3% in those subjected to EGDT with p=0.004, while it increased to 80% in those subjected to conventional therapy with p<0.001.

- **Transfusion of red cells:**

  During the initial six hours, the patients assigned to EGDT received significantly more packed RBCs transfusion (40%) till hematocrit level reach ≥30% to maintain ScvO₂ ≥70%; than those of control group (10%) (p=0.007).

- **Inotropic agents:**

  Out of the 30 patients of EGDT group, 4 patients (13.3%) needed inotropic support to maintain ScvO₂ ≥70% if hematocrit reached ≥30% but still ScvO₂ <70% in 1 st 6hrs, on the other hand, only one patient (3.3%) received inotropic support in 18 6hrs in the control group (p value=0.16). In the following days, only 2 patients of EGDT group (6.6%) Vs. 11 patients of the control group (36.6%) received inotropic support (p=0.01).

III- Evaluation of severity of illness using APACHE IV scoring system:

The severity of illness in each patient on admission was evaluated in the first 6 hours of adm-

mission whether in ER or during hospital stay by using APACHE IV.

When comparing the APACHE IV score between the patients who subjected to EGDT protocol and the control group on admission; it showed no significant difference between them (77.2 ± 14.6 Vs. 79±25.1; p=0.778) Fig. (2). Correlation between APACHE IV and ICU stay was statistically non significant: Pearson correlation 0.275 with p=0.321. Correlation between APACHE IV and overall hospital stay was statistically non significant: Pearson correlation 0.077 with p=0.78.

![Mean APACHE IV score](image)

**Fig. (2):** Mean APACHE IV score of the patients entered into the study.

**IV- Evaluation of severity of illness using SOFA, and MODS scoring system:**

The severity of illness in each patient during ICU stay was evaluated daily by using SOFA score, and MODS, then the initial, mean, and last values were determined.

| Table (2): Mean ± SD of initial SOFA; mean SOFA, and last SOFA scores of the patients entered into the study. |
|--------------------------------------------------|-----------------|-----|
| **Case** | **Control** | **p value** |
| Initial SOFA | 9.5±3.02 | 8.4±3.75 | 0.37 |
| Mean SOFA | 7.31±4.01 | 7.61±3.8 | 0.69 |
| Last SOFA | 6.5±5.33 | 9.13±4.08 | 0.14 |

| Table (3): Mean ± SD of initial MODA; mean MODS, and last MODS scores of the patients entered into the study. |
|--------------------------------------------------|-----------------|-----|
| **Case** | **Control** | **p value** |
| Initial MODS | 7.93±1.75 | 6.86±3.29 | 0.27 |
| Mean MODS | 6.25±3.02 | 6.89±3.43 | 0.49 |
| Last MODS | 7.07±5.99 | 8.13±3.92 | 0.57 |

In the first day of hospital stay, there was non significant difference between both groups, as indicated by initial SOFA (p=0.37) Table (2), and initial MODS (p=0.27), Table (3).
In the following days of hospital course, there was significant difference into the patients subjected to EGDT, as indicated by: SOFA score significantly improved starting from second day (Mean 7.8 ± 3.66) versus (Mean 9.5 ± 3.02) in the first day with \( p = 0.006 \) and MODS score significantly improved starting from second day (Mean 6.86 ± 2.44) versus (Mean 7.93 ± 1.75) in the first day with \( p = 0.03 \).

Also, we found that SOFA and MODS scores significantly improved in the first five days of ICU stay reaching the peak in the 5\(^{th}\) day as regard SOFA score \( (p=0.01) \), and 4\(^{th}\) day as regard MODS score \( (p=0.009) \).

On the other hand, there was non significant difference in control group through out the hospital stay, as indicated by: SOFA score in the first day (Mean 8.4 ± 3.75) versus (Mean 8 ± 3.6) in the second day with \( p = 0.65 \) and MODS score in the first day (Mean 6.86 ± 3.29) versus (Mean 7.15 ± 2.91) in the second day with \( p = 0.98 \).

SOFA score-in both groups-at first day was not correlated with ICU stay (Person correlation coefficient=-0.205 and \( p=0.46 \)), nor with overall hospital stay (Pearson correlation coefficient=0.087 and \( p=0.75 \)), Fig. (3a).

MODS score-in both groups-at first day was not correlated with ICU stay (Person correlation coefficient=-0.103 and \( p=0.71 \)), nor with overall hospital stay (Pearson correlation coefficient=0.369 and \( p=0.17 \)), Fig. (3b).

Receiver operator characteristic (ROC) curves and areas under the curves with (95% confidence intervals) were also calculated for APACHE IV, SOFA and MODS scores in the prediction of ICU mortality at the day of admission: The area under the curve for APACHE IV score was 0.6 (95%CI, 0.510-0.820); optimal cut-off was 86; with a sensitivity of 86.4% and a specificity of 73% with \( p = 0.15 \), Fig. (4a). The area under the curve for SOFA score was 0.5 (95%CI, 0.434-0.699); best cut-off was 8.5; with a sensitivity of 52% and a specificity of 55% with \( p=0.9 \), Fig. (4b). The area under the curve for MODS score was 0.6 (95%CI, 0.520-0.810); optimal cut-off was 7.5; with a sensitivity of 58% and a specificity of 55% with \( p=0.3 \), Fig. (4c).

By evaluating the cut-off points for APACHE IV, SOFA and MODS scores at the day of admission by ROC curve analysis, there was non significant cut-off point that could predict mortality or survival.

Fig. (3a): Trend of SOFA score of the patients entered into the study.

Fig. (3b): Trend of MODS score of the patients entered into the study.

From above mentioned results, we can conclude that neither APACHE IV, nor SOFA, or MODS at the first day of admission correlates with patients outcome of both EGDT and control groups, and EGDT was the only independent factor that improve outcome in the 30 patients subjected to EGDT \( (p = 0.02) \).

V- Effect on clinical course:
- Need for organ supportive measures, readmission and need for emergency surgery:

In relation to the control group, the EGDT group exhibited non significantly lower frequency of those needed vasopressor support (18 “60%” Vs. 26 “86.7%” with \( p=0.1 \)) and non significantly lower frequency of those needed MV (18 “60%” Vs. 24 “80%” with \( p=0.24 \)). Patients needed acute HD exhibited non significantly higher frequency in those subjected to EGDT when compared with the control group (8 “26.7%” Vs. 6 “20%” with \( p=0.67 \)).
patients, there was a significant longer ICU stay in control group than in those subjected to EGDT (39±4.3 vs. 8.2±3.1 with \( p=0.02 \)).

- Mortality:

As regard the 28 days mortality, those subjected to EGDT showed a statistically significant lower incidence of mortality (40%) in relation to the control group (73.3%); \( p=0.009 \).

Discussion

The transition from the systemic inflammatory response syndrome to severe sepsis and septic shock involves a myriad of pathogenic changes, including circulatory abnormalities that result in global tissue hypoxia. These pathogenic changes have been the therapeutic target of previous outcome studies. Although this transition occurs over time, both out of the hospital and in the hospital, in outcome studies interventions have usually been initiated after admission to the intensive care unit [13].

The early identification of the septic patients with global tissue hypoxia accompanied by stable vital signs makes possible the early implementation of goal-directed therapy. If sudden cardiovascular collapse can be prevented, the subsequent need for vasopressors, mechanical ventilation, and pulmonary-artery catheterization (and their associated risks) diminishes. In addition to being a stimulus of the systemic inflammatory response syndrome, global tissue hypoxia independently contributes to endothelial activation and disruption of the homeostatic balance among coagulation, vascular permeability, and vascular tone. These are key mechanisms leading to microcirculatory failure, refractory tissue hypoxia, and organ dysfunction [14,15].

When early therapy is not comprehensive, the progression to severe disease may be well under way at the time of admission to the intensive care unit. Aggressive hemodynamic optimization and other therapy undertaken thereafter may be incompletely effective or even deleterious [1].

Therefore, the objectives of our study are to investigate the concept of EGDT, provided at the earliest stages of severe sepsis and septic shock, whether it affects the patients' outcome as regard the clinical course, organs functions, mortality, and overall hospital stay using the APACHE IV, SOFA, and MODS scoring systems.

The EGDT strategy is based on the early recognition of the oxygen delivery/oxygen consump-

- Length of ICU stay:

The mean length of ICU stay was 11.06±6.29 days for those who subjected to EGDT versus 13.4±17.27 days for the control group \( (p=0.62) \); which signifies a statistically non significant reduction in length of ICU stay, except for surviving patients. 

Fig. (4): ROC curves for
a) APACHE IV
b) SOFA
c) MODS
tion imbalance that precedes traditional shock (hypotension), and then applies an algorithmic approach to correcting and preventing the hemodynamic instability of severe sepsis and septic shock. The strategy aims for normal, rather than supranormal, oxygen delivery by optimizing preload (using CVP monitoring), afterload (using MAP), and contractility (guided by SvO₂) in order to resolve global tissue hypoxia (reflected by lactic acidosis) [7].

The main findings of this study are that EGDT, provided at earliest stage of severe sepsis or septic shock, (1) significantly improve patient outcome as indicated by significant reduction of SOFA and MODS scores from the second day of hospital stay \( p=0.006 \) for SOFA and 0.03 in MODS), (2) significantly reduce the length of ICU stay for surviving patients \( p=0.02 \), (3) significantly reduce the 28 days mortality \( p=0.009 \), (4) significantly reduced the 28 days mortality \( 40\% \) Vs. 73.3%; \( p=0.009 \), (4) non significantly reduced frequency of those needed vasopressor support \( p=0.1 \) and non significantly reduced frequency of those needed MV \( p=0.24 \).

In concordance to our results, Emanuel R, et al., 2001 [1], enrolled two-hundred sixty-three patients diagnosed with sepsis whom had a systolic blood pressure <90mmHg (despite at least 20 to 30cc/kg of crystalloid infusion) and they were randomize to receive either standard therapy or early goal directed therapy; all patients received both arterial and central venous catheterization as well as central venous oximetry (SvO₂) monitoring. Patients receiving EGDT received a six hour protocol with a set progression of endpoints based on CVP, MAP and ScvO₂ monitoring. They reported that EGDT provided in the ED to patients with severe sepsis and septic shock resulted in a significantly lower 28-day mortality than that associated with standard therapy \( 30.5\% \) in the EGDT group Vs. 46.5% in the control group, relative risk 0.58, 95% confidence interval 0.38-0.87; \( p=0.009 \). Baseline characteristics and organ-dysfunction score were the same in both groups. During the period from 7 to 72 hours, the APACHE II score, SAPS II, and MODS were significantly lower in the patient assigned to EGDT \( p<0.001 \) for all comparisons). Fewer patients in the EGDT group received mechanical ventilation \( p=0.02 \), vaso-pressor therapy \( p=0.02 \) and pulmonary artery catheterization \( p=0.01 \). Among patients who survived to discharge from hospital, EGDT decreased hospital stay by a mean of 3.8 days \( p=0.04 \). EGDT also reduced the incidence of sudden cardiovascular collapse by 50% compared to the control group (absolute reduction 10.7%; \( p=0.02 \)).

A larger study by Nguyen, et al., 2005 [17] evaluating the EGDT protocol prospectively enrolled 330 patients over a two-year period after beginning a “sepsis bundle protocol” (including EGDT, antibiotics, assessment for steroids, monitor lactate clearance). They reported that the in-hospital mortality in patients completing EGDT at 6 hours was 25.8 Vs. 38.8% in those patients whom did not complete the protocol \( p=0.03 \). Also, Micek, et al., 2006 [18] reported a 28-day mortality ARR of 18.3% \( p=0.04 \) following the implementation of a standardized order set for septic shock of which EGDT was a significant component.

In a small study of 22 patients, Trzcinski, et al., 2006 [19] demonstrated the feasibility of achieving the endpoints of EGDT in the ED by achieving all end points of resuscitation in 20 of 22 cases following implementation of EGDT. The authors reported a non-significant in-hospital mortality improvement compared to historical controls \( 18.2\% \) Vs. 43.8%; \( p=0.09 \).

On the other hand, Hayes, et al., [20] observed a higher in-hospital mortality rate in patients with septic shock with aggressive hemodynamic optimization in the intensive care unit (71%) than with control therapy (52%). Shapiro, et al., 2006 [21] published a prospective study following the implementation of their institutional sepsis protocol which included EGDT. Though there was no demonstrable mortality benefit, patient quality of care indicators such as fluid administration and antibiotic administration were significantly improved in the post intervention period.

In this study, we measured ScvO₂ (SvO₂ at the right atrium or superior vena cava) instead of the mixed venous oxygen saturation (SvO₂) measured using a sample of blood drawn from the distal port of a pulmonary artery catheter (Catheters equipped with continuous oximetry are also available). SvO₂ gives an estimate of the oxygen saturation of the blood returning to the right side of the heart, which indirectly correlates with tissue oxygen extraction, and the balance between systemic oxygen delivery and demand. Studies evaluating the numeric correlation of ScvO₂ and SvO₂ have concluded that ScvO₂ values are (on average) approximately 5% higher than SvO₂ values. This difference is likely due to the contribution of deoxygenated blood from the coronary sinus. Thus, substituting ScvO₂ for SvO₂ in the calculation of oxygen consumption can make it prone to unacceptably large errors.
balance between oxygen delivery and oxygen de-

benefits arise from the early identification of pa-

tients may die in the ED due to sudden cardio-

vascular collapse or may be admitted to the general

ward without their condition being recognized by

nurses, and consultants with a goal of timely de-

livery of optimal care (within one hour of arrival

at the hospital) will provide the maximal benefits

for patient outcome in septic shock compared with two other

approach to early disease recognition; sepsis has

traditionally been thought of as an “ICU disease”

rather than a hospital disease; inability to mobilize

system resources, difficulties in providing the

required higher level of care because of under-

staffed and overloaded ED that provide adverse

nurse/patient ratio, and the need to expedite the

transfer of the critically ill septic patients to the

ICU in order to alleviate pressure on the ED often

results in the provision of only cursory care to

these patients. Moreover, a significant percentage

of these patients are admitted to the general ward

because of lack of space in the ICU. Thus, septic

patients may die in the ED due to sudden cardio-

vascular collapse or may be admitted to the general

ward without their condition being recognized by

clinical tests performed during the pre-ICU period.
The crucial hours of therapy in the ED are often

missed and unrecognized.

The early recognition of severe sepsis before

the onset of septic shock is central for the success

of EGDT in significantly decreasing patient mor-

tality. Identifying this transition during the earlier

phase of the presentation of the disease, which

frequently occur in the ED, is vital. So, a team

approach that include the emergency physicians,
nurses, and consultants with a goal of timely de-

livery of optimal care (within one hour of arrival

at the hospital) will provide the maximal benefits

of EGDT, with reduced mortality, resource use,

and length of hospital stay.

Conclusion:

Goal-directed therapy provided at the earliest

stages of severe sepsis and septic shock, has sig-

nificant short-term and long-term benefits. These

benefits arise from the early identification of pa-

tients at high risk for cardiovascular collapse and

from early therapeutic intervention to restore a

balance between oxygen delivery and oxygen de-

Reference:

2. NGUYEN H., RIVERS E., HAVSTAD S., et al.: Critical care in the emergency department: A physiologic assess-

3. DAVID F., JESSE M., ROGER A., et al.: Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department; Critical Care Medicine, 38: 1-9, 2010.
5. BONE R., BALK R., CERRA F., et al.: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consen-

6. DELLINGER R., CARLET J., MASUR H., et al.: Sur-


