Editorial

What comes after the Early Goal Directed Therapy for sepsis era?

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The idea of sepsis was introduced in the literature in the 4th century BCE by the ancient Greek Hippocrates when animal and plant decomposition (σηψις, rot) was reported. In the 11th century, Avicenna described the process of acute inflammation and purulence formation, a "blood rot", and he included body temperature, heart rate, and the state of body fluids in his description (1). However, the word "sepsis" was not used until the 19th century. Over the past 30 years, the need to understand the underlying pathophysiological process and to identify better clinical criteria for early detection of sepsis has rapidly evolved because of the increasing number of patients with sepsis receiving advanced organ support systems, including mechanical ventilation, renal replacement therapy, and extracorporeal membrane oxygenation, has taxed health care systems (2,3). Furthermore, our awareness of the morbidity, mortality, and cost associated with this condition has increased.

Despite the fact that we adopt studies that have the best external and internal validity and we know that patients managed according to evidence-based medicine do better than patients treated according to physician judgment and expertise which can vary considerably, there is no doubt that not every positive outcome found in clinical studies on well-defined patient populations can be applied to "real world" situations with extremely heterogeneous patient populations with the expectation of similar results. In this editorial, I will address the conflicting results on the role of the early goal directed therapy (EGDT) in managing sepsis.

In the1990s, there was no standardized protocol for the early identification and treatment of patients with sepsis. The observed mortality then was more than 50%, and this triggered systematic investigations on the early identification and risk stratification of patients with sepsis and septic shock. The well-known study by Rivers *et al.* on EGDT conducted over 3 years (1997–2000) reported a significant 16% absolute decrease in mortality with an aggressive protocol for sepsis resuscitation in the first 6 hours after presentation to the emergency center (4). This study included 263 patients with severe sepsis and septic shock at a single urban Detroit emergency center and compared an EGDT protocol with standard "usual care" treatment. In the EGDT arm, patients received mandatory arterial catheters and central venous catheters with continuous central venous oxygen saturation ($ScvO_2$) measurements. Patients received crystalloid or colloid until prespecified central venous pressures (8–12 mmHg) and a prespecified mean arterial pressures (MAP ≥65 mmHg) were achieved. If their MAPs were below 65 mmHg, treatment with vasopressors was started. If their $ScvO_2$ saturations were less than 70%, patients were transfused until their hematocrits were greater than 30%, and if the $ScvO_2$ remained low, patients were started on dobutamine. Both groups had early cultures.

Despite initial concerns regarding the external validity of the EGDT study, since it was a single center study with a relatively "high" control group mortality of 46.5 %, EGDT was adopted worldwide and became a fundamental element of the sepsis resuscitation bundle for the Surviving Sepsis Campaign. In this study, the total volume of fluid received and the number of patients who received dobutamine were similar in both groups (EGDT *vs.* usual care) at 72 hours. However, the EGDT group received more fluid and dobutamine in the first 6 hours which resulted in higher $ScvO_2$ saturations and lower mean APACHE II scores from 7 to 72 hours. An important question after this study was which intervention(s) in the protocol had the most significant impact on mortality. Some of the EGDT elements have not proved beneficial when tested alone.

For instance, transfusion of packed red blood cells to a goal hematocrit of 30% when $ScvO_2$ is <70% contradicts the results of multiple studies which demonstrate that no mortality differences between restrictive *vs.* liberal transfusion strategies (no transfusion until hemoglobin of 7 g/dL *vs.* hemoglobin level of 10 g/dL). Additionally, central venous pressure measurement has been a controversial tool and poor surrogate for blood volume in critically ill patients. Furthermore, lactate, which correlates with severity in sepsis, was not part of the protocol in directing care and was used only as inclusion criteria (lactate level ≥4 mmol/L).

In an effort to address the above questions, three multicentered randomized controlled trials were published (2014–2015), including ProCESS (Protocol-Based Care for Early Septic Shock) (5), ARISE (Australasian Resuscitation in Sepsis Evaluation) (6), and ProMISe (Protocolized Management in Sepsis) (7). These studies compared the original EGDT protocol with contemporary usual care. As expected, patients in EGDT arm received the same interventions used in the EGDT protocol of the Rivers study. These three studies concluded that EGDT did not reduce the 90-day mortality in patients who received EGDT compared to usual care (8,9). Furthermore, EGDT was associated with increased admission to ICU and higher hospitalization costs across a wide range of patients and hospitals. These results were very surprising and resulted in multiple expert commentaries, especially after The Protocolized Resuscitation in Sepsis Meta-Analysis "PRISM" data were published in March 2017 (9). This meta-analysis pooled data from the "ProCESS, ARISE, and ProMISe trials" to potentially identify subgroups of patients for whom EGDT is effective at reducing mortality compared to usual care and/or identify elements of EGDT/usual care that are associated with lower mortality.

Why is there a discrepancy between the Rivers trial and the three most recent studies? This question must be related to the usual care group since the EGDT protocol in the three trials and the EGDT protocol in the original study were the same. The first disparity noted is that the mortality rates in the usual care group in the Rivers study and the usual care groups in recent trials were different. In the original EGDT study, the baseline mortality for the standard care group was 46.5% compared to the 90-day mortality rates of 18.8% to 29. 2% in the usual care group in ARISE, ProCESS, and ProMISe. This suggests that the usual care group in the Rivers study was significantly sicker. Therefore, is a difference in the baseline patient characteristics the reason that subsequent studies failed to replicate the positive outcome seen in the original EGDT study? This question was answered after a close review of the data. Both Nguyen *et al.* and PRISM investigators used different approaches to identify and match the severely sick patients. For example, PRISM investigators identified subgroups of severely sick patients, and the size of this sample was 4 times larger than the entire cohort studied by Rivers *et al.* These investigators used eight ways to stratify the disease severity and identified the top third of predicted risk of death. However, they found no treatment benefit with EGDT in patients with greater severity of illness (8,9). This failure to replicate the results in the Rivers study suggests that current usual care treatment strategies can provide equal reductions in mortality.

After a focused review of the usual care group of these trials, the usual care group of the recent trials "ProCESS, ARISE, and ProMISe" looked very similar to the EGDT group in the original trial. Patients in the usual care group of the recent three trials received significant volume resuscitation in the emergency center prior to randomization. The median of administered volume is 27.7 mL/kg in usual care group compared to 27.5 mL/kg in the EGDT group as indicated in the PRISM analysis. In fact, most patients received a minimum of 1 liter of fluid to meet one of the inclusion criteria (refractory hypotension) in the three trials. In addition, some of the interventions in the usual care group in the Rivers study were not defined well; the treatment approach was not always clear and depended on the treating clinicians' judgment. For instance, unclear antibiotics timing in the Rivers study could affect outcomes; from the available data we only know the percentage of patients who received antibiotics in the first 6 hours (86% of the patients of EGDT and 92% of the patients of standard care). It would be more helpful if we had data for the percentage of patients who received antibiotics in the first 2–3 hours or for the mean time for the first administered antibiotics in each group. The New York State Department of Health reported results which included 49,331 patients with sepsis treated at 149 hospitals (10). A longer time to the administration of antibiotics was associated with increased mortality (odds ratio: 1.04 per hour, 95% CI: 1.03–1.06). Patients who received antibiotics during hours 3–12 had a 14% higher odds of in-hospital death then patients who received antibiotics within 3 hours.

Therefore, the differences in outcomes in the recent EGDT trials and the original study likely explained by increased awareness of sepsis and efforts related to the Surviving Sepsis Campaign and sepsis bundles over the

past 16 years, and the original experimental protocol has become usual care even if the protocol is not always used or uniformly applied. It has been shown that large prospective studies that have confirmed the external validity and reliability of the EGDT trial provide an equally reliable scientific alternative to randomized control trials (11,12). Actually, the combination of the ongoing significant reduction in sepsis mortality over the last 16 years and decreasing differences in treatment effect between contemporary usual care and EGDT seems to make even valid and reliable studies inconclusive. In this situation, which components of usual care have evolved? Early volume resuscitation and antibiotics have become the new "usual care", and no additional aggressive interventions are needed. Some components of EGDT protocol, such as blood transfusion, continuous $ScvO_2$ monitoring, are unlikely to be advantageous in all patients (13). The 2016 international guidelines for management of sepsis and septic shock "Surviving Sepsis Campaign" based on these recent studies recommend immediate antibiotics and volume resuscitation with additional fluid to be guided by frequent assessment of hemodynamic status and targeting MAP >65 mmHg. Vasopressors should be added when needed. Hemodynamic assessment of cardiac function is recommended if the type of shock is not clear. Furthermore, no routine recommendations are made for mandatory placement of a central venous catheters, continuous measuring ScvO2, transfusing PRBC, etc. (12).

However, there is still unclear guidance for the most effective volume and vasopressors regimens and the best approach to measure volume status or assess fluid responsiveness. What is the best approach to resuscitate patients with sepsis from now on? Conclusions which discount EGDT should not lead clinicians to manage sepsis patients based on individualized care, especially in situations with wide ranges in expertise and opinions. This is the wrong conclusion. Clinicians should intervene quickly with fluids and antibiotics and use their best and repeated clinical judgment to evaluate the patients' responses to therapy.

I am optimistic that future research will provide a better understanding of the pathophysiological processes in sepsis at the cellular level and potentially lead to additional therapy. Until then I think that the measurement of biomarkers at the bedside (point of care) can improve the accuracy of sepsis prediction tools, such as the SIRS criteria and qSOFA. Ljungström *et al.* reported that the combination of procalcitonin, C-reactive protein, lactate, and the neutrophil to lymphocyte ratio predicted the presence of bacteremia with an area under the curve at nearly 0.8 (14). These laboratory tests are readily available at the time of admission and could influence clinical decisions.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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