"Early goal-directed therapy" versus "Early" and "goal-directed" therapy for severe sepsis and septic shock: Time to rationalize

Sahajal Dhooria, Ritesh Agarwal

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, Haryana and Punjab, India
E-mail: sahajal@gmail.com

Early goal-directed therapy (EGDT) proposed by Rivers *et al*. in 2001, a protocolized management of fluid replacement therapy in severe sepsis and septic shock resulted in a significant reduction in mortality (absolute risk reduction by 16%) as compared to the standard therapy.[1] An identical protocol has been recommended by the International Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock.[2] The protocol has received enormous attention and has been adopted either completely or at least in its components in numerous intensive care units worldwide. Recently, three large studies the ProCESS, ARISE, and ProMISe have challenged the benefit of this approach in improving survival in severe sepsis.[3-5] The ARISE study found no difference in mortality between EGDT and the usual care group. Similarly, the ProCESS trial concluded that there was no difference in mortality between the two groups in either of the two comparisons: (a) EGDT versus protocol-based standard therapy; and, (b) protocol-based therapy versus the usual care. Recently, the ProMISe study inferred that the EGDT as compared to usual care led to increased costs but without any improvement in the survival.[5] Contrary to the results of these three studies, in a recent meta-analysis of 13 studies it was found that EGDT did improve mortality with a relative risk reduction of 17%.[6] All these studies have, of late sparked a debate in the international community over the usefulness of EGDT and what path to choose?

In contrast to the original EGDT trial, the recent three studies namely the ProCESS, ARISE, and ProMISe had a lower mortality in the study population.[7] This indicates two aspects of these studies: A less sick patient population (mean APACHE II scores were nearly 20 in ProCESS, 15 in ARISE, and 18 in ProMISe) and a very experienced physician population delivering the usual care. This is unlike the situation in the real world where sicker patients present to a facility, which in addition may have less experienced physicians delivering critical care. In commentaries published elsewhere, the following issues have already been discussed: The lower mortality in the ARISE and ProCESS studies, the decreasing trend in sepsis mortality after the advent of the study by Rivers *et al*. and

improving survival in sepsis despite non-adherence to the surviving sepsis campaign guidelines.[7,8] Herein, we attempt to further analyze the factors that might have led to the apparent conflict between the studies by Rivers *et al*. and the subsequent ProCESS, ARISE, and ProMISe studies. We also make a case for the early and goal-directed components of the EGDT, at the same time questioning the utility of some of its other components.

A CASE FOR "EARLY" THERAPY

The most apparent differences between the two groups (EGDT and standard therapy) in Rivers *et al*. were the use of central venous oxygen saturation ($ScvO_2$) monitoring and the use of dobutamine and blood transfusions to achieve $ScvO_2$ target of 70%. However, two important components: Early administration of antibiotics, and aggressive fluid administration to achieve predefined targets of central venous pressure (CVP, 8-12 mmHg), mean arterial pressure (MAP, >65 mmHg) and urine output (>0.5 mL/kg/hour) were similar between the two groups. Despite the aggressive fluid administration recommended in both the experimental and control groups, the actual amount of fluid administered and the mean CVP achieved in the first 6 hours were significantly lower in the standard therapy group as compared to the EGDT group. So it is possible that a 'more aggressive early fluid management' rather than the rest of the components of EGDT (including $ScvO_2$ monitoring, dobutamine infusion and blood transfusions) resulted in the significant reduction in mortality observed in the study group. Gu *et al*. in their meta-analysis also found that in studies comparing the GDT with standard care, a significant difference in mortality was found only in studies in which the GDT timing was clearly mentioned as early. In those with late or unclear timing, there was no significant difference. Thus, early aggressive fluid replacement is paramount.

A CASE FOR "GOAL-DIRECTED" THERAPY

All the four studies (Rivers *et al*., PROCESS, ARISE, and ProMISe) envisaged "goal-directed" fluid management not only in their EGDT group but also in their standard therapy

groups.[1,3-5] Although the targets varied in the different study groups. The ultimate goal was aggressive fluid resuscitation. As already pointed out above, in the Rivers *et al.* study, a goal-directed approach chasing CVP and MAP targets was indeed planned in the usual care group albeit adequate early fluid resuscitation was not aggressively achieved in that group, possibly explaining the higher mortality as compared to the experimental arm. The PROCESS, ARISE, and ProMISe studies also pursued goal-directed approaches guided by certain clinical parameters to achieve fluid resuscitation in the standard therapy groups.[3-5] Time-sensitive fluid targets were pursued, and fluid status and organ perfusion assessments with urine output and sensorium were indeed performed. Patients in both the groups received early antibiotics and large volumes of intravenous fluids (more than 2 liters in ProCESS and more than 2.5 liters in ARISE, and around 2 liters in ProMISe) prior to randomization. Although central venous catheterization was not mandatory in the usual care group in ProCESS, more than half of patients in that group underwent central venous catheterization. In the ProMISe study also, half of the patients received central venous catheters. It is apparent that aggressive "early" and "goal-directed" fluid resuscitation was pursued even in the control groups of ProCESS, ARISE, and ProMISe studies.

Thus it is abundantly clear that all the four studies pursued early and goal-directed approaches in both the experimental and the control groups. The biggest question that then remains is: What is the utility of targeting a predefined value of $ScvO_2$ in the management of septic shock? Does it offer any advantage over other methods of estimating tissue perfusion such as arterial lactate? The evidence is at best equivocal. A preliminary study suggests that measuring lactate clearance as a target for achieving adequate tissue perfusion may be non-inferior to central venous oxygen saturation.[9] However, another recent study suggests that measurement of $ScvO_2$ might offer additional clinical information as low $ScvO_2$ is common in the initial hours of severe sepsis or septic shock even when clinical resuscitation targets are achieved and even when arterial lactate is normal. Further, a $ScvO_2$ below 70% in the first hours of ICU admission and 6 hours later is associated with increased day-28 mortality.[10] The ARISE study in which the $ScvO_2$ measurements were not permitted in the usual care group during the first 6 hours, the group still had survival similar to the EGDT group.[4] The three studies ProCESS, ARISE, and ProMISe studies do seem to indicate that "mandated use of $ScvO_2$" might not provide any added benefit in the early management of sepsis and septic shock. However, they should not be interpreted as a death knell on "early" and "goal-directed" components of the EGDT.

Another noteworthy issue is that of patients with both acute respiratory distress syndrome (ARDS) and septic shock, in whom a strategy of aggressive initial fluid management is generally followed directed at the management of septic shock.[11,12] In such patients a cautious approach to fluid balance is even more vital. Objective parameters of assessing fluid balance,

from the more familiar methods such as CVP to less used modalities such as inferior cava diameter and collapsibility, and the even more advanced cardiac output monitoring systems might be helpful. More than 60% of the patients in the ProCESS and ARISE studies had sepsis of non-respiratory origin. Therefore, the results of these studies cannot be extrapolated to patients with sepsis and ARDS.

PROTOCOLIZED THERAPY

Protocols help in streamlining of medical care, by reducing variability in the care delivered by different individuals, and decrease errors of both omission and commission.[13] Whether a particular site of care (emergency or intensive care unit) in a certain hospital requires a protocolized management or it can adhere to usual care would depend on how trained and experienced are the physicians manning the site and thus how effective the "usual care" is. If the medical personnel indeed include an experienced critical care specialist adept in dealing with septic shock, usual care might be sufficient as the physician would inevitably take care of two important things: Early antibiotics, and early aggressive fluid management (guided by "experience", CVP, and possibly by more advanced techniques such as echocardiography, ultrasound-based or cardiac output monitoring-based techniques, in order to achieve the urine output and mean arterial pressure goals). Alternatively, for a relatively less experienced trainee supervising the treatment, a preset protocol would help to minimize the chances of errors and variability.

In conclusion, management of severe sepsis and septic shock needs to be "early" and "goal-directed" with early antibiotic administration and aggressive early fluid management. Although the need for a protocol and its various components may vary from centre-to-centre, the above two principles cannot be ignored.

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