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Controversies

Early goal-directed therapy: on terminal life support?☆

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Abstract Early goal-directed therapy (EGDT) has become regarded as the standard of care for the management of patients with severe sepsis and septic shock. The elements of EGDT have been bundled together as the "Sepsis Bundle," and compliance with the elements of the bundle is frequently used as an indicator of the quality of care delivered. The major elements of EGDT include fluid resuscitation to achieve a central venous pressure of 8 to 12 cm of water, followed by the transfusion of packed red cells or an inotropic agent to maintain the central venous oxygen saturation higher than 70%. Although the concept of early resuscitation is a scientifically sound concept, we believe that the major elements of the sepsis bundle are fatally flawed.

In November of 2001, a report by Rivers and collaborators [1] entitled "Early goal-directed therapy in the treatment of severe sepsis and septic shock" was published in the *New England Journal of Medicine*. Although this was a small (n = 263), nonblinded, industry-supported, single-center trial, the concept of "early goal-directed therapy" (EGDT) was rapidly embraced by acute care practitioners around the world, being endorsed by the Joint Commission, the Institute of Healthcare Improvement, the Volunteer Hospitals Association, and the Surviving Sepsis Campaign [2-6]. Subsequently, clinical studies emerged that suggested that EGDT "could reliably be achieved in real-world clinical practice" [7]; and EGDT became accepted as the standard of care. The elements of EGDT were then "bundled" together as the "Sepsis Bundle" [2,3,8]. According to the Institute of Healthcare Improvement, a "bundle is a group of interventions related to a disease process that, when executed together, result in better outcomes than when implemented individually." Indeed, the number of the elements of the sepsis bundle that hospitals achieve (using checklists) is used as an indicator of the quality of care delivered [3,8].

Early goal-directed therapy, best described by Wikipedia, is a "systematic approach to resuscitation which is meant to be started in the emergency department and uses a step-wise approach to optimize cardiac preload, afterload, and contractility, thus optimizing oxygen delivery to the tissues" [9]. Although the concept of early, as opposed to delayed, volume resuscitation and the timely initiation of appropriate antibiotics in patients with severe sepsis and septic shock is a scientifically sound concept, the major elements of the "EGDT bundle" appear to be fatally flawed.

The first step in EGDT is to administer fluids until the central venous pressure (CVP) reaches 8 to 12 cm of water (or 10-15 cm of water in mechanically ventilated patients) [1-5]. The problem with this approach is that the CVP has reproducibly been shown to be a poor predictor of intravascular volume and fluid responsiveness [10,11]. Depending on the characteristics of an individual patients' right ventricular pressure-volume curve, titrating fluid based on the CVP is equally likely to result in either hypovolemia or pulmonary edema. Indeed, the American College of

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Critical Care Medicine practice guidelines for hemodynamic support of sepsis in adult patients state that "fluid infusion should be titrated to a … filling pressure" and that "pulmonary edema may occur as a complication of fluid resuscitation" [12]. Over the last decade, a number of studies have been reported that have used heart-lung interactions during mechanical ventilation to assess fluid responsiveness. Specifically, the pulse pressure variation derived from analysis of the arterial waveform and the stroke volume variation derived from pulse contour analysis have been shown to be highly predictive of fluid responsiveness [11]. Similarly, positive pressure ventilation–induced changes in vena caval diameter have been shown to be predictive of fluid responsiveness [13]. These dynamic indices of volume responsiveness are dependent on the cyclic changes in intrathoracic pressure induced by positive pressure ventilation and are not applicable to spontaneously breathing patients. However, changes in stroke volume induced by passive leg raising in nonventilated patients have been demonstrated to be predictive of volume responsiveness [14]. Furthermore, in spontaneously breathing trauma patients, Yanagawa and colleagues demonstrated that the diameter of the inferior vena cava as measured by ultrasonography was indicative of the adequacy of fluid resuscitation [15]. These dynamic methods of determining preload responsiveness should replace the CVP and other static indices of intravascular volume in the resuscitation of critically ill patients.

Once the target CVP has been reached and vasopressors have been titrated to achieve a mean arterial pressure greater than 65 mm Hg, the next step in EGDT is to transfuse red blood cells until the hematocrit is greater than 30% and/or to add an inotropic agent if the central venous oxygen saturation ($ScvO_2$) is less than 70%. The use of the ScvO2 as the end point of resuscitation and the steps to "normalize" the $ScvO_2$ are counter to our current understanding of the pathophysiologic changes that characterize sepsis. Septic patients usually have a normal or increased $ScvO_2$ because of reduced oxygen extraction [16,17]. A normal $ScvO_2$ therefore does not exclude tissue hypoxia [18]. A low $ScvO_2$ is an important sign of inadequate oxygen delivery to meet systemic oxygen demands. However, it provides no information for the reason for this inadequacy; nor does it provide guidance as to the optimal therapeutic approach. It is noteworthy that, in the study of Rivers et al, the mean $ScvO_2$ was 49%, with 65% of patients having an $ScvO_2$ less than 70%. To our knowledge, no other sepsis study has reproduced this finding, with the mean $ScvO_2$ (on presentation) in most sepsis studies being approximately 70% [18-20]. This suggests that other factors may have been in play to account for the low $ScvO_2$ in the study of Rivers et al [21,22]. These factors include the delayed presentation to hospital (possibly because of socioeconomic factors), greater number of patients with comorbid medical conditions, and a high incidence of alcohol use [22]. Thus, the combination of significant comorbidities (including heart disease) and a more delayed arrival of patients to the emergency department in the study of Rivers et al may have led to a low cardiac output state and, in turn, to the very low $ScvO_2$ values.

The transfusion of packed red blood cells in an attempt to increase $ScvO_2$ is not evidence based and likely to further compromise patient outcome. Extensive data have clearly demonstrated that blood transfusions increase the risk of infections, acute respiratory distress syndrome, and death in critically ill patients [23,24]. Red blood cells become less deformable with storage. In addition, stored blood is proinflammatory and prothrombotic [25,26]. The transfusion of packed red blood cells in patients with sepsis may therefore impair microcirculatory flow and further compromise tissue oxygenation [27-29]. Furthermore, the p50 of stored blood may be as low as 6 mm Hg, allowing the red cells to unload less than 6% of their oxygen load; the $ScvO_2$ may paradoxically increase because of reduced oxygen release [30,31].

The EGDT protocol calls for an inotropic agent (usually dobutamine) should the $ScvO_2$ remain less than 70% after fluid administration (once the CVP is between 8 and 12) and blood transfusion (once the hematocrit is >30%). Patients with "refractory septic shock" and those with indices of insufficient tissue perfusion may have inadequate cardiovascular performance because of decreased preload, depressed contractility, and/or severe vasodilatation. Neither the CVP nor the $ScvO_2$ can distinguish between these hemodynamic profiles. This is important, as each of these scenarios requires a different therapeutic intervention, that is, fluid, an inotropic agent, or a vasoactive agent. The use of dobutamine in a patient who has inadequate preload or excessive vasodilatation (and a hyperdynamic circulation) is likely to further compound the hemodynamic derangement in these patients.

Although the 3 major pillars that form the basis of EGDT are not supported by evidence-based medicine and are potentially harmful, what is more troubling is that the results of the EGDT study are "just too good to be true" and would appear to be scientifically implausible. However, at least 40 clinical studies have been published after the study of Rivers et al claiming that EGDT improves outcome [7,32,33]. Based on these published data, it has been asserted that the number needed to treat to save 1 life is only 6 [34]. It is important to note that these are all before-after studies, which are methodologically limited by numerous factors including patient selection bias, high mortality in the "control" group, different case mix, small sample size, the change in practice over time, invested investigators, and the Hawthorne effect, among others [34-36]. In particular, the early initiation of effective antimicrobial therapy (independent of EGDT) may have had a major effect on outcome in these studies [22]. There is little doubt that the timely diagnosis, (early) resuscitation and administration of appropriate of antibiotics is likely to improve the outcome of patients with sepsis. However, the central tenants of EGDT, namely, targeting a CVP of 8 to 12 cm water and achieving an $ScvO_2$ greater than 70%, are seriously flawed. Despite the lack of

supportive scientific evidence, the EGDT "bundle" has been adopted worldwide with cult-like religious fervor. The Australian Resuscitation in Sepsis Evaluation (Australia), the Protocolized Care for Early Septic Shock (United States), and the Protocolised Management In Sepsis (United Kingdom) studies are national, multicenter randomized controlled trials designed to test "EGDT" in patients with severe sepsis [37]. The final chapter of this sordid tale remains to be written.

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