

Commentary

The outcome of patients presenting to the emergency department with severe sepsis or septic shock

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Abstract

Although multiple studies of acute myocardial infarction, trauma, and stroke have been translated into improved outcomes by applying diagnosis and therapy at the most proximal stage of hospital presentation (before intensive care unit arrival), this approach to the sepsis patient has been lacking. In response to this, a trial comparing early goal-directed therapy (EGDT) versus standard care was performed using internally and externally validated criteria for early identification of high risk patients, established definitions, and a consensus-derived protocol to reverse the hemodynamic perturbations of hypovolemia, vasoregulation, myocardial suppression and increased metabolic demands. That trial of EGDT resulted in significant reductions in morbidity, mortality, vasopressor use, and health care resource consumption. The end-points used in the protocol and the outcome results were subsequently externally validated, revealing similar or better mortality benefit. This commentary examines the rationale and validation for the use of early markers of illness severity. Current evidence support the endpoints in the EGDT protocol, external validity in regards to outcome benefit and the universal need to improve the quality of care for early sepsis.

A recent retrospective, observational study by Ho and coworkers [1] measured the incidence and outcome of septic patients presenting at an Australian emergency department (ED) with criteria for early goal-directed therapy (EGDT) and found significantly fewer EGDT candidates than previous studies [2]. A number of initiatives aiming to reduce worldwide mortality associated with sepsis, such as the Surviving Sepsis Campaign, have previously noted the importance of the tenets of early hemodynamic optimization to try and overcome this devastating disease. In patients with severe sepsis or septic shock, clinicians must be aware that a considerable proportion of those with significant lactic acidosis can have near normal serum bicarbonate or normal calculated anion gap values, which may lead to underestimated disease severity [3-5]. In the EGDT study [2],

of the patients enrolled with a lactate level greater than 4 mmol/l, more than 30% had a bicarbonate level greater than 22 and an anion gap of less than or equal to 15 mEq/l. Other studies have shown that even if an anion gap is present, the mortality rate is significantly higher for lactic acidosis (56%) than for strong ion gap acidosis (39%) and hyperchloremic acidosis (29%) [6]. Despite mentioning lactate as a criterion in the study, Ho and coworkers did not report data regarding the levels or number of measurements found. Thus, it is possible that they underestimated the prevalence of high-risk patients in need of early hemodynamic optimization. This may explain why they strikingly found only 50 patients over 3.5 years (14.2 per year) meeting criteria for severe sepsis and septic shock in a large teaching hospital emergency department (ED) that sees 40,000 patients each year with a 30% admission rate.

The lactate level of 4 mmol/l, as used in the EGDT study, was internally and externally validated. In their study of 1218 patients, Aduen and colleagues [3] found that lactate concentrations above 4 mmol/l were 98.2% specific in predicting the need for hospital admission, 96% specific in predicting mortality in hospitalized nonhypotensive patients, and 87.5% specific in predicting mortality in hypotensive patients. We found that 10% of patients in the EGDT study [2] presented with a mean arterial pressure above 65 mmHg and lactate levels above 4 mmol/l, and had an even greater mortality than did the hypotensive cohorts when randomized to the control group. More recently, Shapiro and coworkers [7] and many others [5,8] confirmed the association of elevated lactate (greater than 4 mmol/l) with increased mortality, ranging between 36% and 39%, in patients with suspected infection.

In their study, the findings of which are reported in the previous issue of *Critical Care*, Ho and coworkers [1] did not

ED = emergency department; EGDT = early goal-directed therapy.

employ any control or protocol group for interventions as a comparator for the EGDT patients. The authors mention timely administration of antibiotics, central venous pressures of 10.8 ± 4.7 mmHg, and use of vasopressor agents in 70% of the patients as an indicator of aggressive intervention in the ED. Although this comparison is respected, these retrospective data transmit other signals. The early use of vasopressors is not necessarily a sign of an aggressive level of care; it may be a sign of inadequate volume resuscitation and of resorting to vasopressors to support blood pressure. In a hypovolemic patient, increasing afterload with vasopressors will falsely increase central venous pressure, which will limit further attempts at volume resuscitation and further impair microcirculatory flow. This has been associated with deleterious outcomes. A prospective, consensus derived, comprehensive strategy to address all facets of hemodynamic perturbations was used in the EGDT trial [9]. These endpoints have also been externally validated [10]. The evolution of improvements in sepsis mortality during the period examined by Ho and coworkers was not just attributable to EGDT but other interventions as well. Therapies such as recombinant activated protein C, glucose control, and use of corticosteroids were not mentioned. If these sepsis therapies are to be questioned or re-studied, then it should be done with respectful scientific methodology.

Although the data presented by the authors based on their retrospective examination of patients at their institution suggest a lower incidence and mortality (26.9%), this contradicts comparative data from other published studies in the same region. A seminal multicenter trial comparing albumin with crystallinoid fluid therapy conducted in New Zealand and Australia [11] found a sepsis mortality of 30.7-35.3%. The patients with acute respiratory distress syndrome had an even higher mortality of 39.3-42.4%. This mortality is more comparable to US assessments. Even though the mortality, as stated by the authors, was lower than that in the EGDT trial, it is still high and unacceptable nonetheless. If these patients were trauma, myocardial infarction, or stroke patients, then this mortality would be unacceptable because international initiatives have reduced mortality in all of these diseases. Interestingly, Ho and coworkers [1] made reference to the work of Shapiro and colleagues [12], who recently found the same relative mortality reduction after implementation of a standard operating procedure using EGDT. Others have found similar baseline mortality rates and improvements in outcome compared to the EGDT study [13-15].

The EGDT trial [2] was performed in a very busy inner city ED by board certified emergency physicians who were experts in the early management of sepsis. A recent Institute of Medicine Report (June 2006) confirmed the merits of early hemodynamic optimization. It reports that critical illness is poorly processed in overcrowded EDs in the USA and is responsible for significant mortality. The EGDT trial emphasized that management of the septic patient must

begin at the point of diagnosis, which is frequently outside the intensive care unit. Although the models of providing this care may vary from institution to institution, providing this missing link to the chain of care is significantly cost-effective and life saving, which makes it even more generalizable [16]. This call into question the inference that differences in mortality result from the different health care systems. The authors' claim that the processing of critical illness from the ED to hospitalization in Australia is unique contradicts findings reported by Parkhe and coworkers [17] (Victoria Hospital in Melbourne). That study similarly showed that patients transferred to the intensive care unit within 24 hours of ward admission from the ED had a significant increase in 30-day mortality (relative risk of 2.46) compared with patients admitted to the intensive care unit directly from the ED.

Conclusion

The emerging role of the ED in severe sepsis and septic shock is a much needed and evolving part of the landscape of critical care medicine [18]. Although the merits of EGDT and frequency of eligible patients are minimized by Ho and coworkers and followed by a call for a multicenter trial, the Society of Critical Care Medicine and Surviving Sepsis Campaign has opted not to wait but to adopt the same rational approach of subspecialists such as surgeons, cardiologists, and neurologists in applying 'right care, right now'.

Competing interests

In the past ER has received consultancy or speaker fees from Edwards Lifesciences, Eli Lilly and Biosite.

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