AAEM Clinical Practice Statement

Does Early Goal-Directed Therapy Decrease Mortality Compared with Standard Care in Patients with Septic Shock?

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Answer: No. However, standard care has significantly improved since the publication of the original EGDT trial. Early recognition of sepsis, prompt administration of appropriate antimicrobial therapy, urgent source control, intravenous fluid, and maintenance of adequate mean arterial pressure are critical interventions in the care of patients with septic shock. Routine central venous pressure or central venous oxygenation measurements are not required.

Critical components of the management of emergency department (ED) patients with septic shock include early recognition, prompt administration of appropriate antimicrobial therapy, urgent source control, and hemodynamic resuscitation. Current international guidelines for the treatment of patients with severe sepsis and septic shock recommend hemodynamic resuscitation targeted to predefined endpoints for central venous pressure (CVP), mean arterial pressure (MAP), urine output, and central venous oxygen saturation (ScvO2). Importantly, these recommendations are largely based on a landmark trial that evaluated a well-defined early goal-directed therapy (EGDT) protocol.

In 2001, Rivers et al performed a randomized controlled trial of 263 patients with severe sepsis or septic shock who presented to a single, urban, academic emergency department (ED). Patients were randomized either to EGDT or standard care. Patients assigned to EGDT received an intensive treatment protocol before admission to the intensive care unit that targeted a CVP of 8 to 12 mmHg, a MAP ≥ 65 mmHg, a urine output ≥ 0.5 ml/kg/hr, and an ScvO2 ≥ 70%. In-hospital mortality was markedly reduced in patients receiving EGDT compared with those patients receiving standard care (absolute risk reduction of 15.9%). Based upon the improvement in mortality, EGDT became a central recommendation in current guidelines for the initial resuscitation of patients with severe sepsis and septic shock.

Criticisms and concerns of the EGDT study by Rivers et al are numerous and include its single center design, high mortality rate in the standard care group, the use of CVP for volume assessment, the use of ScvO2 for assessment of global perfusion, and the use of blood transfusions. In addition, the EGDT protocol was criticized as being resource intensive. As a result, widespread implementation of the EGDT protocol has been limited.

Over the past decade, several studies have been published that have evaluated a variety of sepsis protocols and interventions. Though most of these studies did report favorable patient outcomes, none exactly replicated the randomized controlled design of the original EGDT trial. In fact, during the time period between the publication of the EGDT trial and the recent ProCESS trial, all studies identified by this search process were before-and-after prospective observational trials that compared outcomes with historical control patients. Recently, three landmark trials have been published that specifically compared the EGDT protocol by Rivers et al with standard care. These trials (ProCESS, ARISE, and ProMIse) were part of an international collaborative effort to specifically evaluate the external validity of the original EGDT trial.
The ProCESS trial was a multicenter, randomized trial performed in 31 sites in the United States. These sites were academic hospitals that did not have an established EGDT protocol for the resuscitation of patients with septic shock. Patients were randomized to one of three intervention groups: protocol-based EGDT, protocol-based standard care, and usual care. Patients in the protocol-based EGDT group received the EGDT protocol, as defined by Rivers et al. Patients in the protocol-based standard care received a modified treatment protocol different from the EGDT protocol. For patients randomized to usual care, the treating clinician made all management decisions. A total of 1,351 patients were enrolled in the ProCESS trial. The primary endpoint of 60-day in-hospital mortality did not differ among the three groups. In addition, there was no difference in 90-day mortality rate or hospital length of stay.

The ARISE trial was a prospective, randomized, parallel-group trial conducted in 51 centers in Australia, New Zealand, Finland, Hong Kong, and Ireland. Similar to the ProCESS trial, centers in the ARISE trial could not have established EGDT protocols for sepsis resuscitation. Patients were randomized to two groups: EGDT and usual care. Patients in the EGDT group received the protocol defined by Rivers et al, whereas patients in the usual care group were managed at the treating physician's discretion. A total of 1,588 patients were included in the ARISE trial. The primary outcome of 90-day all-cause mortality did not differ between the groups. Intensive care unit mortality rate, 28-day mortality, duration of mechanical ventilation, and need for renal replacement therapy did not differ between the groups.

The ProMIse trial was a pragmatic, open, multicenter, parallel-group, randomized, controlled trial conducted in 56 centers in the United Kingdom. Similar to the ProCESS and ARISE trials, centers could not have an established protocol for the resuscitation of patients with septic shock. Patients were randomized to the EGDT protocol, as defined by Rivers et al, or usual care. A total of 1,260 patients were enrolled in the ProMIse trial. Similar to the ProCESS and ARISE trials, the primary outcome of 90-day all-cause mortality did not differ between the groups.

The ProCESS, ARISE, and ProMIse trials are practice changing contributions to the sepsis literature. Cumulatively, the trials enrolled over 4,000 patients across a variety of clinical settings. Trial designs were robust with few patients lost to follow-up in all three studies. In addition to providing no clinical outcome benefit when compared to usual care, EGDT was associated with placement of more central venous catheters, increased utilization of vasopressors and blood transfusions, and increased intensive care unit admissions. Ultimately, these three trials demonstrated that central hemodynamic monitoring and the use of central venous oxygen saturation did not affect patient outcomes.

It is important to highlight that usual care has substantially improved since the time of the EGDT study by Rivers and colleagues. In fact, improvements in usual care can largely be attributed to the emphasis that the EGDT study placed on caring for patients with sepsis. Patients in the usual care arms of the ProCESS, ARISE, and ProMISE trials received aggressive intravenous fluids and early antibiotic medications. Based on the results of these latest trials, initial management of ED patients with severe sepsis or septic shock

should focus on early recognition, prompt administration of appropriate antimicrobial therapy, urgent source control, aggressive intravenous fluid administration, and maintenance of an adequate mean arterial pressure.