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Washington University Emergency Medicine Journal Club
The Role of Early Goal-Directed Therapy in Severe Sepsis and Septic Shock

Vignette

You are working a shift in TCC one busy afternoon when a patient is brought in by EMS for flank pain and a fever. You enter the room the find a 60-year female with a history of hypertension who is in no distress. She complains of dysuria, right flank pain, and fever for the last 3 days.

On physical exam, you note a temperature of 39 degrees Celsius, a heart rate of 128, a blood pressure of 97/40, a respiratory rate of 18, and an oxygen saturation of 98% on room air. Aside from right CVA tenderness and tachycardia, the remainder of the exam is normal.

Recognizing that the patient likely has pyelonephritis and has at least 2 SIRS criteria, you order a set of labs that include a UA, urine culture, blood cultures, CBC, BMP, and a serum lactate. The lactate is run as a point of care and comes back at 6.4 mmol/L.

You realize quickly that the patient meets criteria for severe sepsis. You immediately order antibiotics and fluids while awaiting the lab results, but wonder what other interventions should be instituted. You remember reading about early goal-directed therapy and wonder if you should obtain central IV access to begin monitoring central venous pressure and central venous oxygen saturation. The patient's blood pressure is up to 105/50 after one liter of fluid, and you don't plan to place a central line for pressors, so wonder if it's really necessary.

After discussion with the attending you decide to hold off on the central line and admit the patient to the ICU, but after your shift you consider your question again and begin searching the literature for answers.

PICO Question
Population: Adult patients with severe sepsis or septic shock
Intervention: Early goal-directed therapy
Comparison: Usual care or other standardized protocols
Outcome: Mortality, ICU admission rate, ED/ICU/hospital length of stay, cost

Search Strategy

The original article on early goal-directed therapy by Rivers et al was chosen, in addition to three recent large multi-center trials that conducted in coordination (ProCESS, ProMISe, and ARISE).

Article 1: Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001 Nov 8;345(19):1368-77. Answer Key.

Article 2: ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014 May 1;370(18):1683-93. Answer Key.

Article 3: Mouncey PR, Osborn TM, Power GS, et al; ProMISe Trial Investigators. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015 Apr 2;372(14):1301-11. Answer Key.

Article 4: ARISE Investigators; ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014 Oct 16;371(16):1496-506. Answer Key.

Bottom Line

Patients with severe sepsis and septic shock carry a high mortality risk. The mortality for severe sepsis alone approached 35% in the early 2000s. Mortality has decreased significantly since then, with estimated rates of less than 20% in 2012 (Kaukonen 2014). Much of this mortality reduction has been attributed to the introduction and widespread acceptance of early goal-directed therapy (EGDT) protocols. In 2001, Dr. Emanuel Rivers and colleagues conducted a study comparing EGDT with standard care in 263 patients with severe sepsis or septic shock presenting to Henry Ford Hospital in Detroit. They reported a reduction in mortality among patients receiving EGDT of 12.6% (NNT of 8).

Based in large part on these results, the surviving sepsis campaign incorporated the components of the EGDT into its guidelines in 2004. However, the protocol was not without its opponents, some of whom argued that it was impossible to sort out which components of the EGDT bundle actually resulted in improved outcomes. Others argued that increased recognition of the disease process combined with prompt antibiotic administration and aggressive fluid resuscitation are the keys to improving outcomes in sepsis. In particular, many challenged the routine use of central venous oxygen saturation measurement due to its invasive nature, and one study published in 2010 demonstrated no benefit to this strategy when compared with serial lactate measurements (Jones 2010) which does not require central venous access.

As a result of the changing landscape of sepsis care, three independent but coordinated trials were conducted to assess the use of EGDT. The ProCESS trial, published in May of 2014 was conducted at 31 academic hospitals in the US; the ARISE trial, published in October of 2014, was conducted at 51 hospitals in a variety of settings (academic, community, and rural) in 5 countries; and the ProMISe trial was conducted at 56 hospitals in the UK. None of these large, randomized trials found any reduction in mortality with the use of EGDT compared to usual care. In general, these studies demonstrated an increase in the use of central venous

catheters, increased ICU admission rates, and increased ICU length of stay in the EGDT groups, despite finding no benefit.

There were interesting differences to note between these three trials and the initial study by Rivers et al that may explain the different outcomes seen. Patients in the more recent studies received anywhere from around 2 to 2.5 liters of fluid prior to randomization and entry into the study. While the amount of fluid received prior to randomization was not reported in the Rivers study, it was likely significantly less. The mean initial ScvO2 recorded in the Rivers study was quite low (~50%), while in the subsequent studies it was much higher (~70%), likely a reflection of the more aggressive resuscitation undertaken prior to randomization. Finally, the mortality rates observed in the three recent studies were much lower (~20%) than that seen in the EGDT group in the initial study (30.5%).

While these current data suggest that there is no benefit to EGDT in the management of severe sepsis and septic shock, it's important to remember that the initial study by Rivers et al did a great deal to advance our management of these conditions. The study demonstrated that early recognition and management were vital, and it was likely this increased awareness that has resulted in the drastic reduction in mortality observed.