

Early Goal-Directed Therapy in the Treatment of Sepsis: A Brief Review

Introduction

Sepsis remains a leading cause of death both worldwide and in the US. It is estimated that nearly 1,000,000 cases of sepsis occur each year, with 700,000 of these falling into the high-risk group of severe sepsis and septic shock. This group carries a mortality rate between 30–40%.¹ In contrast, mortality rates from acute myocardial infarction and stroke are around 20% respectively, according to 2005 data.² The outcomes in acute myocardial infarction and stroke have improved with early recognition and standardized treatment.^{3,4} Rivers and colleagues hypothesized that this same concept could be applied to improve outcomes in patients with sepsis. In 2001, they published a randomized controlled trial comparing standard treatment with an approach that Dr. Rivers termed “early goal-directed therapy.”⁵ Through the use of rapid recognition and treatment of septic patients with early goal-directed therapy (EGDT), patient outcomes may be profoundly affected. This brief review summarizes the pathophysiologic basis of EGDT, its clinical application, and the controversies surrounding it.

Definitions and Pathophysiology of Sepsis

The consensus definition of sepsis is suspected infection in the presence of the systemic inflammatory response syndrome (SIRS).⁶ A diagnosis of SIRS requires at least two of the following: $T > 38.3^{\circ}\text{C}$ (100.4°F) or $< 36^{\circ}\text{C}$ (96.8°F), $\text{HR} > 90/\text{minute}$, respiratory rate $> 20/\text{minute}$, and $\text{WBC} > 12,000/\text{mm}^3$ or $< 4000/\text{mm}^3$ or with $> 10\%$ bands. Classically, the *sine qua non* of sepsis was demonstration of bacteremia. However, this is not universally true as sepsis may be caused by novel pathogens such as fungi and up to 20% of blood cultures in septic patients will be negative for bacteria.⁷ Furthermore, the recognition of the patient as septic must take

place days before the blood culture results will be available. Severe sepsis is the diagnosis of sepsis with evidence of organ dysfunction. Septic shock is severe sepsis with hypotension after adequate volume resuscitation.⁶

A complete understanding of the pathophysiology of sepsis has yet to be elucidated. However, it is clear that diverse derangements occur involving multiple organ systems leading to hemodynamic compromise. The mediators of these abnormalities include pro-inflammatory, anti-inflammatory and apoptotic molecules. Initially, there is circulatory insufficiency resulting from hypovolemia, myocardial depression, increased metabolic rate and vasoregulatory perfusion abnormalities.⁸ This leads to an imbalance between oxygen demand and oxygen delivery, resulting in tissue hypoxia and shock.

As oxygen demand increases at the tissue level, oxygen extraction from hemoglobin increases, which is reflected in decreases in central venous oxygen saturations (ScvO_2) or mixed venous oxygen saturations (SvO_2). Once the limits of oxygen extraction have been reached, the tissues shift to anaerobic metabolism with subsequent production of lactate. This phase, known as global tissue hypoxia, is an important transition from sepsis to severe sepsis and may occur even in patients with normal vital signs.⁹ As illustrated below, central venous oxygen saturation and lactate levels are useful surrogates for monitoring severity of illness and guiding treatment in septic patients.

Early Goal-Directed Therapy

Treatment of sepsis consists of hemodynamic management and administration of antibiotics. The early administration of antibiotics is essential. In septic shock, mortality increases with each hour of delay in

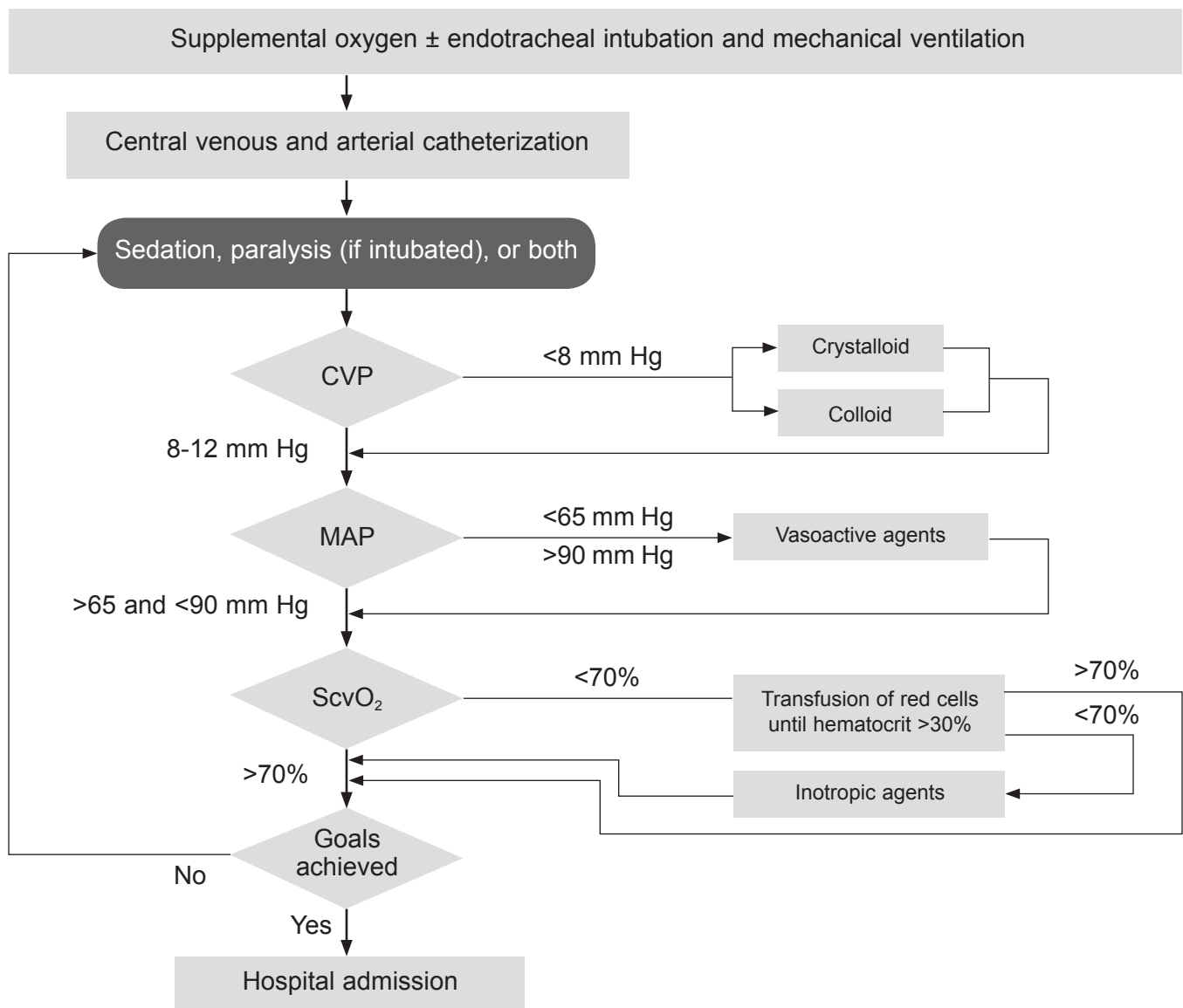
antibiotic administration.¹⁰ Hemodynamic management involves intravenous access and administration of fluids and vasoactive medications. Goal-directed therapy provides a straightforward approach to hemodynamic management in septic patients.

The concept of goal-directed therapy for critically ill patients is not new. Several studies examined optimizing hemodynamic parameters in critically ill patients after admission to the ICU, but results were largely negative.^{11,12} With EGDT, the patients at high risk for cardiovascular collapse are recognized soon after hospital arrival, generally while still in

the emergency department, and early therapeutic intervention is initiated to restore a balance between oxygen delivery and oxygen demand.

In Rivers original article, 263 patients were enrolled, 130 to the EGDT group and 133 to standard therapy.⁵ Patients in the standard therapy group were treated at the clinicians' discretion using a Society of Critical Care Medicine hemodynamic support guideline.¹³ All patients in the EGDT group had a central venous catheter placed with the capability of continuously measuring a central venous oxygen saturation and central venous pressure (CVP). (Figure 1)

Figure 1. Protocol for Early Goal-Directed Therapy from Rivers et al.⁵



CVP=central venous pressure

MAP=mean arterial pressure

ScvO₂=central venous oxygen saturation

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The first step is to optimize volume status. Most septic patients are relatively volume depleted, and require an initial bolus of intravenous fluids. The amount of fluid given often varies by clinician. Fluid requirements in the initial resuscitation of patients with septic shock are often large, with up to 10 L required in the first 24 hours.¹⁴ Instead of arbitrary administration of fluids, the Rivers protocol uses invasive monitoring of CVP to determine the adequacy of volume resuscitation. Frequent 500 ml boluses of crystalloid are given to achieve a CVP of 8–12 mm Hg.⁵

Concurrently, blood pressure is addressed. If mean arterial pressure (MAP) is less than 65 mm Hg, vasopressors are given to maintain MAP of at least 65 mm Hg. The choice of vasopressor is not considered to be of primary importance, although some studies in septic shock suggest that norepinephrine and dopamine are preferred.¹⁵ If MAP is greater than 90, vasodilators were given until it was 90 mm Hg or less. This was the case in only a very small group of patients in the original trial.⁵

Finally, central venous oxygen saturation is used to reflect tissue oxygenation. In septic patients, the metabolically active and hypoxic tissue extracts a higher percentage of oxygen, so ScvO₂ will be low. If central venous oxygen saturation is less than 70%, red blood cells are transfused to obtain a hematocrit of at least 30%. If the goal of 70% is still not met despite an adequate hematocrit and meeting the first two goals, an inotrope (dobutamine) is added to increase cardiac output.⁵

In the study by Rivers et al, in-hospital mortality was reduced by 16% with the use of early goal-directed therapy. In-hospital mortality was 30.5% for the patients in the early goal-directed therapy group and 46.5% in the standard therapy group. His group concluded that the goal-directed therapy initiated at the earliest stages of severe sepsis and septic shock has significant benefit. These results have led to widespread endorsement of this concept by professional societies and the incorporation of the Rivers protocol into the Surviving Sepsis Guidelines, an initiative of three specialty societies.⁵

Controversies and Future Directions

The concept and subsequent implementation of early goal-directed therapy has not been without controversy. Questions about EGDT include:

1. How generalizable is EGDT to other populations?
2. How are time and resources utilized so that the EGDT protocol is accomplished?

3. How cost-effective is EGDT?

4. Which components of EGDT actually make a difference in outcomes?

Some authors have questioned whether this protocol is generalizable to other populations.¹⁶ Rivers enrolled a very ill patient cohort at an inner city hospital. In addition, all of the enrolled patients presented to the emergency department; none were hospital inpatients who deteriorated.⁵ The original study remains the only randomized control trial using this protocol. Several authors have implemented the protocol and shown reductions in mortality.^{17,18} However, only one of these studies was prospective, using a before and after design.¹⁹ Notably lacking is a large prospective trial comparing standard therapy and early goal-directed therapy. Currently, there are at least three trials ongoing that seek to investigate this further.^{20,21}

Another point of criticism has been that early goal-directed therapy is too time and resource intensive for practical application. Much of this criticism centers on the use of a central venous catheter. In order to accurately measure CVP and ScvO₂, this must be either a subclavian or internal jugular central line; placement of the line can take several minutes. While most emergency physicians and intensivists are facile with these lines, comfort levels vary. The initial study was performed in a large teaching hospital with a dedicated unit with dedicated personnel, a faculty with a strong critical care background, and an abundance of residents eager to perform procedures. In addition to the limitations of the central line requirement, nurses must be trained in CVP and ScvO₂ measurements. This is a significant time investment and continuing education must be performed to ensure that skills remain current.²²

The cost-effectiveness of EGDT remains unknown. An analysis by Huang suggested that EGDT could be cost-saving by reducing length of stay and mortality.²³ However, in the study by Jones and colleagues, ICU and hospital lengths of stay were longer in the EGDT group.¹⁹ The increased resource utilization in this study occurred in patients with lower severity of illness. Cost-benefit analyses are needed to determine the true economic impact of EGDT.²⁴ Along these lines, a secondary outcome measure of the ongoing ProCESS study is resource use and cost of alternative resuscitation strategies.²¹

Finally, several authors have questioned which aspects of early goal-directed therapy actually lead to the improvement in mortality. The patients in the early

goal-directed therapy group received significantly more fluids than the standard group, receiving approximately 1.5 liters more in the first six hours. However, by 72 hours total fluids administered were similar between the two groups. Perhaps the outcome difference was due to fluids alone. Similarly, patients in the early goal-directed therapy group received significantly more RBC transfusions in the first six hours (64.1% vs 18.5%).⁵ Blood transfusion carries with it significant risks, including virus transmission, hemolytic reactions, bacterial contamination and acute lung injury. Moreover, a previous large multicenter study favored a restrictive transfusion strategy for most critically ill patients, rather than the aggressive strategy employed in EGDT.²⁵ While CVP and ScvO₂ can be valuable in monitoring, it may not be essential to improving outcomes. Early studies suggest that noninvasive near-infrared spectroscopy derived tissue hemoglobin oxygen saturation (StO₂) may correlate closely with invasive hemodynamic measurements in severe sepsis.^{26,27} The current unfinished trials should shed some light on these questions.

Conclusion

The emergence of early goal-directed therapy has changed the treatment of sepsis, particularly in the emergency department. It has raised the profile of sepsis and led to a time-critical paradigm for the treatment of septic patients.²⁸ With further investigations, the concept will be refined and will evolve. While the specific elements and some of the methods of Rivers' protocol remain controversial, the concept of early recognition and treatment of septic patients is of paramount importance for improving patient care.

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