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DOES EARLY GOAL-DIRECTED THERAPY DECREASE MORTALITY COMPARED WITH STANDARD CARE IN PATIENTS WITH SEPTIC SHOCK?

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□ **Abstract—Background: Current international guidelines for the treatment of patients with severe sepsis and septic shock recommend that patients receive targeted care to various physiologic endpoints, thereby optimizing tissue perfusion and oxygenation. These recommendations are primarily derived from a protocol published >15 years ago, which was viewed by many as complex and was therefore not widely adopted. Instead, many emergency physicians focused on the administration of early antibiotics, source control, aggressive fluid resuscitation, vasoactive medications as needed to maintain mean arterial blood pressure, and careful monitoring of these patients. The primary goal of this literature search was to determine if there is a mortality benefit to the early goal-directed protocol recommended by current international sepsis guidelines compared to current usual care. Methods: A MEDLINE literature search was performed for studies published between January 1, 2010 and December 31, 2015. Studies were limited to the English language, human randomized controlled trials, meta-analyses, prospective trials, and retrospective cohort trials that met specific keyword search criteria. Case reports, case series, and review articles were excluded. All selected articles then underwent a structured review by the authors. Results: Seven thousand four hundred twenty studies were initially screened; after the final application of inclusion and exclusion criteria, 10 studies were formally analyzed. Each study then underwent a rigorous review and evaluation from which a formal recommendation was made. Conclusion: There is no difference in mortality between current usual care and the goal-directed approach recommended by current international guidelines for patients with severe sepsis and septic shock.** © **2016 Elsevier Inc. All rights reserved.**

□ **Keywords—early goal-directed therapy; protocolized care; sepsis; septic shock; severe sepsis; usual care**

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INTRODUCTION

Patients with severe sepsis and septic shock are frequently managed in the emergency department (ED). In 2001, there were >750,000 inpatient admissions and 215,000 deaths in the United States attributed to sepsis (1,2). Importantly, the prevalence continues to rise. In the ED, the critical components in the management of patients with septic shock include early recognition, prompt and appropriate antibiotic administration, source control, aggressive resuscitation with fluids, and the use of vasoactive medications when needed. In 2002, the Surviving Sepsis Campaign (SSC) was created by an international group of physicians, pharmacists, and nurses to promote the best practice for septic patients and provide guidelines to improve outcomes (3). In 2012, they released their most recent guidelines for the management of patients with severe sepsis and septic shock, which recommend early aggressive resuscitative

goals specifically targeting predefined values for central venous pressure (CVP), mean arterial pressure (MAP), urine output, and central venous oxygenation ($ScvO_2$) (4). The basis for these resuscitation recommendations come primarily from a single-center trial, which showed a marked decrease in mortality patients with severe sepsis and septic shock who were managed in the ED with a protocol that emphasized achieving strict physiologic endpoints in the initial 6 h (5).

In this landmark clinical trial, 263 patients were randomized to either usual care or early goal-directed therapy (EGDT). EGDT is an aggressive care protocol that attempts to optimize various physiologic parameters to ensure adequate tissue perfusion and oxygenation, defined as achieving a $ScvO_2$ >70%. As part of the protocol, patients received central venous access and fluid resuscitation to first ensure a CVP between 8 to 12 mm Hg, followed by invasive blood pressure measurement and vasopressor therapy (if needed) to reach a MAP between 65 and 90 mm Hg. Urine output was also monitored and maintained above 0.5 cc/kg. In this protocol, patients with an $ScvO_2$ <70% were transfused blood by packed red blood cells if the hemoglobin value was <10 g/dL. If the $ScvO_2$ value remained <70% despite the hemoglobin target, patients received dobutamine to improve perfusion. Patients in the EGDT group had an in-hospital mortality of 30.5% compared to 46.5% in the control group. The impact of this trial had a profound effect upon the management of patients with severe sepsis and septic shock and formed the basis for the SSC guidelines.

Despite a marked decrease in mortality in the EGDT trial, there have been numerous concerns about the protocol. Indeed, the Rivers study involved a small number of patients and was performed at a single, urban, academic center. Critics noted that certain aspects of the algorithm were unnecessary, such as the need for invasive procedures, and that parameters, such as CVP and $ScvO_2$, had no evidence-based rationale for their inclusion in the protocol (6,7). Additional studies published since the original EGDT trial questioned certain endpoints central to EGDT, showing that less invasive targets, such as lactate clearance, were noninferior to $ScvO_2$ and that lactate can be used to help guide resuscitation (8,9). There have also been numerous trials that have shown a significant decrease in mortality with other interventions, such as the administration of early antibiotics and bundled care protocols (10–12). As a result, many emergency providers (EPs) who treat patients with septic shock focus on aggressive fluid resuscitation, early and appropriate antibiotic administration, and achieving a MAP of 65 mm Hg while forgoing the placement of invasive catheters and following the other strict physiologic parameters recommended by the SSC (13–15). Recently, three large randomized, prospective trials designed to compare usual care to EGDT found that EGDT did not improve survival in patients with severe sepsis and septic shock (16–18).

Following the publication of these studies, the use of the EGDT protocol in the management of patients with septic shock in the ED has again been challenged. The goal of this article is to review the recent medical literature on EGDT and provide EPs an evidence-based recommendation on the mortality benefit of EGDT compared to current usual care. This work was requested, completed, and published as a statement by the American Academy of Emergency Medicine Clinical Practice Committee.

MATERIALS AND METHODS

A structured literature review was accomplished using MEDLINE to search for articles involving EGDT in the management of patients with septic shock. The literature search was limited to studies published between January 1, 2010 and December 31, 2015 involving only human subjects and composed only in English. Abstracts were identified in three separate literature searches that can be seen in Table 1. All abstracts that met the initial screening criteria were then independently reviewed by two authors to determine which should be further evaluated for relevance and inclusion based on the predefined criteria. Additional refinements in the inclusion criteria required that the studies be randomized controlled trials, meta-analyses, prospective trials, or retrospective cohort trials. We excluded all review articles, case series, and case reports. References in the selected articles were reviewed to determine if additional studies should be included. All selected articles were then subject to a "grade of evidence" review by at least two of the study authors and given a score, as referenced in Table 2, based upon the focus of the study, the methodology, and overall study design. In addition, all included studies were given a separate "quality ranking score" based upon the strengths of the methodology and design. The specific categories can be found in Table 3.

RESULTS

The three separate literature searches identified a total of 7420 abstracts that met the initial screening criteria, of which 1046 were deemed relevant for further review. Of these, 1036 did not meet the final inclusion criteria, leaving a total of 10 studies that were used to form the clinical guideline.

Recommendation

There is no mortality benefit from EGDT compared to current usual care in patients presenting to the ED with severe sepsis or septic shock. Level of recommendation: A.