Severe Sepsis and Septic Shock Trials (ProCESS, ARISE, ProMISe)

What is Optimal Resuscitation?

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KEYWORDS

• Severe sepsis • Septic shock • Resuscitation • Usual care • Lactate
• Hyperlactatemia • Sepsis

KEY POINTS

- Three large international randomized trials (Process, ARISE and Promise) confirmed that in the general population of patients with severe sepsis and septic shock, early goal-directed therapy did not confer a mortality benefit compared with usual resuscitation. The ability to generalize depends on the consistency of treatment provided as part of usual resuscitation in individual hospitals.
- All 3 trials used the established definitions for identifying septic patients. Until the SEPSIS-3 definitions are prospectively evaluated, their associated risks and benefits are unclear.
- Usual care in all 3 trials included early identification using standardized screening protocols, including lactate measurement, early intravascular fluid administration, and early antibiotics.
- Normotensive patients with lactate level greater than or equal to 4 mmol/L had a similar mortality to patients with refractory hypotension with a normal lactate level.

INTRODUCTION

Between 2014 and 2015, 3 independent, multicenter, government-funded, randomized controlled trials (RCTs) evaluating early goal-directed therapy (EGDT) were published. These trials were Protocolized Care for Early Septic Shock (ProCESS) from the United States,[1] Australasian Resuscitation in Sepsis Evaluation (ARISE),[2] and Protocolised Management in Sepsis (ProMISe)[3] in the United Kingdom.

The care of septic patients has progressed significantly over the years; mortality has significantly decreased but there is still much controversy and confusion. Which definition should be used to identify septic patients? Given that there was no survival

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benefit of EGDT compared with usual resuscitation, how should usual resuscitation be defined in the context of the data? What interventions do clinicians need to provide and what is time dependent? This article reviews key findings of the 3 sepsis trials and reviews the following:

- Background on sepsis care before the original EGDT trial by Rivers and colleagues.[4]
- Key elements of ProCESS, ARISE, and ProMISe to assist comprehensive evaluation.
- Options for operationalization and future direction in the evolving care of septic patients.

Background

Death is not the enemy but occasionally needs help with timing.

—Peter Safar

Sepsis mortality before 2001 was traditionally high, with reports of mortality ranging between 30% and 60%.[5–9] There was no universal concept of urgency in the treatment of septic patients. Care was generally fractured, with little collaboration between the service line silos of the prehospital service, emergency department (ED), the intensive care unit (ICU), and the wards. Treatment might focus on using vasopressors to augment blood pressure with less emphasis on end-organ perfusion, resulting in ischemic limbs and colloquial names such as "leave 'em dead" for levophed.[10] In addition, universal use of ultrasonography in EDs or ICUs was nonexistent during this period.

After observing severe sepsis and septic shock mortality of 50% in local hospitals, an institutional quality improvement initiative led to a randomized controlled trial evaluating EGDT from 1997 to 2000.[4] In 2001, Rivers and colleagues[4] reported results of a new, protocolized resuscitation termed EGDT. EGDT was described as a structured treatment protocol that incorporated elements consistent with consensus guidelines.[11] EGDT is designed to optimize tissue oxygen transport through early identification and time-dependent hemodynamic optimization of oxygen delivery using continuous monitoring of prespecified physiologic targets.

- Preload: central venous pressure (CVP) was used as a surrogate target for intravascular volume.
- Afterload: mean arterial pressure (MAP) was targeted after volume repletion with vasoactive agents.
- Contractility and oxygen carrying capacity: central venous oxygen saturation ($Scvo_2$) guided delivery of inotropes and red blood cell transfusions.

At the time of publication, this protocol was novel because of the absolute mortality reduction, the time dependency element, and focus on the level of care rather than location of care. The absolute mortality benefit of 16% (46.5% to 30.5%) suggested that this was one of the most effective modalities to date.[12–14] Subsequent observational studies supported a mortality benefit of varying degrees.[15]

Although medicine traditionally functioned in silos, this study emphasized the level of care rather than location of care. During this period of time, central venous access, arterial access, and use of inotropes was generally reserved for the ICU. It was unique to provide several critical care modalities in locations outside of traditional critical care settings. Although novel in application, the idea was not a unique concept. Dr Peter Safar[16] described critical care as a continuum beginning prehospital, continuing with ED intervention, and culminating in ICU admission and management.

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