Hyperlactemia and hypotension: looking at septic shock from different perspectives

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Abstract

The last decade has witnessed significant improvements in the treatment of patients with severe sepsis and septic shock, and a reduction in mortality from septic syndromes has been described by several epidemiological studies. Nevertheless, different inclusion criteria make it difficult to interpret and compare the data of the literature.

Introduction

Among the most relevant breakthroughs in septic syndromes research, many would consider early goal directed therapy (EGDT). Under this name goes a bundle of interventions that, when applied within 6 h from patients’ arrival to the emergency department (ED), has shown to decrease absolute in-hospital mortality by 15%.

Although the efficacy of EGDT has been proven by a single randomized clinical trial, its results have been supported by many historically-controlled studies that document similar improvements in mortality after a switch from previous practices to EGDT. Early goal directed therapy aims at restoring tissue perfusion in the shortest time possible so that adequate oxygen delivery to essential organs may be maintained, irreversible mitochondrial energy failure may be averted and the development of multi-organ failure (MOF) prevented.

In practice, the reference study by Rivers et al. reached these results administering the treatment group a higher volume of fluids and a much higher rate of red blood cells (RBC) transfusions than those delivered to the control group. After an initial fluid challenge, further fluid administration and the use of vasoactive drugs, inotropes and RBC transfusion was guided by predefined goals expressed as values of central venous pressure (CVP), mean arterial pressure (MAP) and central venous oxygen saturation (ScvO2). This study has been criticized under many aspects, for example the characteristics of the enrolled population, the use of CVP as an indicator for fluid responsiveness, the liberal use of transfusions. Apart from controversies about the specific components of EGDT, it must be recognized that EGDT is a bundle of interventions and that it is not yet known which of these are essential to its efficacy, which could be avoided or substituted, which might even prove detrimental.

In order to answer the many questions that are still open, it is foreseeable that many studies will be produced in the near future. To produce results capable of changing clinical practice, it is fundamental that these studies share common definitions, select their populations adequately and express their results in such a way that comparisons can be easier. In this paper we shall discuss one of the aspects that make it difficult to read and compare clinical literature on severe sepsis and septic shock, namely the criteria utilized to define septic shock.

Opinion Report

During the Conference on international sepsis definitions organized in 2001 by the Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM), the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS), severe sepsis was defined as sepsis complicated by organ dysfunction and septic shock as a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Hypotension is defined by a systolic arterial pressure below 90 mm Hg (or, in children, <2 SD below normal for their age), a MAP <60, or a reduction in systolic blood pressure of >40 mm Hg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension. Although still valid in essence, this definition is not sufficiently precise to guarantee uniform inclusion criteria into clinical trials. Let us leave severe sepsis aside for a moment and concentrate on septic shock. What should we consider as an adequate volume resuscitation? In 2006, the emergency department sepsis education program and strategies to improve survival (ED-SEPSIS) working group of the American College of Emergency Physicians stated that we should consider a patient in septic shock when his/her hypotension is unresponsive to a crystalloid fluid challenge of 20 to 40 mL/kg. Although this is a much more operative indication, it still leaves us with two problems. First: 20 to 40 mL/kg means anything between 1500 and 3000 mL of saline rapidly administered to an average 70 Kg man. Not a little difference. Second: how should we consider colloids, which are still widely used in the resuscitation of shocked patients? Rules of thumb (i.e. 100 mL of colloids equal 300 mL crystalloids) do not hold true in the setting of microcirculatory and endothelial derangement typical of sepsis and have not been supported by clinical evidence.

A smaller span in fluid deliverance (i.e. 20 to 30 mL/Kg) and a clear indication of crystalloids as the only fluids to use in the resuscitation phase of EGDT should be used in the future to ease the comparison between clinical studies. One more problem must now be considered. If the essence of shock is an inadequate tissue delivery of oxygen, should not a marker of hypoperfusion be included in the definition of septic shock? In fact, this was first done by Emmanuel Rivers in his reference study published on the New England Journal of Medicine in 2001 and was then taken over by the Surviving Sepsis Campaign which, in its 2008 International Guidelines, stated that sepsis induced shock should be defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration >4 mmol/L). This would sound reasonable if high blood lactates were added to unresponsive hypotension in the definition of septic shock, while it leaves us with some open questions when the two conditions are proposed as possible alternatives: how should we consider hypotensive patients with normal lactates? Would patients who are just hypotensive have the same prognosis of those who are just hyperlactacidemic? And would the combination of the two add to global mortality?

Some studies have tried to answer these questions, but unfortunately they have not brought much light to the scene. To start again from the reference study by Rivers et al., patients treated with EGDT had a mortality of 15% if they had high lactates but no hypotension (cryptic shock), and a much higher mor-
tality (42%) if they were hypotensive (this group included both patients with high and low levels of lactate). In 2011, Puskarich et al. addressed the problem comparing two groups of patients of similar severity who differed in the definition of shock (53 had cryptic shock with average lactate values of 5.8 mmol/L, and 247 had overt hypotensive shock after the administration of 20 ml/Kg of fluids with average lactate values of 2.6 mmol/L). Comparison was made according to the sequential organ failure assessment (SOFA) and simplified acute physiology score II (SAPS II) scores. Mortality was around 20% in both groups at variance with the results by Rivers et al. who, as we said before, documented a much higher mortality for hypotensive patients and a clear difference in prognosis for patients in the two groups. To add confusion to the whole story, Hernandez et al. recently published an observational study enrolling 124 patients admitted to intensive care unit (ICU) for fluid unresponsive septic shock and treated with vasopressors. Among the 38 patients with lactates <2.5 mmol/L, in-hospital mortality was 7.9% while it was 20.9% among the 86 with lactates >2.5 mmol/L. In an earlier retrospective study, the same authors had shown even wider differences in a group of 302 patients admitted to ICU for septic shock. Mortality was 7.7% among the 104 patients who never developed lactates >2.4 mmol/L and 42.9% among the 198 patients who had a value of lactates >2.4 mmol/L at least once in the first 24 h.

From these studies we can infer that, in accordance with a wider literature, patients with higher lactates have a worse prognosis. It seems also clear that the group of hypotensive patients is a very heterogeneous one since it may contain patients who are just hypovolemic and patients who are more or less severely underperfused. These groups of patients are likely to have different mortality rates, so future intervention studies on sepsis should probably analyze separately the results obtained for the groups of normotensive/high lactates, hypotensive/high lactates and hypotensive/low lactates patients.

Conclusions

In conclusion, the last decade has seen significant advances in the treatment of septic shock. In the near future it will be our task to investigate more deeply the different presentations of this syndrome. Hopefully, this will help us better appreciate the studies that have adopted the EGDT bundle in order to explore which of its components are really beneficial and for which patients.

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