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Rebuttal From Dr Jones

In their counterpoint, Dr Rivers and colleagues present the theoretical view that patients with septic shock present in very distinct “hemodynamic phases” and that Jones et al enrolled patients in a different phase of septic shock than did Rivers et al. According to their theory, decreased central venous oxygen saturation (ScvO2) always precedes the appearance of lactate—a concept not observed in my clinical practice. Clinicians who routinely care for the critically ill encounter patients with elevated lactate and normal ScvO2. Furthermore, as shown in Table 1, the hemodynamic patterns of the subjects enrolled by Rivers et al are markedly different from any other reported populations of patients with septic shock treated with quantitative resuscitation. The study by Rivers et al patients had much higher lactate, much lower ScvO2, and much higher mortality than described elsewhere. Possible explanations for this discrepancy may include that patients with septic shock in Detroit between 1997 and 2000 were markedly different than any other septic shock population reported in the world’s literature and/or that systematic selection bias was a significant problem in the their study. In such a scenario, their results have questionable external validity. Supporting either of these assertions is the fact that mortality in the control group of the Rivers et al study was 20% higher than any septic shock mortality reported in the recent literature, leaving one to question exactly what care they received. Little evidence supports the contention that Jones et al enrolled patients in a different phase of septic shock.
Because data from an experimental clinical trial are the only way to scientifically deduce the clinical efficacy of lactate clearance vs ScvO₂, and because data from a large multicenter clinical trial demonstrated that lactate clearance is not inferior to ScvO₂ as an end point of early sepsis resuscitation, as described herein, lactate clearance has principles that may make it the more appropriate end point to choose.

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Rebuttal From Dr Rivers et al

An End Point Must Be Consistently Present to Be Generalized

Levrault et al\(^1\) stated, “It is common knowledge that many septic patients develop multiple organ failure and die despite normal blood lactate levels.” Below the critical systemic oxygen delivery, central venous oxygen saturation (Scv\(_{2}\)) decreases; however, lactate level elevation may not occur. More importantly, an Scv\(_{2} \geq 70\%\) is not the only goal, as achievement of all early goal-directed therapy (EGDT) goals actually resulted in an Scv\(_{2} \geq 77.3\%\). According to Dr Jones,\(^2\) a study byGattinoni et al\(^3\) did not show an outcome benefit of reaching a mixed venous oxygen saturation of 70% up to 48 h after ICU admission. However, Chamberlaine et al\(^4\) found in a meta-analysis that patients resuscitated to this end point within a more reasonable 6 h were twice as likely to survive than those without it.

A Repeat Look at a Previously Quoted Study

Dr Jones\(^2\) cites the study by Jansen et al\(^5\) as supportive of lactate clearance, but not all patients in that study were septic. Furthermore, the reduction of lactate was no faster when the control group therapy was compared with the lactate-guided aggressive resuscitation group. In fact, these authors concluded that “this observation might actually argue against lactate level as a target of hemodynamic therapy. However, given that Scv\(_{2}\) monitoring was mandatory in the lactate group and control group, we cannot exclude the possibility that this had an impact on the observed outcome difference.”\(^5\)

Does Noninferiority Mean Equivalency? Be Careful What You Read

Noninferiority is a double negative that may confuse clinicians because of the complexity of study design. Noninferiority trials are controversial and difficult to design, conduct, analyze, and interpret for trialists, clinicians, reviewers, and editors.\(^6\) The low number of interventions observed by Jones et al\(^7\) bias toward the conclusion of noninferiority. Thus, for appropriate interpretation, one must be aware of and apply the CONSORT (Consolidated Standards of Reporting Trials) recommendations on noninferiority and equivalence trials (Table 1).\(^6,10\)

Responding to Perceived Barriers

Barriers specified by Dr Jones\(^2\) are unacceptable as excuses for our failure to save lives. We do not avoid complex interventions for trauma, stroke, or myocardial infarction. Severe sepsis carries a mortality risk far in excess of these acknowledged emergencies. Surely, placement of central lines, as well as continuous or intermittent venous saturation measurement, should be well within the capabilities of competent emergency and critical care practitioners.

Conclusion

Today’s clinical tools for assessing tissue perfusion, including Scv\(_{2}\) and lactate level, have benefits and limitations. Scv\(_{2}\) has a half-life of seconds, providing value as an early goal of resuscitation with interpretation potentially confounded by changes in systemic oxygen delivery, tissue extraction, and distribution of blood flow at both the macrocirculatory and microcirculatory levels. Serum lactate levels may remain normal before and throughout resuscitation or fluctuate due to the complexities of lactate kinetics, causing one to question the clinical usefulness of lactate clearance. Moreover, a 10% drop in serum lactate level has different implications if the initial value is 12 mmol/L rather than 4 mmol/L. The concept of lactate clearance as the single goal of resuscitation is, therefore, flawed and potentially dangerous. Today’s prudent clinician will use both normalization of Scv\(_{2}\) and lactate levels to guide resuscitation rather than rely on one parameter alone.

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