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Rebuttal From Dr Rivers et al

AN END POINT MUST BE CONSISTENTLY PRESENT TO BE GENERALIZED

Levraut et al¹ 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 (ScvO₂) decreases; however, lactate level elevation may not occur. More importantly, an ScvO₂ ≥ 70% is not the only goal, as achievement of all early goal-directed therapy (EGDT) goals actually resulted in an ScvO₂ ≥ 77.3%. According to Dr Jones,² a study by Gattinoni et al³ did not show an outcome benefit of reaching a mixed venous oxygen saturation of 70% up to 48 h after ICU admission. However, Chamberlain et al⁴ 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 Jones² cites the study by Jansen et al⁵ 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 ScvO₂ 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 al⁷ 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 Jones² 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 ScvO₂ and lactate level, have benefits and limitations. ScvO₂ 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 ScvO₂ and lactate levels to guide resuscitation rather than rely on one parameter alone.

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Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: In the past 3 years, Dr Rivers has received funding from the National Institutes of Health, Aggennix AG, and Alere Corporation. He has been a one-time consultant for Aggennix AG; Eisai Co, Ltd; Idaho Technologies Inc; AstraZeneca; Massimo; and Sangard. He is a consultant to the Institute of Medicine, National Academies. The Early Goal-Directed Therapy (EGDT) study was performed without external industry support or funding of any kind. Any intellectual properties associated with Dr Rivers' research are exclusively owned by Henry Ford Hospital. Dr Rivers holds no past or present intellectual properties and has never received royalties or stock interest related to technologies in EGDT research and practice. Dr Elkin has received funding from the Gordon and Betty Moore Foundation, has been a one-time consultant for Eisai Co, Ltd, and participated on the speaker's bureau for Edwards Lifesciences LLC on three occasions. Dr Cannon has been a one-time consultant for Aggennix AG and Eisai Co, Ltd.

Table 1—CONSORT Checklist for Reporting Noninferiority or Equivalence Trials in Rivers et al⁸ and Jones et al⁷

Topic		Commentary	
Requirements and Considerations		Jones et al ^{7,10}	Rivers et al ⁸
Background	Scientific background and explanation of rationale, including the rationale for using a noninferiority or equivalence design.	<p>Intermittent or continuous ScvO₂ as part of EGD and recommended by the SSC⁹ is not generalizable because of the following issues:</p> <ul style="list-style-type: none"> • The need for specialty equipment and training, such as continuous ScvO₂ spectrophotometer and catheter. • This technology is described as “technically difficult, unavailable in many tertiary care EDs, too complex, costly and takes time away from the patient.” • ScvO₂ is a “controversial” method of determining tissue oxygen delivery. <p>Assumption, LC is equivalent to ScvO₂:</p> <ul style="list-style-type: none"> • Increased lactate levels are ubiquitous in all patients with severe sepsis and septic shock. <p>Rationale for a noninferiority design:</p> <ul style="list-style-type: none"> • To establish equipoise because comparing EGD to a control group in a prospective randomized trial with informed consent would be unethical based on robust evidence of previous studies. 	<p>Background of EGD⁷:</p> <ul style="list-style-type: none"> • It has been replicated in various multiple studies comprising >40 studies totaling >10,000 patients. • Reduces absolute mortality by 16%-18% in patients of equal illness severity. • It is cost effective and decreases health-care resource consumption. • The ScvO₂ technology is >40 y old, requires seconds to calibrate, and is optional with intermittent sampling according to the SSC recommendations.
Methods			
Interventions	Precise details of the interventions intended for each group, detailing whether the reference treatment in the noninferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy and how and when they were actually administered.	<p>LC triggered interventions:</p> <ul style="list-style-type: none"> • Blood transfusions to hematocrit of 30% • Dobutamine to a 10% decrease in LC 	<p>EGD triggered interventions over 6 h:</p> <ul style="list-style-type: none"> • Supplemental oxygen • Fluid therapy • Vasopressor therapy • Blood transfusions • Inotropes use • Mechanical ventilation • Prevention of sudden cardiopulmonary complications
Objectives	Specific objectives and hypotheses, including the hypothesis concerning noninferiority or equivalence.	<p>Objective:</p> <ul style="list-style-type: none"> • To address the potential utility of LC as a substitute for ScvO₂. <p>Hypothesis:</p> <ul style="list-style-type: none"> • Targeting LC as the marker of adequacy of Do₂ was noninferior to the currently recommended ScvO₂ monitoring for the outcome of in-hospital mortality. 	

(Continued)

Table 1—Continued

Topic	Requirements and Considerations	Commentary	Rivers et al ⁸
		Other objectives: <ul style="list-style-type: none"> Disassemble a protocol “too complex” for the providers of care. Prove evidence that checking serial lactates is easier and a reliable equivalent to ScvO₂. Find a simpler and more generalizable method to monitor the adequacy of DO₂ as a research imperative in the treatment of patients with severe infection. The primary end point was absolute in-hospital mortality rate. Secondary end points were ICU length of stay, hospital length of stay, ventilator-free days, and new onset multiple organ failure. Other end points assessed were the number of resuscitative goals achieved, administered treatments, and predefined protocol-related serious adverse events. Using a one-sided test of noninferiority, assuming a control group mortality rate of 25% and $\alpha = .05$, a sample size of 150 per group gave 71 % power to determine the intervention did not increase mortality by $\geq 10\%$. The required size of noninferiority trials is usually larger than that for superiority trials.⁶ Blinding does not protect against bias nearly as well in a noninferiority trial as it does in a superiority trial. 	Prevailing mortality in previous before and after intervention studies show a higher mortality. ⁸ <ul style="list-style-type: none"> Baseline mortality of 47.6% $\pm$ 5% After intervention mortality of 27.5% $\pm$ 13%
Outcomes	Clearly defined primary and secondary outcome measures, detailing whether the outcomes in the noninferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).		
Sample size and statistical methods	How sample size was determined, detailing whether it was calculated using a noninferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice. When applicable, explanation of any interim analyses and stopping rules (and whether related to a noninferiority or equivalence hypothesis).		
Blinding (masking)	Whether participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.		
Results			
Participant flow and recruitment	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the trial protocol, and analyzed for the primary outcome. Describe protocol deviations from trial as planned, together with reasons.	One should avoid features that might dilute true differences between EGD ^T and LC, thereby enhancing the risk of erroneously concluding noninferiority: <ul style="list-style-type: none"> Poor adherence to the protocol Dropouts Recruitment of patients unlikely to need or respond to interventions (low illness severity and mortality) treatment crossovers. 	
Baseline data of the participants	Baseline demographic and clinical characteristics of each group. Eligibility criteria for participants (detailing whether participants in the noninferiority or equivalence trial are similar to those in any trial[s] that established efficacy of the reference treatment) and the settings and locations where the data were collected.	At baseline compared to the Rivers et al ⁸ study, Jones et al ⁷ patients were characterized by: <ul style="list-style-type: none"> Younger age Fewer comorbidities Lower illness severity Lower mortality risk Lower lactate levels Higher ScvO₂ (normal range) Higher CVP (normal range) 	

(Continued)

Table 1—Continued

Topic		Requirements and Considerations		Commentary	
				Jones et al ^{7,10}	Rivers et al ⁸
Numbers analyzed		Number of participants (denominator) in each group included in each analysis and whether “intention-to-treat” and/or alternative analyses were conducted. State the results in absolute numbers when feasible (e.g., 10 of 20, not 50%).		Jones et al ⁷ reported 30 interventions in 300 patients randomized: <ul style="list-style-type: none"> 10% (n = 29) got to the point in the protocol where one of the two treatments being evaluated were administered (Scvo₂; n = 13) and (LC; n = 16). 	
Outcomes and estimation		For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (eg, 95% CI). For the outcome(s) for which noninferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.		Patients were treated in the ED from the time of randomization until all treatment goals were achieved or 6 h had elapsed: <ul style="list-style-type: none"> No 6-h hemodynamic end points are reported. Although hematocrit was a therapeutic end point, no data were reported in reaching this end point in either group. There was no method to assess whether an indicated therapeutic action was performed in response to a parameter below the intended goal. 	
Adverse events		All important adverse events or side effects in each intervention group.		Delayed hemodynamic deterioration was not reported.	
Interpretation and generalizability		Generalizability (external validity) of the trial findings.		<ul style="list-style-type: none"> LC cannot be used in patients with nonelevated lactate levels. LC is unproven in patients with more complex presentations who require multiple interventions. 	
Overall evidence		General interpretation of the results in the context of current evidence.		<ul style="list-style-type: none"> This study is underpowered to provide enough evidence to use LC as a replacement of Scvo₂. 	
Additional contributions					
Untested hypothesis		Clinicians must be confident that the new treatment would have been shown to be efficacious if a placebo-controlled trial had been performed.		<ul style="list-style-type: none"> Is there an outcome difference between a LC from 10 to 9 vs 4 to 3.6, both 10% clearance but different outcomes? How many lactate levels were required per patient to complete therapy and the time duration? Is LC cost effective as shown in EGD⁷? What is the technology assessment comparing the clinical utility of a precalibrated Scvo₂ and hourly or even more frequent lactate levels? 	
Competing interests		This may potentially influence the editorial process and interpretation of the results.		<ul style="list-style-type: none"> The section editor of the journal where Jones et al⁷ is published is a principle investigator for competing research on EGD⁷. The author of the accompanying editorial is participating in competing research on EGD^{7,10}. 	

CONSORT = Consolidated Standards of Reporting Trials; CVP = central venous pressure; DO₂ = systemic oxygen delivery; EGD⁷ = early goal directed therapy; LC = lactate clearance; Scvo₂ = central venous oxygen saturation; SSC = surviving sepsis campaign.

Delayed hemodynamic deterioration is an important feature in up to 20% of patients which was reduced to 10% with EGD⁷.

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DOI: 10.1378/chest.11-2599

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