REFERENCES

- Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
- Rivers EP. Point: adherence to early goal-directed therapy: does it really matter? Yes. After a decade, the scientific proof speaks for itself. *Chest*. 2010;138(3):476-485.
- Dellinger RP, Levy MM, Carlet JM, et al; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36(1):296-327.
- Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med*. 2004;32(8):1637-1642.
- Nguyen HB, Loomba M, Yang JJ, et al. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. *J Inflamm (Lond)*. 2010;7:6.
- Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8):739-746.
- Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA*. 2006;295(10):1152-1160.
- Kruse J. Lactic acidosis, part 1: understanding pathogenesis and causes. As mechanisms are elucidated, some assumptions are being revised. *J Crit Illness*. 1999;14(8):456-466.
- Levrant J, Ichai C, Petit I, Ciebia J, Perus O, Grimaud D. Low exogenous lactate clearance as an early predictor of mortality in normolactatemic critically ill septic patients. *Crit Care Med*. 2003;31(3):705-710.
- Astiz ME, Rackow EC, Kaufman B, Falk JL, Weil MH. Relationship of oxygen delivery and mixed venous oxygenation to lactic acidosis in patients with sepsis and acute myocardial infarction. *Crit Care Med*. 1988;16(7):655-658.
- Rivers EP, Kruse JA, Jacobsen G, et al. The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock. *Crit Care Med*. 2007;35(9):2016-2024.
- Rady MY, Rivers EP, Nowak RM. Resuscitation of the critically ill in the ED: responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate. *Am J Emerg Med*. 1996;14(2):218-225.
- Brun-Buisson C, Doyon F, Carlet J, et al; French ICU Group for Severe Sepsis. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. *JAMA*. 1995;274(12):968-974.
- Carr GE, Edelson DP, Yuen TC, et al. In-hospital cardiac arrest among patients with coexisting pneumonia: a report from the American Heart Association's Get With The Guidelines—Resuscitation Program. *Am J Respir Crit Care Med*. 2011;183:A6339.
- Sevransky JE, Nour S, Susla GM, Needham DM, Hollenberg S, Pronovost P. Hemodynamic goals in randomized clinical trials in patients with sepsis: a systematic review of the literature. *Crit Care*. 2007;11(3):R67.
- Mizock BA. The hepatosplanchnic area and hyperlactatemia: A tale of two lactates. *Crit Care Med*. 2001;29(2):447-449.
- Hernandez G, Castro R, Romero C, et al. Persistent sepsis-induced hypotension without hyperlactatemia: is it really septic shock? *J Crit Care*. 2010;26(4):435.e9-e14.
- Dugas A, Mackenhauer J, Joyce N, et al. Prevalence and characteristics of non-lactate and lactate excretors in septic shock [abstract]. *Crit Care Med*. 2009;37:A227.
- Cannon CM; Multicenter Severe Sepsis and Septic Shock Collaborative Group. The GENESIS Project (GENeralization of Early Sepsis InterventionS): a multicenter quality improvement collaborative. *Acad Emerg Med*. 2010;17(11):1258.
- Nguyen HB, Rivers EP, Havstad S, et al. Critical care in the emergency department: a physiologic assessment and outcome evaluation. *Acad Emerg Med*. 2000;7(12):1354-1361.
- Ising P, Smith TW, Simpson SQ. Effect of intermittent vs continuous ScvO₂ monitoring on sepsis bundle compliance and mortality [abstract]. *Chest*. 2009;136(4):21S.

Rebuttal From Dr Jones

In their counterpoint, Dr Rivers and colleagues¹ present the theoretical view that patients with septic shock present in very distinct “hemodynamic phases” and that Jones et al² enrolled patients in a different phase of septic shock than did Rivers et al.³ 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 1,²⁻¹⁰ the hemodynamic patterns of the subjects enrolled by Rivers et al³ are markedly different from any other reported populations of patients with septic shock treated with quantitative resuscitation. The study by Rivers et al³ 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 al³ study was 20% higher than any septic shock mortality reported in the recent literature, leaving one to question exactly what care they received.³ Little evidence supports the contention that Jones et al² enrolled patients in a different phase of septic shock

Table 1—Summary of Initial Clinical Characteristics and Mortality Rates of Recent Studies of Quantitative Resuscitation for Septic Shock

Study	No.	Lactate, mmol/L	ScvO ₂ , %	Mortality, %
Rivers et al ³				
EGDT group	130	7.7	48.6	30.5
Control group	133	6.9	49.2	46.5
Jones et al ²				
ScvO ₂ group	150	4.2	74	23
LC group	150	3.9	...	17
Shapiro et al ⁴	116	4.4	72	20
Jones et al ⁵	77	3.6	69-81	18
Nguyen et al ⁶	197	3.4-4.4	62-69	...
Kortgen et al ⁷	30	2.6	...	27
van Beest et al ⁸	125	2.7	74	26
Peake et al ⁹	324	6.9 ^a	...	23
Xiao-Zhi et al ¹⁰	16	5.3	66	18

The most abnormal values in each column are present in bold and italic text. EGDT = early goal-directed therapy; LC = lactate clearance; ScvO₂ = central venous oxygen saturation.

^aOnly 98 had lactate measured.

than did Rivers et al,³ because the population enrolled by Jones et al² used inclusion criteria identical to the Rivers et al³ study. Furthermore, the population in the Jones et al³ study appears to be an accurate contemporaneous population from three US EDs; it has characteristics, including mortality rates, nearly identical to those described from other studies (Table 1).

Rivers et al³ have raised the issue of potential methodologic limitations. They state that one must consider “weaknesses of the non inferiority study design” in the Jones et al² study. However, our study did not show equivalence (not worse than and not better than) but rather noninferiority (not worse than and maybe better than). This study design is the only design that could test the hypothesis at hand and, furthermore, the methodologic quality of a noninferiority and superiority randomized controlled trial is the same if properly conducted. So it is unclear exactly what “weaknesses” in our study are being criticized. On the other hand, there appear to be real methodologic concerns in the Rivers et al³ trial. They failed to follow recommendations by not reporting whether any patients were randomized but not analyzed or performing an intention-to-treat analysis that could easily change the statistically significant results of the trial.

Finally, the counterpoint¹ states that 45% of patients with septic shock present with a normal lactate and suggest that because of this, lactate is an inconsistent guide of resuscitation.¹ In fact, >65% of patients in contemporaneous studies present with an ScvO₂>70%, and using their argument, these data make ScvO₂ an even more inconsistent resuscitative guide, particularly given that there is no therapy for markedly elevated and pathologic ScvO₂ (ie, >90%).^{2,5}

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.

Alan E. Jones, MD
Jackson, MS

Affiliations: From the Department of Emergency Medicine, University of Mississippi Medical Center.

Financial/nonfinancial disclosures: The author has reported to *CHEST* the following conflicts of interest: Dr Jones has received funding from the National Institutes of Health to study lactate clearance in sepsis resuscitation. Dr Jones has never been assigned patents, received patent royalties, honoraria, consulting fees, or other monetary or nonmonetary payments at any time related to the use of lactate or lactate clearance.

Correspondence to: Alan E. Jones, MD, Department of Emergency Medicine, University of Mississippi Medical Center, 2500 N State St, Jackson, MS 39216; e-mail: aejones@umc.edu

© 2011 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (<http://www.chestpubs.org/site/misc/reprints.xhtml>).

DOI: 10.1378/chest.11-2597

REFERENCES

1. Rivers EP, Elkin R, Cannon CM. Counterpoint: should lactate clearance be substituted for central venous oxygen saturation as goals of early severe sepsis and septic shock therapy? *No. Chest*. 2011;140(6):1408-1413.
2. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8):739-746.
3. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
4. Shapiro NI, Howell MD, Talmor D, et al. Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. *Crit Care Med*. 2006;34(4):1025-1032.
5. Jones AE, Focht A, Horton JM, Kline JA. Prospective external validation of the clinical effectiveness of an emergency department-based early goal-directed therapy protocol for severe sepsis and septic shock. *Chest*. 2007;132(2):425-432.
6. Nguyen HB, Corbett SW, Steele R, et al. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med*. 2007;35(4):1105-1112.
7. Kortgen A, Niederprüm P, Bauer M. Implementation of an evidence-based “standard operating procedure” and outcome in septic shock. *Crit Care Med*. 2006;34(4):943-949.
8. van Beest PA, Hofstra JJ, Schultz MJ, Boerma EC, Spronk PE, Kuiper MA. The incidence of low venous oxygen saturation on admission to the intensive care unit: a multi-center observational study in The Netherlands. *Crit Care*. 2008;12(2):R33.
9. Peake SL, Bailey M, Bellomo R, et al; ARISE Investigators, for the Australian and New Zealand Intensive Care Society Clinical Trials Group. Australasian resuscitation of sepsis evaluation (ARISE): a multi-centre, prospective, inception cohort study. *Resuscitation*. 2009;80(7):811-818.

10. Wang XZ, Lü CJ, Gao FQ, Li XH, Yan WF, Ning FY. Efficacy of goal-directed therapy in the treatment of septic shock [in Chinese]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue*. 2006;18(11):661-664.

Rebuttal From Dr Rivers et al

AN END POINT MUST BE CONSISTENTLY PRESENT TO BE GENERALIZED

Levrant 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.

*Emanuel P. Rivers, MD, MPH, FCCP
Detroit, MI
Ronald Elkin, MD
San Francisco, CA
Chad M. Cannon, MD
Kansas City, KS*

Affiliations: From the Department of Emergency Medicine and Surgery (Dr Rivers), Henry Ford Hospital, Wayne State University; Department of Medicine (Dr Elkin), Pulmonary and Critical Care Medicine, California Pacific Medical Center; and Department of Emergency Medicine (Dr Cannon), University of Kansas Hospital.

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.