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C. S. Deutschman

Zucker School of Medicine at Hofstra/Northwell

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Translational Research: The Model Matters

Clifford S. Deutschman, MS, MD, MCCM

Vice-Chair, Research, Dept of Pediatrics, Professor of Pediatrics and Molecular Medicine, Hofstra - Northwell School of Medicine, Professor, Elmezzi Graduate School of Molecular Medicine and the Feinstein Institute for Medical Research, Room 3140, 350 Community Drive, Manhasset, NY 11030

Because critical care research is so diverse and complex, the readers of *Critical Care Medicine* often find it difficult to fully understand, internalize and apply to practice the material presented each month. Therefore, authors submitting to the journal are encouraged to present their findings in a way that is clinically “accessible”, that is, in a manner that maximizes the ability of each individual reader to apply the material to their daily practice. This emphasis on clinical context is perhaps most daunting for those engaged in “translational research”, where bedside observations need to be reproduced in a model (most often an animal) in hopes of identifying some aspect of the underlying biology/pathobiology that can lead to novel therapeutic approaches to “translate” back to critically ill patients. The failed attempts to identify specific therapies for sepsis over several decades bear witness to the difficulty of this approach (1). Perhaps these failures reflect an incomplete assessment of the pathobiologic processes that lead to sepsis (2). But recent work also highlights the importance of the model (3,4). It is essential that the chosen model mimic *the human condition of interest, the standard approaches to the management of that condition and the outcome criteria used to assess efficacy* as closely as possible. That is, the model matters.

The paper by Lewis et al in this edition of the journal presents a case in point (5). In a previous publication the authors demonstrated that an early 10% change in core temperature (T) and heart rate (HR) following cecal ligation and puncture (CLP, a mouse model of sepsis) was associated with a significant risk of death within 7 days (6). The T and HR alterations were associated with changes - increases in cytokines and cystatin-C (indicative of renal dysfunction), decreases pH/base excess – consistent with a pathobiological state that might well underlie the high risk of death. In the current study, the authors used a similar approach to examine the effects of antibiotics and/or fluid resuscitation administered either at the time when animals met T/HR criteria or after a delay of 2–4 hours, bookending the Surviving Sepsis Campaign (SSC) guideline recommendation of 3 hours (7). Thus, the experiments were designed as a randomized trial where entry criteria mimicked the situation faced by most clinicians, who must initiate interventions based on patients’ clinical findings. The study demonstrated that mortality was similar if fluid was given at the time when T/HR

Cell phone: 610 308-0454, cdeutschman@northwell.edu.

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criteria were met or when resuscitation was delayed. However, similar delays in the administration of antibiotics were associated with a significant increase in mortality. When a combination of fluids and antibiotics was investigated, a delay of 4 hours, but not 2 hours, reduced survival. These findings are consistent with a recent analysis of data from nearly 50,000 patients entered into the New York State Department of Health Sepsis database (8).

The study by Lewis et al represents a potentially paradigm-shifting advance in the development of a model system to study human sepsis, one in which therapy is initiated based on the sorts of clinical data that confront clinicians. The authors also deserve commendation for identifying changes in easily measured clinical variables that strongly correlate with an adverse outcome, mimicking the approach used by the Sepsis-3 task force in developing the new clinical criteria for sepsis/septic shock (9–11) and for using these variables to identify an associated CLP-induced state that may identify the pathobiological changes underlying adverse outcomes. Indeed, this study sets a standard that others in the field should seek to replicate.

But – there’s always a “but”. In formulating their experimental paradigm, Lewis et al chose to duplicate the SSC guidelines for resuscitation. Initiating treatment when clinical indicators strongly suggest sepsis, as recommended, is appropriate. However, the actual treatment provided to the mice in the trial may not be. As per SSC guidelines, resuscitation was initiated with a fluid bolus of 30ml/kg (7). This dose may be a good starting point for patients with presumed sepsis, but it is insufficient for a mouse subjected to CLP. Most CLP investigators provide a minimum initial bolus of 40ml/kg, a substantially greater volume; some (myself included) believe that more is required (12). Failure to provide this amount leads to death from hypovolemia, not sepsis, a concern reinforced by the 100% mortality in the mice studied by Lewis et al. Further, the SSC guidelines recommend that fluid resuscitation be continued after the initial bolus, until the resuscitation is “adequate”. Providing an animal subjected to CLP with a single bolus of an insufficient amount of fluid cannot be construed as “adequate”. Indeed, Lewis et al might have followed the SSC paradigm and provided additional fluid based on clinical criteria, avoiding the risk of hypovolemia and more completely replicating the clinical situation. Similarly, a single dose of antibiotics is not sufficient for either septic patients or mice undergoing CLP, although the optimal length of treatment is unknown and may differ in patients and mice. Lewis et al replaced “time” with “pathobiological state” to improve concordance between a clinical disorder, sepsis, and the animal model used to study that disorder, CLP. Unfortunately, they did not seek similar equivalencies in the chosen interventions. Basically, treatment across species needs to be equivalent, not identical.

Finally, the 100% mortality of the mice in this study is also problematic. Philosophically, one could argue that delaying death by a day or two is not a desirable outcome. More importantly, mortality this high is unusual for CLP; with use of fluids and antibiotics, about 40% of mice survive (12). And this mortality most assuredly is not consistent with clinical sepsis; even recent reports on septic shock indicate about 50% survival (10); for sepsis, data indicate mortality of about 20% (13).

In summary, improving the model to more closely mimic the clinical situation is tremendously important. As such, the report by Lewis et al, and the fact that their findings replicate recent clinical data, may make their approach the new standard. But the study also highlights that application of guidelines designed for humans may not be appropriate when using an animal model such as CLP. The model matters; but so does pathobiological equivalence.

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