might have been better explained and we take this opportunity to do so. We chose the terms absolute and classic to describe adrenal insufficiency that may occur, for example, in patients under stress with recent discontinuation of chronic steroids or who have acute bilateral adrenal hemorrhage where the adrenal gland is incapable of producing adequate steroids. This would differentiate it from what is thought to occur in some adult patients with septic shock where, regardless of serum cortisol level, the adrenal gland is "exhausted" and cannot produce more steroids. Originally called "relative adrenal insufficiency," it was subsequently redefined as "critical illness-related corticosteroid insufficiency." We agree that there is no evidence to support the use of steroids in pediatric septic shock to target this second entity.

The author has disclosed that he does not have any potential conflicts of interest.

Joseph A. Carcillo, MD for the Surviving Sepsis Campaign Guidelines Pediatric Subcommittee, Children's Hospital of Pittsburgh, Pittsburgh, PA

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Does Cecal Ligation and Puncture–Induced Murine Sepsis Cause Lung Injury or Not?

To the Editor:

We read the recent article published in *Critical Care Medicine* by Iskander et al (1) with great interest. Iskander et al (1) noted that cecal ligation and puncture (CLP)–induced murine sepsis does not cause lung injury, and pulmonary injury cannot be considered the etiology of death in the acute phase. This is an interesting work, because the findings are contrary to previous published reports. The evidence is impressive, but we still have some puzzles about this study.

We find out that there are significant differences shown in the indexes of respiratory rate, peak inspiratory flow, peak expiratory flow, and tidal volume when comparing the normal saline group with any of the sepsis groups (24-hr Live-P, 24-hr Die-P, 48-hr Live-P, or 48-hr Die-P). The total protein, albumin, and IgM levels in the bronchoalveolar lavage fluid of all the groups have significant difference too. Should these results be considered that lung injury exists in sepsis groups compared with normal saline group?

The CLP-inducing sepsis model in the study was consistent with the method described by Ebong et al (2), which means continued antibiotic treatment with 25 mg/kg imipenem (started 2 hr after surgery and every 12 hr up to 5 d) was performed to make sepsis nonlethal. The use of imipenem was proved leading to less mortality and morbidity (2). So we are confused whether antibiotic treatment influences the coming out of lung injury after CLP-caused sepsis, thus maybe reducing the significant differences into nonsignificant differences especially in a small sample size study. Meanwhile, the plasma interleukin (IL)-6 concentrations were so different between Live-P and Die-P groups, probably suggesting that the different sensitivity of mice to antibiotic, which were displayed by different IL-6 levels, led to the survival or death?

According to the survival investigation, eight experimental mice died (47 in all) during 3 days post-CLP in the study by Iskander et al (1); however, no death occurred in the study by Ebong et al (2). Considering the most notable difference was a subcutaneous injection of 1 mL normal saline performed in the study by Ebong et al (2) but not in the study by Iskander et al (1), we presume maybe the loss of volume resuscitation resulted in the different mortality. Thus, we think it is an interference factor which may impact the study by Iskander et al (1) about sepsis and lung injury. Furthermore, most death of septic mice appeared during 48–72 hours after CLP in the study, when Iskander et al (1) did not investigate the pulmonary situation of experimental mice. Was it possible lung injury caused by sepsis developed between 48 hours after CLP to 72 hours after CLP?

In fact, we agree with Bastarache and Matthay (3) that this excellent original work developed a novel approach to studying sepsis in mice and using IL-6 as a plasma biomarker to predict mortality. It is a well-evidenced conclusion that lung injury was not directly associated with significantly increased mortality of CLP-induced sepsis. Although we appreciate this meaningful work, we think that there are still some doubts about CLP-induced murine sepsis causing lung injury or not. Correspondingly, it will be more persuasive if our puzzles could be clarified kindly.

Mr. Li and Dr. Luo contributed equally to this work. Dr. Xia is the corresponding author.

The authors have disclosed that they do not have any potential conflicts of interest.

Jiahui Li, MS, Pengfei Luo, MD, Zhaofan Xia, MD
Department of Burn Surgery, Changhai Hospital, Second Military Medical University, Shanghai, China

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The authors reply:

We appreciate the interest of Li et al (1) in our article (2), providing data demonstrating that lung injury is not present in mice after sepsis induced by cecal ligation and puncture (CLP). Our study was designed to determine if there was lung injury in mice that would die after CLP compared with those that would survive. Two control groups were included: a positive control of mice

with lung injury induced by bacterial pneumonia and a negative control group of mice receiving only normal saline. Our study (2) did not focus on the differences in lung injury in septic mice compared with normal mice. Unfortunately, Li et al (1) have misinterpreted our results. The data specifically show that there is no lung injury after CLP, but there is lung injury in mice with bacterial pneumonia. The figure legends compared the positive control, bacterial pneumonia, with the negative control, normal saline. Although the septic mice show some respiratory physiology changes, tidal volume was maintained, and importantly, no hypoxemia developed indicating no loss of lung function due to injury following CLP. There was also a concern that antibiotics were altering the development of lung injury. It should be pointed out that all the mice that underwent CLP received antibiotic therapy, so this would not account for the differences. As highlighted in the *Discussion* section in (2), organ injury happens in patients with sepsis even if they receive antibiotic treatment and an animal model of disease should be taken into account what already is common practice in the clinical scenario. The study by Ebong et al (3) published in 1999 was also done by our laboratory and was listed as reference 27 in our article (2). The fluid resuscitation protocol was identical in both articles. There was one significant difference between the two models; the original article by Ebong et al (3) used the inbred mouse strain BALB\c, whereas our article (2) used outbred mice. The focus of our article (2) was not to compare sepsis models but rather to determine if there was lung injury in CLP mice that are predicted to die compared with those mice that are predicted to live. We have used the outbred mouse model for several publications (4–6). There was also a concern that lung injury developed in the last 24 hours prior to death. In the editorial (7) that accompanied the publication, several reasons were provided why it is unlikely that significant pulmonary injury would develop in the late stages of peritonitis, reasons with which we agree. We also stated that mice were monitored for the first 5 days, and no hypoxia was present during the 48- to 72-hour time interval. Due to space constraints, these data were not shown. Since hypoxia did not develop in the CLP mice that would die at any time prior to their death, it would be appropriate to conclude that lung injury never develops after CLP in mice. We hope that this information clarifies the issues.

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Daniel Remick, MD, Florin Craciun, MD, PhD, Department of Pathology and Laboratory Medicine, Boston University School of Medicine and Boston Medical Center, Boston, MA; **Kendra Iskander, MD, MPH,** Department of Surgery, Boston University School of Medicine and Boston Medical Center, Boston, MA

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