Journal of Inflammation Research

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RESPONSE TO LETTER

Preclinical Mouse Models in Sepsis: Don't Throw the Baby Out with the Bathwater [Response to Letter]

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Dear editor

Thank you, Dr. Joffre, for your interest in our manuscript. We appreciate your efforts to identify additional standardizable and non-standardizable parameters affecting sepsis mortality in the cecal ligation and puncture (CLP) model, based on a selection of published articles. Although we agree that the CLP model may yield variable results according to these factors, the same can be said for many animal models, as well as clinical conditions among different study populations. Our study[1] essentially highlights biological and technical variables that influence sepsis mortality and does not construe a criticism of the CLP model, and this was not implied in our manuscript. Instead, our report[1] was intended to reveal some essential characteristics of animals and the laboratory environment that should be considered in the experimental design for sepsis studies. Our report[1] found that sepsis mortality rates were influenced by the timing of antibiotic administration, animal weight and the season (summer vs non-summer seasons), and this occurred differently in males vs females. These effects are not unique to the CLP model. Rather, they reflect essential components of mammalian biology that affect a wide range of diseases, including preclinical and clinical sepsis. For example, sex and gender affect the incidence and prognosis of cancer,[2] diabetes,[3] cardiovascular disease[4] and sepsis (extensive literature on this topic is summarized in the supplemental tables of our original report).[1] Weight influences the prevalence and severity of diabetes, cancer, and cardiovascular diseases,[5] as well as sepsis.[6–9] Furthermore, seasonal variations in disease severity and incidence have been reported for psychiatric disorders,[10] cardiovascular disease,[11] cancer,[12] and sepsis.[13]

We appreciate that sepsis researchers should prioritize experimental settings and parameters that can be standardized in sepsis research to increase the integrity, validity and reproducibility of preclinical sepsis models. Recently, an international panel of experts was convened to establish Minimum Quality Threshold in Pre-Clinical Sepsis Studies (MQTiPSS) to improve animal modeling in sepsis for the CLP model and related models.[14] Of note, these recommendations were formulated in 2018 and post-date most of the years that were randomly selected for Dr. Joffre's analysis (1999, 2004, 2009, 2014, and 2019). While no animal model is perfect, the CLP model continues to serve as a gold standard in the field, and complementary models also provide great value, including those described in our recent book Sepsis: Methods and Protocols.[15] We believe that by incorporating the MQTiPSS recommendations, and by carefully matching experimental animals for important variables (including those described in our manuscript),[1] we can continue to use our valuable preclinical animal models to elucidate biological mechanisms and potential treatments for sepsis, and maximize the scientific rigor of our studies. We agree that we should continue to strive to improve our animal models of sepsis, and pursue the 3 R's to replace, reduce and refine the humane use of animals in research.

Received: 14 April 2023
Accepted: 28 April 2023
Published: 11 May 2023

Disclosure

The author reports no other conflicts of interest in this communication.

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https://doi.org/10.2147/JIR.S417208